



(51) International Patent Classification:

A61K 31/436 (2006.01) *A61K 31/41* (2006.01)
A61K 31/352 (2006.01) *A61K 31/519* (2006.01)
A61K 31/34 (2006.01) *A61K 31/495* (2006.01)
A61K 31/404 (2006.01) *A61P 25/04* (2006.01)

(21) International Application Number:

PCT/US2012/040168

(22) International Filing Date:

31 May 2012 (31.05.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/491,828 31 May 2011 (31.05.2011) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: MU-OPIOID RECEPTOR BINDING COMPOUNDS

(57) Abstract: A pharmaceutical composition, comprising (i) a mu opioid receptor modulating compound selected from the group consisting of Group I compounds, Matching Compounds, and their pharmaceutically acceptable derivatives, (ii) a pharmaceutically acceptable carrier, and (iii) optionally, another therapeutic agent. Also described are therapeutic methods of administering mu opioid receptor modulating compounds, and cocktail formulations with other mu opioid receptor compounds, e.g., morphine, (+)-morphine, methadone, (+)-methadone, 3-methoxynaltrexone, etorphine, or naltrexone.



MU-OPIOID RECEPTOR BINDING COMPOUNDS**CROSS-REFERENCE TO RELATED APPLICATION**

[0001] The benefit of priority of U.S. Provisional Patent Application No. 61/491,828 filed May 31, 2011 is hereby claimed under the provisions of 35 USC §119. The disclosure of such U.S. Provisional Patent Application No. 61/491,828 is hereby incorporated herein by reference in its entirety, for all purposes.

FIELD

[0002] The present disclosure relates to mu opioid receptor binding compounds having utility as therapeutic and diagnostic agents, and more specifically to mu opioid receptor binding compounds having ligand affinity for 6-transmembrane and 7-transmembrane structures of the mu opioid receptor. The disclosure also relates to pharmaceutical compositions including such receptor binding compounds, and to methods of making and using such compounds and compositions.

BACKGROUND

[0003] The mu(μ)-type opioid receptor (MOR-1) is a member of the G-protein-coupled receptor (GPCR) family. It possesses an extracellular N-terminus and an intracellular C-terminus, with seven membrane-spanning domains forming a binding pocket for exogenous drugs. When activated, these seven transmembrane (7TM) domain GPCRs initiate molecular changes that result in inhibition of nerve, immune, and glial cells involved in onset and maintenance of pain. The MOR-1 induces analgesia via pertussis toxin-sensitive inhibitory G protein, which inhibits cAMP formation and calcium conductance and activates potassium conductance, causing hyper-polarization of cells and exerting an inhibitory effect.

[0004] The major form of MOR-1 binds endogenous and exogenous opioids to mediate analgesia, basal nociception and agonist responses. Opioids are the most commonly prescribed analgesics for treatment of moderate to severe pain. Although clinically used opioids such as morphine are generally extremely effective analgesic agents, there is a significant degree of individual variation in the degree of opioid analgesia and adverse side effects, including nausea, vomiting, sedation, cognitive

impairment, constipation, tolerance, dependence, neurotoxicity, life-threatening respiratory depression, and paradoxical hyperalgesia, and such side effects may become severely exacerbated by prolonged use of opioids. Decades of research have been devoted to developing an opioid analgesic that has the analgesic efficacy of morphine but is devoid of its adverse effects.

[0005] On the cellular level, MOR-1 activation associated with binding of opioid compounds can involve cellular excitation and inhibition effects. Excitatory effects evidenced by increased calcium levels are associated with opioid side effects, while lowered calcium levels incident to MOR-1 activation are associated with cellular inhibitory effects mediating analgesia.

[0006] In addition to the 7TM canonical form of MOR-1, a six transmembrane (6TM) form exists. Activation of the 7TM form results in major cellular inhibitory effects, while activation of the 6TM form results in cellular excitation and pro-inflammatory reactions.

[0007] 7TM mu-opioid receptor agonists therefore include desirable analgesics, and 7TM mu-opioid receptor antagonists include agents that are useful in treatment of opioid addiction or in modulating side effects. 6TM mu-opioid receptor agonists increase nociceptive effects, while 6TM mu-opioid receptor antagonists are useful in blocking cellular excitatory effects and promoting cellular inhibitory effects that mediate analgesia.

[0008] There is therefore significant continuing interest in MOR-1 receptor binding ligands, as therapeutic agents and/or as analytical and diagnostic agents.

SUMMARY

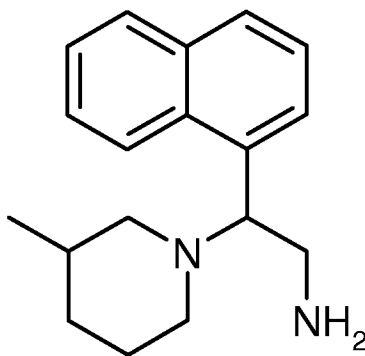
[0009] The present disclosure relates to MOR-1 receptor binding compounds, and to use of same as therapeutic, analytical and diagnostic agents, as well as pharmaceutical compositions comprising such compounds, and methods of making and using such compounds and compositions.

[0010] The present disclosure relates to mu opioid receptor binding compounds having utility as therapeutic and diagnostic agents, and more specifically to mu opioid receptor binding compounds having ligand affinity for 6-transmembrane and 7-transmembrane structures of the mu opioid receptor. The disclosure also relates to pharmaceutical compositions including such receptor binding compounds, and to methods of making and using such compounds and compositions.

[0011] In one aspect, the disclosure relates to a pharmaceutical composition, comprising (i) a mu opioid receptor modulating compound selected from the group consisting of Group I compounds and their pharmaceutically acceptable derivatives, (ii) a pharmaceutically acceptable carrier, and (iii) optionally, another therapeutic agent.

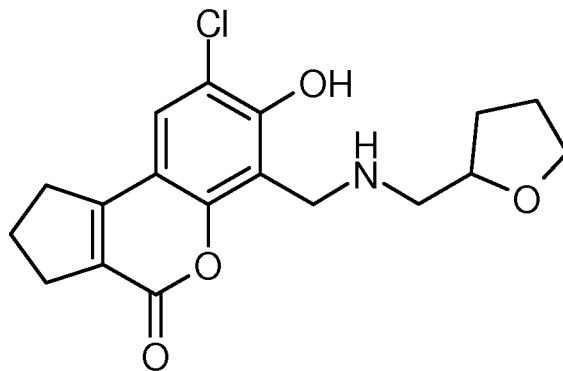
[0012] In another aspect, the disclosure relates to a pharmaceutical composition, comprising (i) a mu opioid receptor modulating compound binding a 7TM structure of said receptor, selected from the group consisting of

(i) 2-(3-methylpiperidin-1-yl)-2-(naphthalene-1-yl)ethan-1-amine



Compound K

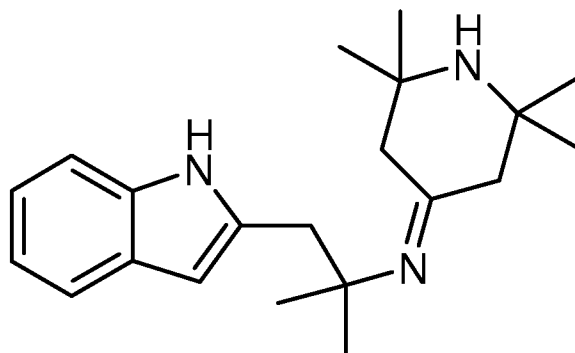
(ii) 8-chloro-7-hydroxy-6[(tetrahydrofuran-2-ylmethylamino)methyl]-2,3-dihydro-1H-cyclopenta[c]chromen-4-one



Compound L

and

(iii) N-[2-(1H-indol-2-yl)-1,1-dimethylethyl]-2,2,6,6-tetramethyl-piperidin-4-imine



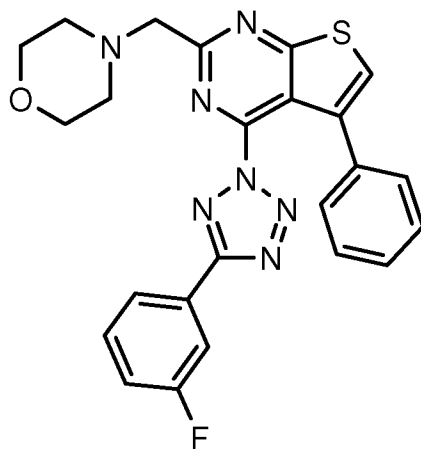
Compound M

and their pharmaceutically acceptable derivatives, and

(ii) a pharmaceutically acceptable carrier.

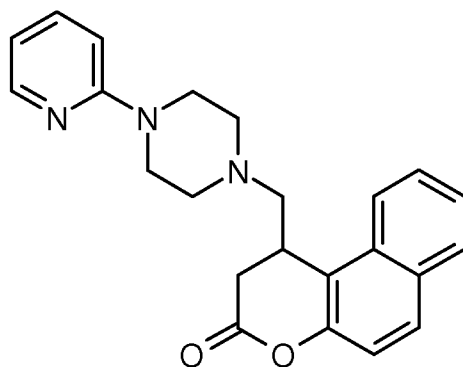
[0013] In a further aspect, the disclosure relates to a pharmaceutical composition, comprising (i) a mu opioid receptor modulating compound binding a 6TM structure of said receptor, selected from the group consisting of

(i) 4-(5-(3-fluorophenyl)-2H-tetrazol-2-yl)-2-(morpholinomethyl)-5-phenylthieno[2,3-d]pyrimidine



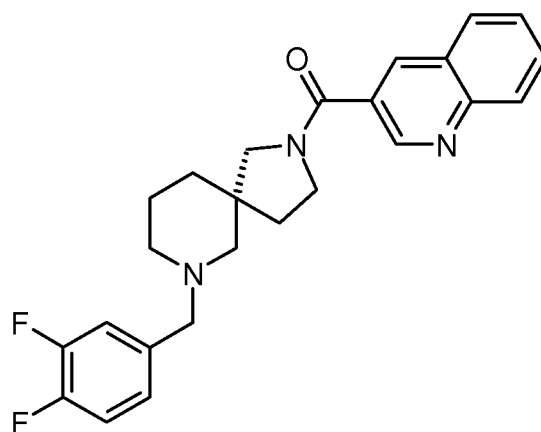
Compound A

(ii) 1-[[4-(2-pyridyl)piperazin-1-yl]menthyl]benzo[f]chromen-3-one



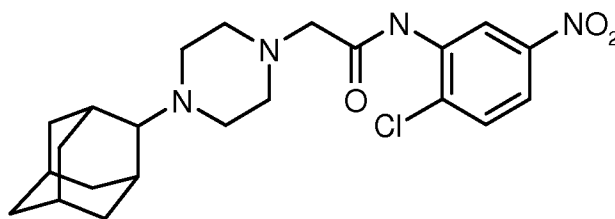
Compound B

(iii) [7-[(3,4-difluorophenyl)methyl]-2,7-diazaspiro[4.5]decan-2-yl]-(3-quinolyl)methanone



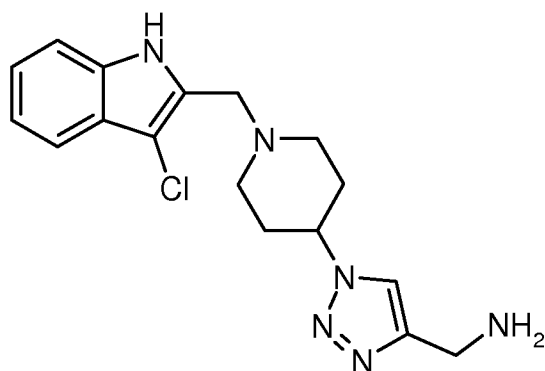
Compound C

(iv) 2-[4(adamantan-2-yl)piperazin-1-yl]-N-(2-chloro-5-nitrophenyl)acetamide



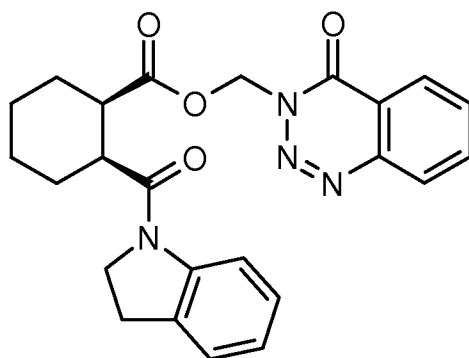
Compound D

(v) [1-[1[(3-chloro-1H-indol-2-yl)methyl]-4-piperidyl]triazol-4-yl]methanamine



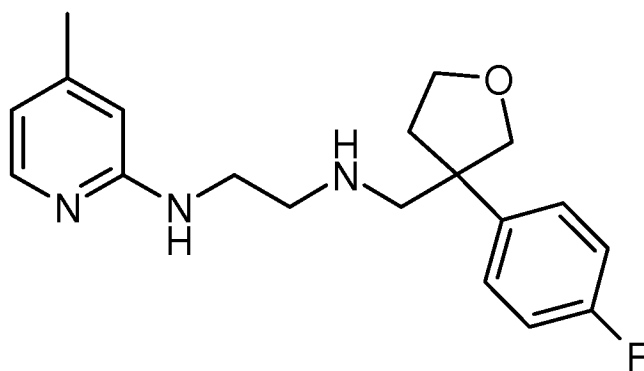
Compound E

(vi) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1R,2S)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



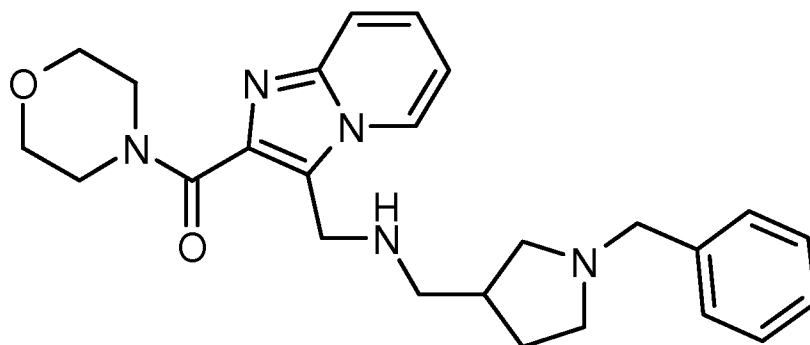
Compound F

(vii) N'-[[3-(4-fluorophenyl)tetrahydrofuran-3-yl]methyl]-N-(4-methyl-2-pyridyl)ethane-1,2-diamine



Compound G

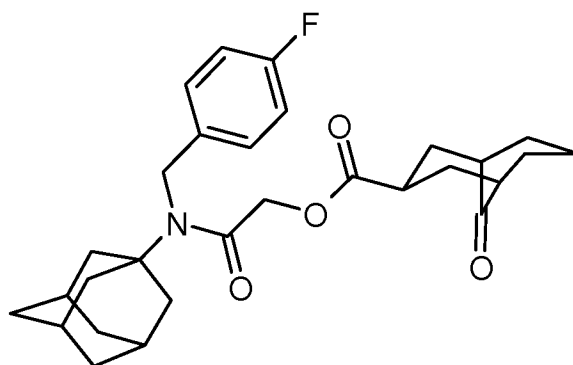
(viii) [(1-benzylpyrrolidin-3-yl)methyl]({2-[(morpholin-4-yl)carbonyl]imidazo[1,2-a]pyridine-3-yl}methyl)amine



Compound I

and

(ix) [(adamantan-1-yl)[(4-fluorophenyl)methyl]carbamoyl]methyl 9-oxobicyclo[3.3.1]nonane-3-carboxylate



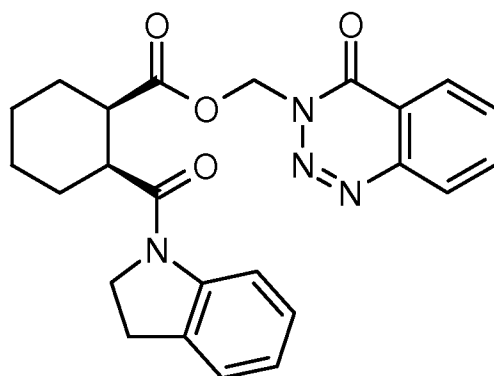
Compound N

and their pharmaceutically acceptable derivatives, and

(ii) a pharmaceutically acceptable carrier.

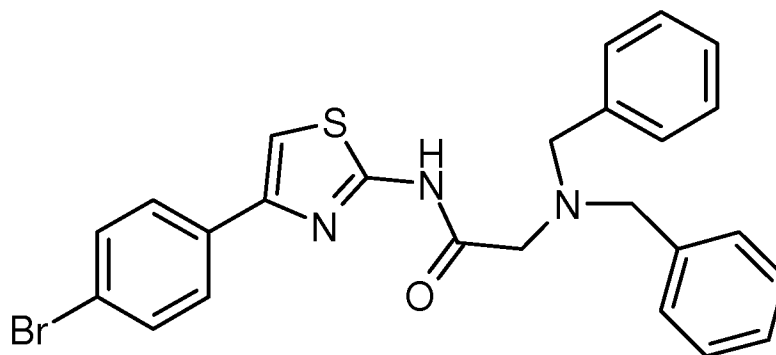
[0014] A further aspect of the disclosure relates to a pharmaceutical composition, comprising (i) a mu opioid receptor modulating compound binding both 6TM and 7TM structures of said receptor, selected from the group consisting of

(i) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1R,2S)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



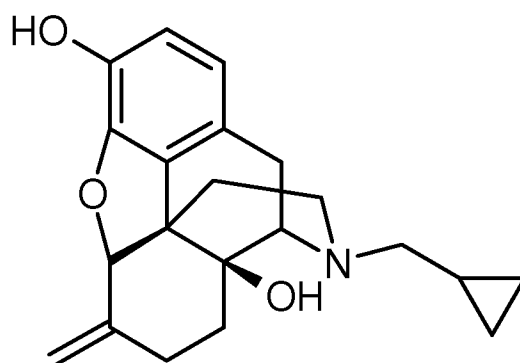
Compound F

(ii) N-[4-(4-bromophenyl)thiazol-2-yl]-2-(dibenzylamino)acetamide



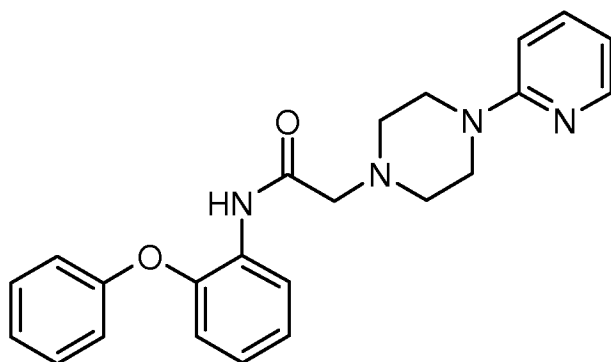
Compound H

(iii) 17-(cyclopropylmethyl)-4,5-epoxy-6-methylene-morphinan-3,14-diol



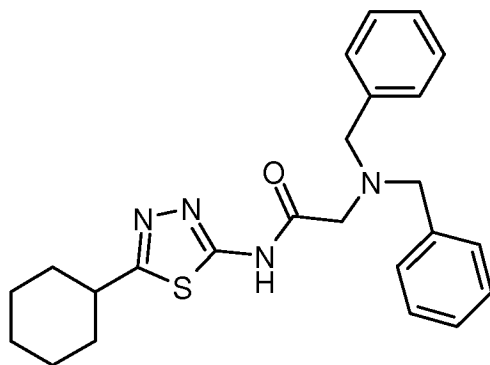
Compound J

(iv) N-(2-phenoxyphenyl)-2-[4-(2-pyridyl)piperazin-1-yl]acetamide



Compound O

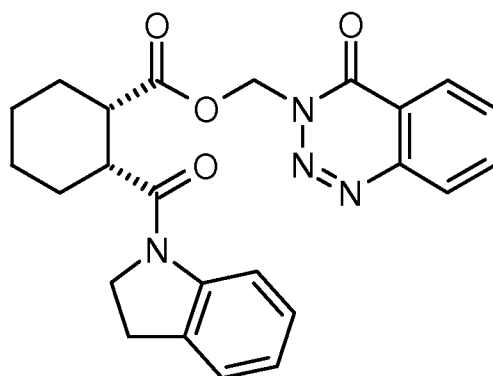
(v) N-(5-cyclohexyl-1,3,4-thiadiazol-2-yl)-2-(dibenzylamino)acetamide



Compound P

and

(vi) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1S,2R)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



Compound Q

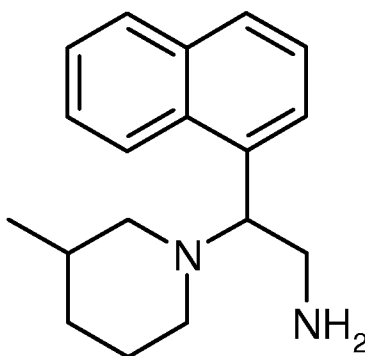
and their pharmaceutically acceptable derivatives, and

(ii) a pharmaceutically acceptable carrier.

[0015] A still further aspect of the disclosure relates to a method of modulating mu opioid receptor response in a subject in need thereof, comprising administering to the subject an effective amount for said response modulation of a mu opioid receptor modulating compound selected from the group consisting of Group I compounds and their pharmaceutically acceptable derivatives.

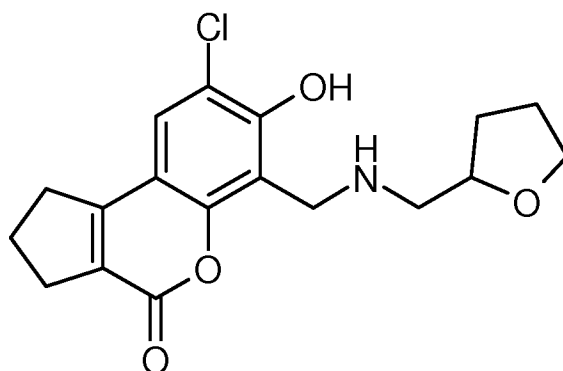
[0016] Yet another aspect of the disclosure relates to a method of modulating mu opioid receptor response in a subject in need thereof, comprising administering to the subject an effective amount for said response modulation of a mu opioid receptor modulating compound binding a 7TM structure of said receptor, selected from the group consisting of

(i) 2-(3-methylpiperidin-1-yl)-2-(naphthalene-1-yl)ethan-1-amine



Compound K

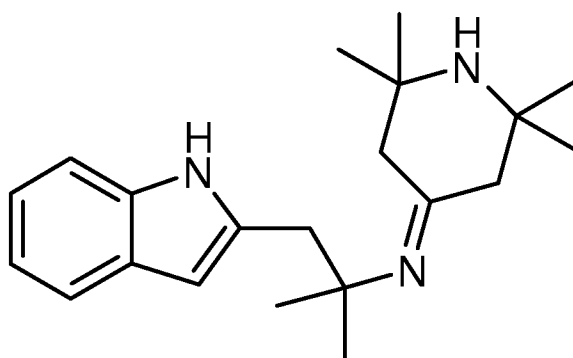
- (ii) 8-chloro-7-hydroxy-6[(tetrahydrofuran-2-ylmethylamino)methyl]-2,3-dihydro-1H-cyclopenta[c]chromen-4-one



Compound L

and

- (iii) N-[2-(1H-indol-2-yl)-1,1-dimethylethyl]-2,2,6,6-tetramethyl-piperidin-4-imine

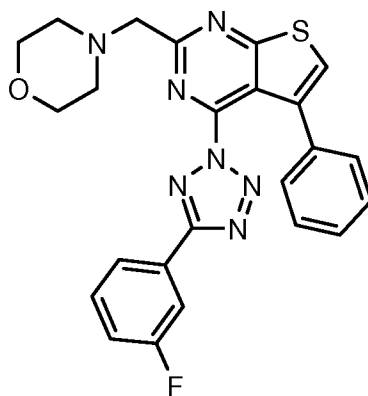


Compound M

and their pharmaceutically acceptable derivatives.

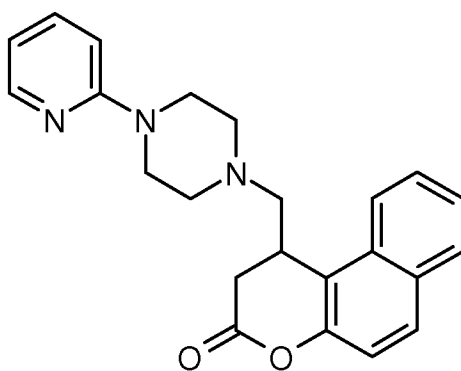
[0017] A further aspect of the disclosure relates to a method of modulating mu opioid receptor response in a subject in need thereof, comprising administering to the subject an effective amount for said response modulation of a mu opioid receptor modulating compound binding a 6TM structure of said receptor, selected from the group consisting of

- (i) 4-(5-(3-fluorophenyl)-2H-tetrazol-2-yl)-2-(morpholinomethyl)-5-phenylthieno[2,3-d]pyrimidine



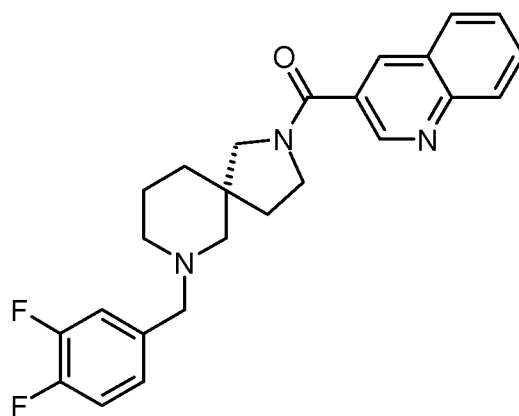
Compound A

(ii) 1-[[4-(2-pyridyl)piperazin-1-yl]menthyl]benzo[f]chromen-3-one



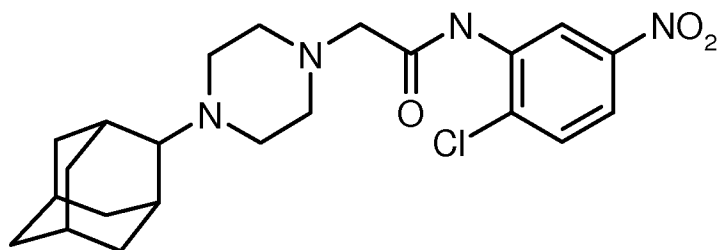
Compound B

(iii) [7-[(3,4-difluorophenyl)methyl]-2,7-diazaspiro[4.5]decan-2-yl]-(3-quinolyl)methanone



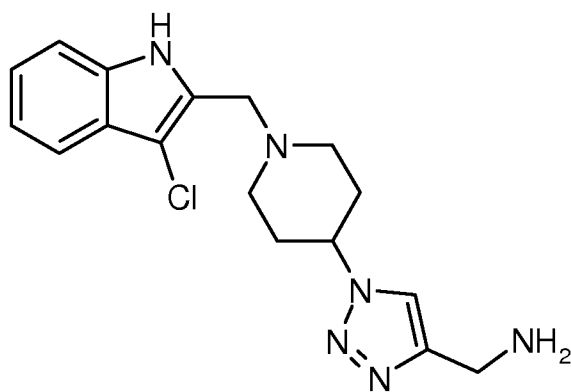
Compound C

(iv) 2-[4(adamantan-2-yl)piperazin-1-yl]-N-(2-chloro-5-nitrophenyl)acetamide



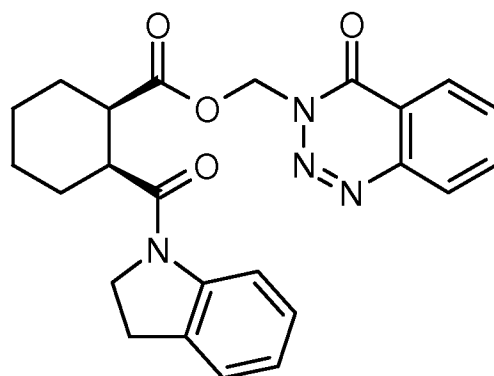
Compound D

(v) [1-[1[(3-chloro-1H-indol-2-yl)methyl]-4-piperidyl]triazol-4-yl]methanamine



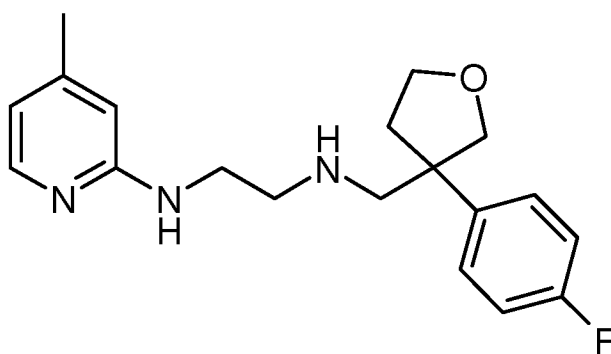
Compound E

(vi) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1R,2S)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



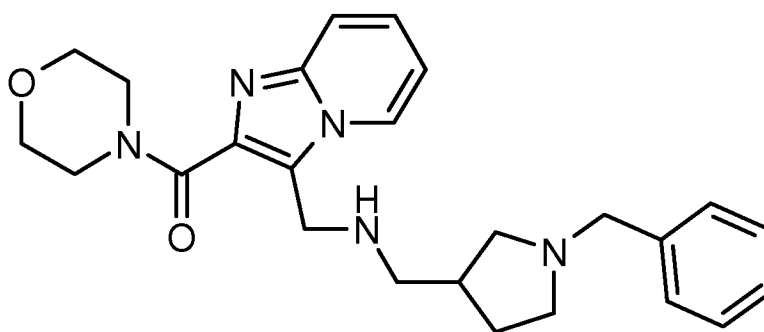
Compound F

(vii) N'-[[3-(4-fluorophenyl)tetrahydrofuran-3-yl]methyl]-N-(4-methyl-2-pyridyl)ethane-1,2-diamine



Compound G

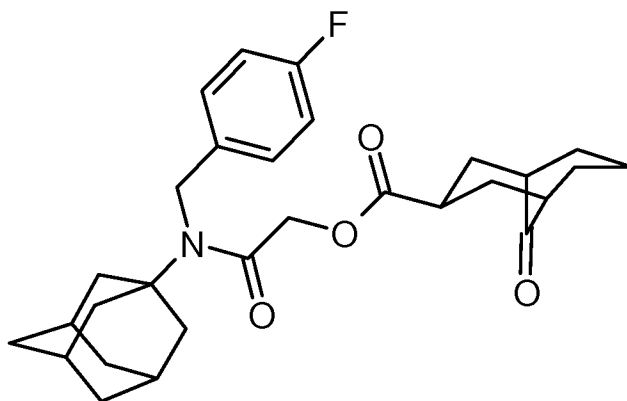
(viii) [(1-benzylpyrrolidin-3-yl)methyl]({2-[(morpholin-4-yl)carbonyl]imidazo[1,2-a]pyridine-3-yl}methyl)amine



Compound I

and

(ix) [(adamantan-1-yl)[(4-fluorophenyl)methyl]carbamoyl]methyl 9-oxobicyclo[3.3.1]nonane-3-carboxylate

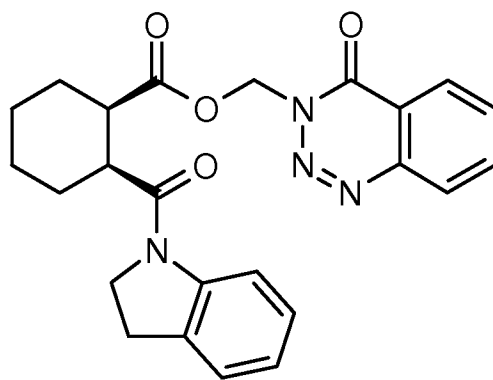


Compound N

and their pharmaceutically acceptable derivatives.

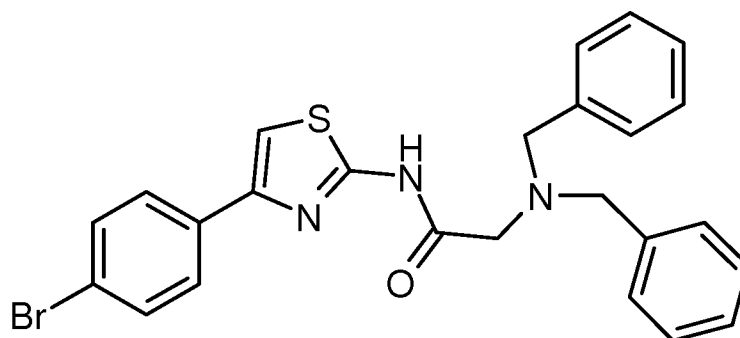
[0018] The disclosure in a further aspect relates to a method of modulating mu opioid receptor response in a subject in need thereof, comprising administering to the subject an effective amount for said response modulation of a mu opioid receptor modulating compound binding both 6TM and 7TM structures of said receptor, selected from the group consisting of

(i) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1R,2S)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



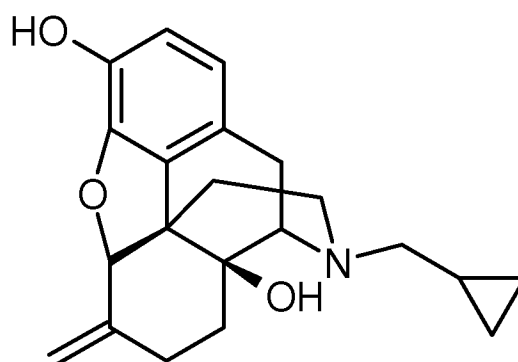
Compound F

(ii) N-[4-(4-bromophenyl)thiazol-2-yl]-2-(dibenzylamino)acetamide



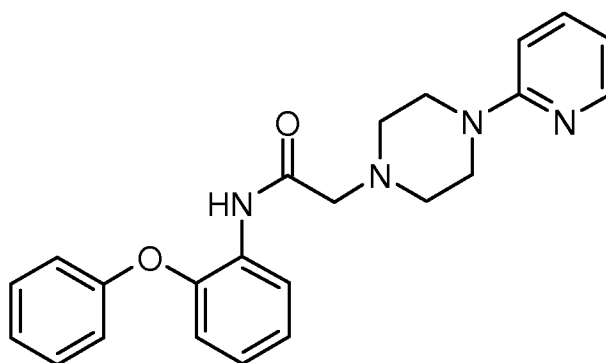
Compound H

(iii) 17-(cyclopropylmethyl)-4,5-epoxy-6-methylene-morphinan-3,14-diol



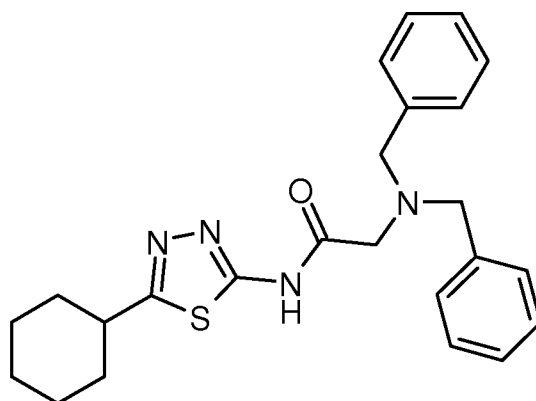
Compound J

(iv) N-(2-phenoxyphenyl)-2-[4-(2-pyridyl)piperazin-1-yl]acetamide



Compound O

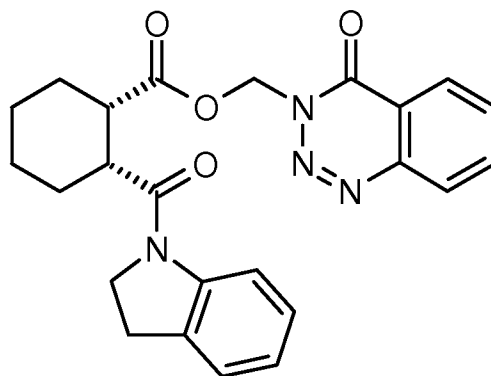
(v) N-(5-cyclohexyl-1,3,4-thiadiazol-2-yl)-2-(dibenzylamino)acetamide



Compound P

and

(vi) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1S,2R)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



Compound Q

and their pharmaceutically acceptable derivatives.

[0019] Yet another aspect of the disclosure relates to a pharmaceutical composition, comprising (i) a mu opioid receptor modulating compound selected from the group consisting of Matching Compounds and their pharmaceutically acceptable derivatives, (ii) a pharmaceutically acceptable carrier, and (iii) optionally, another therapeutic agent.

[0020] Another aspect of the disclosure relates to a method of modulating mu opioid receptor response in a subject in need thereof, comprising administering to the subject an effective amount for

said response modulation of a mu opioid receptor modulating compound selected from the group consisting of Matching Compounds and their pharmaceutically acceptable derivatives.

[0021] A still further aspect of the disclosure relates to a therapeutic cocktail formulation, including (i) at least one Group I compound, Matching Compound, or pharmaceutically acceptable derivative thereof, and (ii) at least one compound selected from the group consisting of morphine, (+)-morphine, methadone, (+)-methadone, 3-methoxynaltrexone, etorphine, and naltrexone.

[0022] Other aspects, features and embodiments of the disclosure will be more fully apparent from the ensuing description and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. 1A depicts a human mu opioid receptor model exhibiting a seven-transmembrane-helix topology conserved among G-protein coupled receptors (GPCRs), wherein N and C-termini are colored blue and red, respectively.

[0024] FIG. 1B is a Ramachandran plot mapping the Phi and Psi torsion angles of each residue. Regions bounded by dark blue are allowed conformations while those bounded by cyan are favored conformations.

[0025] FIG. 2A depicts the mapping of mutations in the mu opioid receptor model, showing sites where mutations significantly affect ligand binding.

[0026] FIG. 2B depicts the mapping of mutations in the mu opioid receptor model that do not significantly affect ligand binding. These include V128A (TM II); T139E, I140L, I144A, I146L, and N152A (TM III); I200V and V204I (TM IV); K235 to R, A, H, and L (TM V); and H299 to Q and N (TM VI). In the mu opioid receptor model, these residues are either far or their side chains face away from the ligand-binding pocket.

[0027] FIG. 3 is a depiction of the calculated surface charge distribution of the mu opioid receptor model.

[0028] FIG. 4 is a depiction of the packing of a bilayer of the lipid DPPC (dipalmitoylphosphatidylcholine) around the mu opioid receptor.

[0029] FIG. 5 shows the conformational result of an equilibrium simulation performed on the mu opioid receptor model embedded in the DPPC bilayer for 8 ns, with the final structure (green) being ~3 Å root mean square deviation (RMSD) with respect to the starting conformation (cyan).

[0030] FIG. 6 is a graph of RMSD as a function of time in nanoseconds, for such molecular dynamics simulation of FIG. 5, showing that the model is stable during the molecular dynamics simulations.

[0031] FIG. 7 shows the structure of the 7TM variant, and the first transmembrane helix H1, which does not directly interact with bound morphine.

[0032] FIG. 8 shows the putative binding pocket of the human mu opioid receptor 6TM variant.

[0033] FIG. 9 shows the 6TM variant molecular dynamics simulation.

[0034] FIG. 10 is a graph of the root mean square deviation (RMSD) of the protein backbone with respect to the initial conformation of the 6TM structure.

[0035] FIG. 11 shows the superposition of the human mu opioid receptor 6TM variant conformation before simulation (in cyan color) and after simulation (in green color).

[0036] FIG. 12 shows a corresponding superposition view from the extracellular side of the superposition of the human mu opioid receptor 6TM variant conformation before simulation (in cyan color) and after simulation (in green color).

[0037] FIG. 13 is a plot of the root mean square fluctuations (RMSF), in Angstroms, for each residue during the simulation of the 7TM variant with and without morphine.

[0038] FIG. 14 is a depiction of the 7TM variant with and without morphine, with the RMSF values mapped onto the protein structure.

[0039] FIG. 15 is a plot of the root mean square fluctuations (RMSF), in Angstroms, for each residue during the simulation of the 6TM variant with and without morphine.

[0040] FIG. 16 is a depiction of the 6TM variant with and without morphine, with the RMSF values mapped onto the protein structure.

[0041] FIG. 17 shows the binding pocket residues with their calculated contact frequencies for the 7TM variant (left panel) and the 6TM variant (right panel), together with a contact probability scale shown at the far right for the 7TM and 6TM panels.

[0042] FIG. 18 shows residues specific to both 6TM and 7TM variant binding pockets.

[0043] FIG. 19 shows mutation sites that affect binding to the 7TM variant more than to the 6TM variant.

[0044] FIG. 20 shows mutation sites that affect binding to the 6TM variant more than to the 7TM variant.

[0045] FIG. 21 is a schematic flow chart for the virtual screening process for identifying binding ligands to a protein target, as utilized to identify modulator compounds for 7TM and 6TM human mu opioid receptor variants.

DETAILED DESCRIPTION

[0046] The present disclosure relates to MOR-1 receptor binding compounds, including agonist and antagonist compounds effective to modulate MOR-1 receptor activity. Such compounds include receptor modulating compounds having binding affinity for 6-transmembrane (6TM) and 7-transmembrane (7TM) structures of the mu opioid receptor. The disclosure also relates to compositions containing such compounds, and to methods of making and using such compounds and compositions.

[0047] The mu opioid receptor 6TM binding compounds include 6TM agonists that increase nociceptive effects and 6TM antagonists that mediate analgesia. The mu opioid receptor 7TM binding compounds include 7TM agonists that mediate analgesia, and 7TM antagonists that increase nociceptive effects.

[0048] The present disclosure further relates to pharmaceutical compositions in which mu opioid receptor binding compounds are utilized in combination with other therapeutic agents, such as therapeutic agents that enhance therapeutic efficacy, such as by increasing analgesia, decreasing side effects, e.g., respiratory depression, otherwise incident to administration of opioid receptor binding compounds, decreasing tolerance to mu opioid receptor binding compounds, etc. Compounds of the present disclosure may also be utilized in combination with therapeutic agents that potentiate opioid-mediated analgesia so that lower dosage of the compounds is possible to produce somatosensory or other therapeutic benefit.

[0049] The various compounds of the present disclosure may be structurally varied and derivatized within the skill of the art, based on the disclosure herein. For example, ester substituents in compounds including same may be replaced with an amide or thioamide moiety to increase the *in vivo* stability. Carbamate, thiocarbamate, urea, thiourea, ether, and thioether moieties can also be substituted for ester moieties. Aryl rings can be replaced with heteroaryl rings, such as thiophene rings in these compounds. The compounds disclosed herein can optionally be substituted with a morpholinyl or piperidinyl moiety, which can be desirable to increase hydrophilicity.

[0050] Novel compounds may also be formed in a combination of substituents which creates a chiral center or another form of an isomeric center. In this embodiment, the compound may variously exist as a racemic mixture, a pure enantiomer, and any enantiomerically enriched mixture.

[0051] The compounds can occur in varying degrees of enantiomeric excess, and racemic mixtures can be purified using known chiral separation techniques.

[0052] The compounds can be in a free base form or in a salt form (e.g., as pharmaceutically acceptable salts). Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, dichloroacetate, galactarate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, p-toluenesulfonate, and ascorbate; salts with an acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium and potassium; alkaline earth metal salts such as magnesium and calcium; ammonium salt; organic basic salts such as trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine, and N,N'-dibenzylethylenediamine; and salts with a basic amino acid such as lysine and arginine. The salts can be in some cases hydrates or ethanol solvates. The stoichiometry of the salt will vary with the nature of the components.

[0053] The compounds described herein can be derivatized in any suitable manner, e.g., by formation of salts, esters, solvates, polymorphs or prodrugs of the specifically disclosed compounds. Compounds including at least one aryl or heteroaryl ring can be substituted on one or more of these rings with one or more substituents. Those skilled in the art will readily understand that incorporation of other substituents onto an aryl or heteroaryl ring used as a starting material to prepare the compounds described herein, and other positions in the compound framework, can be readily realized. Such substituents can provide useful properties in and of themselves or facilitate further synthetic elaboration.

[0054] Benzene rings (and pyridine, pyrimidine, pyrazine, and other heteroaryl rings) can be substituted using known chemistry. For example, the nitro group on nitrobenzene can be reacted with sodium nitrite to form the diazonium salt, and the diazonium salt manipulated to form the various substituents on a benzene ring.

[0055] Diazonium salts can be halogenated using various known procedures, which vary depending on the particular halogen. Examples of suitable reagents include bromine/water in concentrated HBr, thionyl chloride, pyr-ICl, fluorine and Amberlyst-A.

[0056] A number of other analogs, bearing substituents in the diazotized position, can be synthesized from the corresponding amino compounds, via the diazocyclopentadiene intermediate. The diazo compounds can be prepared using known chemistry, for example, as described above.

[0057] Nitro derivatives can be reduced to the amine compound by reaction with a nitrite salt, typically in the presence of an acid. Other substituted analogs can be produced from diazonium salt intermediates, including, but are not limited to, hydroxy, alkoxy, fluoro, chloro, iodo, cyano, and mercapto, using general techniques known to those of skill in the art.

[0058] For example, hydroxy-aromatic/heteroaromatic analogs can be prepared by reacting the diazonium salt intermediate with water. Halogens on an aryl or heteroaryl rings can be converted to

Grignard or organolithium reagents, which in turn can be reacted with suitable aldehyde or ketone to form alcohol-containing side chains. Likewise, alkoxy analogs can be made by reacting the diazo compounds with alcohols. The diazo compounds can also be used to synthesize cyano or halo compounds, as will be known to those skilled in the art. Mercapto substitutions can be obtained using techniques described in Hoffman et al., *J. Med. Chem.* **36**: 953 (1993). The mercaptan so generated can, in turn, be converted to an alkylthio substituent by reaction with sodium hydride and an appropriate alkyl bromide. Subsequent oxidation would then provide a sulfone. Acylamido analogs of the compounds can be prepared by reacting the corresponding amino compounds with an appropriate acid anhydride or acid chloride using techniques known to those skilled in the art of organic synthesis.

[0059] Hydroxy-substituted analogs can be used to prepare corresponding alkanoyloxy-substituted compounds by reaction with the appropriate acid, acid chloride, or acid anhydride. Likewise, the hydroxy compounds are precursors of both the aryloxy and heteroaryloxy *via* nucleophilic aromatic substitution at electron deficient aromatic rings. Such chemistry is well known to those skilled in the art of organic synthesis. Ether derivatives can also be prepared from the hydroxy compounds by alkylation with alkyl halides and a suitable base or *via* Mitsunobu chemistry, in which a trialkyl- or triarylphosphine and diethyl azodicarboxylate are typically used. See Hughes, *Org. React. (N.Y.)* **42**: 335 (1992) and Hughes, *Org. Prep. Proced. Int.* **28**: 127 (1996) for typical Mitsunobu conditions.

[0060] Cyano-substituted analogs can be hydrolyzed to afford the corresponding carboxamido-substituted compounds. Further hydrolysis results in formation of the corresponding carboxylic acid-substituted analogs. Reduction of the cyano-substituted analogs with lithium aluminum hydride yields the corresponding aminomethyl analogs. Acyl-substituted analogs can be prepared from corresponding carboxylic acid-substituted analogs by reaction with an appropriate alkyllithium using techniques known to those skilled in the art of organic synthesis.

[0061] Carboxylic acid-substituted analogs can be converted to the corresponding esters by reaction with an appropriate alcohol and acid catalyst. Compounds with an ester group can be reduced with sodium borohydride or lithium aluminum hydride to produce the corresponding hydroxymethyl-substituted analogs. These analogs in turn can be converted to compounds bearing an ether moiety by reaction with sodium hydride and an appropriate alkyl halide, using conventional techniques. Alternatively, the hydroxymethyl-substituted analogs can be reacted with tosyl chloride to provide the corresponding tosyloxymethyl analogs, which can be converted to the corresponding alkylaminoacyl analogs by sequential treatment with thionyl chloride and an appropriate alkylamine. Certain of these amides are known to readily undergo nucleophilic acyl substitution to produce ketones.

[0062] Hydroxy-substituted analogs can be used to prepare N-alkyl- or N-arylcarbamoyloxy-substituted compounds by reaction with N-alkyl- or N-arylisocyanates. Amino-substituted analogs can be used to prepare alkoxycarboxamido-substituted compounds and urea derivatives by reaction with alkyl chloroformate esters and N-alkyl- or N-arylisocyanates, respectively, using techniques known to those skilled in the art of organic synthesis.

[0063] Compounds of the present disclosure can be utilized to modulate mu opioid receptor activity, and to mediate analgesia or nociceptive response, or to elicit or combat other receptor response, depending on the appertaining agonistic or antagonistic character of such compounds. The compounds can be used to characterize tissues as to presence and density of mu opioid receptors, or 6TM or 7TM structures of such receptors. The compounds can be used diagnostically to predict or determine pain sensitivity, to modify pain sensitivity, or to characterize and treat somatosensory disorders.

[0064] Such modulation of mu opioid receptor activity within the scope of the present disclosure also includes modulation of splice variant forms of the human mu opioid receptor, such as the six transmembrane isoforms encoded by MOR-1K1 and MOR-1K2. Such MOR-1 splice variant forms are more fully described in International Patent Application PCT/US 2009/054300 filed August 19, 2009, the disclosure of which is hereby incorporated herein by reference in its entirety, for all purposes.

[0065] The present disclosure contemplates use of the compounds described herein, in pharmaceutical formulations for therapeutic administration. In such pharmaceutical formulations, the active pharmaceutical ingredient preferably is utilized together with one or more pharmaceutically acceptable carrier(s) therefor and optionally any other therapeutic ingredients. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and therapeutically beneficial to the recipient thereof. The active pharmaceutical ingredient is provided in an amount effective to achieve the desired pharmacological effect, and in a quantity appropriate to achieve the desired dose on a daily or other temporal basis.

[0066] In therapeutic usage, the present disclosure contemplates a method of treating an animal subject having or latently susceptible to a disease state or physiological condition for which a compound of the present disclosure is beneficially administered, comprising administering to such subject an effective amount of a compound of the present invention that is therapeutically effective for said condition or disease state. Subjects to be treated by the compounds of the present invention include both human and non-human animal (e.g., bird, dog, cat, cow, horse) subjects, and are preferably mammalian subjects, and most preferably human subjects.

[0067] Depending on the specific condition or disease state to be combatted, animal subjects may be administered compounds of the present invention at any suitable therapeutically effective and safe

dosages, as may readily be determined within the skill of the art and without undue experimentation, based on the disclosure herein.

[0068] For example, compounds of the present invention may be administered in specific embodiments at a dosage between about 0.01 and 200 mg/kg, preferably between about 1 and 90 mg/kg, and more preferably between about 10 and 80 mg/kg.

[0069] The compounds of the present disclosure may be administered per se as well as in the form of pharmaceutically acceptable esters, salts, and other physiologically functional derivatives thereof.

[0070] The compounds may be utilized in a wide variety of pharmaceutical formulations, both for veterinary and for human medical use, which comprise as the active pharmaceutical ingredient one or more compound(s) of the present disclosure.

[0071] The formulations include those suitable for parenteral as well as non-parenteral administration, and specific administration modalities include, but are not limited to, oral, rectal, buccal, topical, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, intrathecal, intra-articular, intra-arterial, sub-arachnoid, bronchial, lymphatic, vaginal, and intra-uterine administration. Formulations suitable for oral and parenteral administration are preferred, with formulations suitable for oral administration most preferred.

[0072] When a compound is utilized in a formulation comprising a liquid solution, the formulation advantageously may be administered orally or parenterally. When a compound of the present disclosure is employed in a liquid suspension formulation or as a powder in a biocompatible carrier formulation, the formulation may be advantageously administered orally, rectally, or bronchially.

[0073] When a compound of the present disclosure is utilized directly in the form of a powdered solid, the compound may advantageously be administered orally. Alternatively, it may be administered bronchially, via nebulization of the powder in a carrier gas, to form a gaseous dispersion of the powder that is inspired by the patient from a breathing circuit comprising a suitable nebulizer device.

[0074] The formulations comprising a compound of the present disclosure may conveniently be presented in unit dosage forms and may be prepared by any of the methods well known in the art of pharmacy. Such methods generally include the step of bringing a compound of the present invention into association with a carrier that constitutes one or more accessory ingredients. Typically, the formulations are prepared by uniformly and intimately bringing a compound of the present disclosure into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into dosage forms of the desired formulation.

[0075] Formulations of the present disclosure suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of a compound of the present disclosure as a powder or granules, or a suspension in an aqueous liquor or a non-aqueous liquid, such as a syrup, an elixir, an emulsion, or a draught.

[0076] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, with the active compound being in a free-flowing form such as a powder or granules which optionally is mixed with a binder, disintegrant, lubricant, inert diluent, surface active agent, or discharging agent. Molded tablets comprised of a mixture of the powdered active compound with a suitable carrier may be made by molding in a suitable machine.

[0077] A syrup may be made by adding a compound of the present disclosure to a concentrated aqueous solution of a sugar, for example sucrose, to which may also be added any accessory ingredient(s). Such accessory ingredient(s) may include, for example, flavorings, suitable preservatives, agents to retard crystallization of the sugar, and agents to increase the solubility of any other ingredient, such as a polyhydroxy alcohol, for example glycerol or sorbitol.

[0078] Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of a compound of the present invention, which preferably is isotonic with the blood of the recipient (e.g., physiological saline solution). Such formulations may include suspending agents and thickening agents or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose form.

[0079] Nasal spray formulations comprise purified aqueous solutions of a compound of the present invention with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the nasal mucus membranes.

[0080] Formulations for rectal administration may be presented as a suppository with a suitable carrier such as cocoa butter, hydrogenated fats, or hydrogenated fatty carboxylic acid.

[0081] Ophthalmic formulations are prepared by a similar method to the nasal spray, except that the pH and isotonic factors are preferably adjusted to match that of the eye.

[0082] Topical formulations comprise a compound of the present disclosure dissolved or suspended in one or more media, such as mineral oil, petroleum, polyhydroxy alcohols, or other bases used for topical pharmaceutical formulations.

[0083] In addition to the aforementioned ingredients, specific formulations may further include one or more accessory ingredient(s) selected from diluents, buffers, flavoring agents, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants), and the like.

[0084] In specific embodiments, active pharmaceutical compounds of the present disclosure can be used in therapeutic compositions that may further comprise one or more other medicaments, including, by way of example, but not limited to anti-inflammatory agents such as mesalamine, sulfasalazine, balsalazide, and olsalazine; immunomodulators such as azathioprine, 6-mercaptopurine, cyclosporine and methotrexate; steroidal compounds such as corticosteroids; and antibiotics such as metronidazole and ciprofloxacin, as well as other ingredients such as excipients, disintegrants, release modifiers, etc.

[0085] Representative compounds of the present disclosure (hereafter referred to as “Group I compounds” for ease of reference) include:

	ZINC ID ¹	SMILES ²	Name
(1)	ZINC05035394	<chem>O=C(NCC1CCCCC1)C(C)Sc1nnnn1c1ccccc1</chem>	(2S)-N-(cyclohexylmethyl)-2-(1-phenyltetrazol-5-yl)sulfanyl-propanamide
(2)	ZINC05037099	<chem>O=C(N1CCc2ccccc2C1)C(C)OC(=O)c1cc2ccccc2[nH]1</chem>	[(1S)-2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-methyl-2-oxo-ethyl] 1H-indole-2-carboxylate
(3)	ZINC05652245	<chem>CCc1ccccc1NC(=O)CSc1nnnn1c1ccccc1</chem>	N-(2-ethylphenyl)-2-(1-phenyltetrazol-5-yl)sulfanyl-acetamide
(4)	ZINC06139335	<chem>N#C[C@@](C)(NC(=O)CSc1nnnc(c2ccccc2)n1C)C1CC1</chem>	N-[(1S)-1-cyano-1-cyclopropyl-ethyl]-2-[[4-methyl-5-(4-pyridyl)-1,2,4-triazol-3-yl]sulfanyl]acetamide
(5)	ZINC06697480	<chem>N#Cc1ccccc1NC(=O)CSc1nc(C)c([nH]1)c1ccccc1</chem>	N-(2-cyanophenyl)-2-[[4-methyl-5-phenyl-3H-imidazol-2-yl]sulfanyl]acetamide
(6)	ZINC07033908	<chem>O=c1cc(COC(=O)C2CCCO2)c2c(cc3ccccc23)o1</chem>	(3-oxobenzof[chromen-1-yl)methyl (2S)-tetrahydrofuran-2-carboxylate
(7)	ZINC07492291	<chem>N#Cc1ccccc1NC(=O)C(C)OC(=O)Cc1cccc(F)c1</chem>	[(1S)-2-[(2-cyanophenyl)amino]-1-methyl-2-oxo-ethyl] 2-(3-fluorophenyl)acetate
(8)	ZINC07602428	<chem>Nc1nnnn1NCc1c(OCc2ccccc2)ccc2ccccc12</chem>	N-[(2-benzyloxy-1-naphthyl)methyl]tetrazole-1,5-diamine
(9)	ZINC07693689	<chem>C#CCNC(=O)CSc1nc2cc(Cl)ccc2c(=O)n1C(C)C</chem>	2-(7-chloro-3-isopropyl-4-oxo-quinazolin-2-yl)sulfanyl-N-prop-2-ynyl-acetamide
(10)	ZINC07814689	<chem>O=C(OCc1nnnn1c1ccccc1)Cc1coc2cc(C)ccc12</chem>	(1-phenyltetrazol-5-yl)methyl 2-(6-methylbenzofuran-3-yl)acetate
(11)	ZINC07911348	<chem>O=C(N1CCCCC1)c1cn(Cc2ccccc2)nc1c1ccccc1</chem>	(1-benzyl-3-phenyl-pyrazol-4-yl)-(1-piperidyl)methanone
(12)	ZINC08351587	<chem>O=c1[nH]c(CSc2nnnn2C2CCCC2)nc2ccccc12</chem>	2-[(1-cyclohexyltetrazol-5-yl)sulfanylmethyl]-1H-quinazolin-4-one
(13)	ZINC08943315	<chem>O=C(N1CCCCC1)c1ccccc1NC(=O)c1oc2ccccc2c1C</chem>	3-methyl-N-[2-(pyrrolidine-1-carbonyl)phenyl]benzofuran-2-carboxamide
(14)	ZINC09154410	<chem>C#CCNS(=O)(=O)c1cccc(c1)C(=O)Nc1sc(C)c(C)n1</chem>	3-methyl-N-[2-(pyrrolidine-1-carbonyl)phenyl]benzofuran-2-carboxamide
(15)	ZINC09156590	<chem>O=C(CCCc1cccs1)NC(C)c1ccc(cc1)n1cnc1</chem>	N-[1-(4-imidazol-1-ylphenyl)ethyl]-4-(2-thienyl)butanamide
(16)	ZINC09470353	<chem>Cc1ccccc1n1cnc1SCc1nnnn1c1ccccc1</chem>	5-[[4-(o-tolyl)-1,2,4-triazol-3-yl]sulfanylmethyl]-1-phenyl-tetrazole

¹ Irwin and Shoichet, *J. chem. Inf. Model.* 2005;45(1): 177-82

² Smiles (Simplified Molecular Input Line Entry System) www.daylight.com/dayhtml/doc/theory/theory.smiles.html

	ZINC ID ¹	SMILES ²	Name
(17)	ZINC09809243	<chem>O=C(CSc1nnc(c2ccccc2Cl)n1C)Nc1ccc(cc1)c1ccccc1</chem>	
(18)	ZINC11311718	<chem>CC1CCC(CC1)N(C)C(=O)CSc1nnnn1Cc1ccco1</chem>	
(19)	ZINC12096403	<chem>CC1CCN(CC1)C(=O)C(C)OC(=O)c1ccccc1n1cnnn1</chem>	[1-methyl-2-(4-methyl-1-piperidyl)-2-oxo-ethyl] 3-(tetrazol-1-yl)benzoate
(20)	ZINC12324222	<chem>O=C(CCc1nnc2cccn12)Nc1ccccc1N1CCCC1</chem>	N-[2-(1-piperidyl)phenyl]-3-([1,2,4]triazolo[4,5-a]pyridin-3-yl)propanamide
(21)	ZINC12582679	<chem>CC(NC(=O)c1c(C)onc1c1ccccc1)c1nc2ccccc2[nH]1</chem>	N-[1-(1H-benzimidazol-2-yl)ethyl]-5-methyl-3-phenyl-isoxazole-4-carboxamide
(22)	ZINC13369793	<chem>O=C1OC2CC3CC2C1C3C(=O)N1CCC(CC1)Cc1ccccc1</chem>	c1ccc(cc1)CC2CCN(CC2)C(=O)C3C4CC5C3C(=O)OC5C4
(23)	ZINC13628053	<chem>O=C(CN1C(=O)C2CCCCN2C(=O)c2ccccc12)c1ccccc1</chem>	5-phenacyl-7,8,9,10-tetrahydro-6aH-pyrido[2,1-c][1,4]benzodiazepine-6,12-dione
(24)	ZINC14173219	<chem>N#C[C@@](C)(NC(=O)COC(=O)c1sccln1ccccc1)C1CC1</chem>	
(25)	ZINC14547613	<chem>c1ccc(en1)C1Nc2c(cccc2C2C=CCC12)OCC1CCCO1</chem>	
(26)	ZINC14805534	<chem>O=C(NCCc1ccc(F)cc1)CSc1nnc([nH]1)C1CCCC1</chem>	2-[(5-cyclopentyl-4H-1,2,4-triazol-3-yl)sulfanyl]-N-[2-(4-fluorophenyl)ethyl]acetamide
(27)	ZINC16290785	<chem>CC(Sc1nnnn1C(C)(C)C)C(=O)c1c(C)[nH]c2ccccc12</chem>	
(28)	ZINC16459982	<chem>CCn1nnnc1SCc1cc(=O)oc2ccc3ccc(cc3c12)</chem>	
(29)	ZINC17380409	<chem>CC(C)N(C(C)C)C(=O)C1CC=CCC1C(=O)N(C(C)C)C(C)C</chem>	N,N,N',N'-tetraisopropylcyclohex-4-ene-1,2-dicarboxamide
(30)	ZINC17483293	<chem>O=C(OCc1nnnn1c1ccccc1)Cc1ccccc2ccccc12</chem>	
(31)	ZINC18991361	<chem>N#CC(C=NCC1(CCCCC1)N1CCCC1)c1sc(C)n1</chem>	
(32)	ZINC19671354	<chem>NCC(Oc1ccccc2ccncc12)c1ccccc1(Cl)c1</chem>	
(33)	ZINC19741238	<chem>CC(NCc1c[nH]nc1c1ccc(cc1)c1ccccc1c1n[nH]1)</chem>	N-[[3-(4-phenylphenyl)-1H-pyrazol-4-yl]methyl]-1-(1H-1,2,4-triazol-5-yl)ethanamine
(34)	ZINC19750484	<chem>NC(Cc1ccccc1)c1nc2ccccc2n1CCc1ccccc1</chem>	
(35)	ZINC19793243	<chem>Cc1[nH]c2ccc(Oc3ccccc3)cc2c(=O)c1CN1CCCCC1</chem>	2-methyl-6-phenoxy-3-(1-piperidylmethyl)-1H-quinolin-4-one
(36)	ZINC19848790	<chem>OC1=C(C=NCC2NCCc3ccccc23)C(=O)CC(C1)c1ccco1</chem>	5-(2-furyl)-2-[(1,2,3,4-tetrahydroisoquinolin-1-ylmethylamino)methylene]cyclohexane-1,3-dione
(37)	ZINC20027815	<chem>NC[C@@](C)(CCc1ccccc1)N1CCc2ccccc2C1</chem>	
(38)	ZINC20081644	<chem>NCC(N1CCCC(C)C1)c1ccccc2ccccc12</chem>	
(39)	ZINC20098540	<chem>COc1ccc(cc1)Cn1nnnc1C(C(C)C)N1CCN(C)CC1</chem>	1-[1-[1-[(4-methoxyphenyl)methyl]tetrazol-5-yl]-2-methyl-propyl]-4-methyl-piperazine
(40)	ZINC20123483	<chem>CCC(NC(C)c1ccccc1)c1cc(Br)ccc1O</chem>	
(41)	ZINC20256570	<chem>C1CN(CC(C1)NCc1ccccc1)n1cccn1Cc1ccccc1</chem>	N-[(3-pyrazol-1-ylphenyl)methyl]-1-(2-pyridylmethyl)piperidin-3-amine

	ZINC ID ¹	SMILES ²	Name
(42)	ZINC20403482	<chem>Clc1cc2c(oc(=O)c3CCCCc23)c(CNC2CCCCO2)c1O</chem>	8-chloro-7-hydroxy-6-[(tetrahydrofuran-2-ylmethylamino)methyl]-2,3-dihydro-1H-cyclopenta[c]chromen-4-one
(43)	ZINC20551710	<chem>CC1(C)CC(=NC(C)(C)Cc2[nH]c3c3ccc3c2)CC(C)(C)N1</chem>	N-[2-(1H-indol-2-yl)-1,1-dimethyl-ethyl]-2,2,6,6-tetramethyl-piperidin-4-imine
(44)	ZINC20595810	<chem>CN(C)CC(C)(C)CNC1CCN(C1)Cc1ccccc1</chem>	
(45)	ZINC21001129	<chem>O=C(CCCSc1ccc(F)cc1)Nc1nnc(o1)c1ccno1</chem>	
(46)	ZINC21782724	<chem>CSc1ncc(C(=O)NNC(=S)NC(C)C)n1c1ccccc1</chem>	
(47)	ZINC22014240	<chem>O=C(NCCOc1cccc(C)c1)CN1CCC1C(=O)N(C)C</chem>	N,N-dimethyl-1-[2-[2-(3-methylphenoxy)ethylamino]-2-oxo-ethyl]pyrrolidine-2-carboxamide
(48)	ZINC22129845	<chem>Oc1ccc2CC3N(CC[C@@]45C(Oc1c24)C(=C)CC[C@]35O)CC1CC1</chem>	Morphinan-3,14-diol, 17-(cyclopropylmethyl)-4,5-epoxy-6-methylene-, (5.alpha.)-
(49)	ZINC22508970	<chem>CCC1CCCCN1C(=O)C(C)Nc1cc(c1c1OC)NC(=O)C</chem>	
(50)	ZINC22527267	<chem>O=C(NCC1CC2c3cccc3C1c1ccccc21)c1ccccc1</chem>	
(51)	ZINC22840489	<chem>CN1CCN(C(=O)c2noc(c2)c2ccccc2)C(C1)c1ccccc1</chem>	(4-methyl-2-phenyl-piperazin-1-yl)-(5-phenylisoxazol-3-yl)methanone
(52)	ZINC23055148	<chem>O=C(NCC1CC2c3cccc3C1c1ccccc21)c1ccccc1</chem>	
(53)	ZINC23055155	<chem>O=C(NCC1CC2c3cccc3C1c1ccccc21)c1ccccc1</chem>	
(54)	ZINC23447753	<chem>COc1cccc(c1)CN(C)C(=O)CSc1nnc(c2ccccc2F)n1CC(C)C</chem>	
(55)	ZINC23448010	<chem>Oc1ccc(cc1)C=C1CCc2c1nc1ccccc1c2C(=O)OCc1nnc(C)o1</chem>	
(56)	ZINC23448013	<chem>Oc1ccc(cc1)C=C1CCc2c1nc1ccccc1c2C(=O)OCc1c(C)noc1C</chem>	(3,5-dimethylisoxazol-4-yl)methyl 3-[(4-oxo-1-cyclohexa-2,5-dienylidene)methyl]-2,4-dihydro-1H-cyclopenta[b]quinoline-9-carboxylate
(57)	ZINC23448063	<chem>Cc1nnc(COC(=O)c2c3CCCC(=Cc4ccco4)c3nc3ccccc23)o1</chem>	
(58)	ZINC23448069	<chem>CCCNC(=O)COC(=O)c1c2CCCC(=Cc3ccco3)c2nc2ccccc12</chem>	(2-oxo-2-propylamino-ethyl) 4-(2-furylmethylene)-2,3-dihydro-1H-acridine-9-carboxylate
(59)	ZINC23448071	<chem>Cc1nnc(C)c1COC(=O)c1c2CCCC(=Cc3ccco3)c2nc2ccccc12</chem>	(3,5-dimethylisoxazol-4-yl)methyl 4-(2-furylmethylene)-2,3-dihydro-1H-acridine-9-carboxylate
(60)	ZINC23448074	<chem>CCNC(=O)NC(=O)COC(=O)c1c2CCCC(=Cc3ccco3)c2nc2ccccc12</chem>	[2-(ethylcarbamoylamino)-2-oxo-ethyl] 4-(2-furylmethylene)-2,3-dihydro-1H-acridine-9-carboxylate
(61)	ZINC23448082	<chem>CCCNC(=O)NC(=O)COC(=O)c1c2CCCC(=Cc3ccco3)c2nc2ccccc12</chem>	[2-oxo-2-(propylcarbamoylamino)ethyl] 4-(2-furylmethylene)-2,3-dihydro-1H-acridine-9-carboxylate
(62)	ZINC23449458	<chem>N#CC(=c1sc2ccccc2[nH]1)C(=O)C(C)Sc1nnc(c2cccs2)n1CC</chem>	
(63)	ZINC23449492	<chem>Cc1nnc(COC(=O)c2c3CCCC(=Cc4ccc(cc4)[N](=O)O)c3nc3ccccc23)o1</chem>	

	ZINC ID ¹	SMILES ²	Name
(64)	ZINC23449495	<chem>Cc1noc(C)c1COC(=O)c1c2CCC(=Cc3ccco3)c2nc2ccccc12</chem>	(3,5-dimethylisoxazol-4-yl)methyl 3-(2-furylmethylene)-1,2-dihydrocyclopenta[b]quinoline-9-carboxylate
(65)	ZINC23449497	<chem>Cc1nnc(CSc2nc3sc(cc3c(=O)n2c2ccccc2C)c2ccccc2)o1</chem>	
(66)	ZINC23449884	<chem>Fe1ccc(cc1)CN(C(=O)COC(=O)C1CC2CCCC(C1)C2=O)C12CC3CC(C1C(C3)C2)C1</chem>	
(67)	ZINC23450092	<chem>O=C(COC(=O)C1CCCCC1C(=O)N1CCc2ccccc12)N1CCOCC1</chem>	
(68)	ZINC23450156	<chem>O=C(NCC1CCCCC1)COC(=O)C1CCCCC1C(=O)N1CCc2ccccc12</chem>	
(69)	ZINC23450183	<chem>O=C(COC(=O)C1CCCCC1C(=O)N1CCc2ccccc12)NC1CCCC1</chem>	
(70)	ZINC23450215	<chem>O=C(OCn1nnc2ccccc2c1=O)C1CCC1C(=O)N1CCc2ccccc12</chem>	
(71)	ZINC23452876	<chem>OC(=Nc1nnc(s1)C1CCCCC1)CN(Cc1ccccc1)Cc1ccccc1</chem>	N-(5-cyclohexyl-1,3,4-thiadiazol-2-yl)-2-(dibenzylamino)acetamide
(72)	ZINC23457077	<chem>COC(=O)c1ccc2c(c1)nc(SCC(=O)c1cccn1C)n(c1ccccc1)c2=O</chem>	
(73)	ZINC23457388	<chem>CCc1ccc(cc1)NC(=O)COC(=O)c1c(c(ccc1Br)S(=O)(=O)NC(C)C</chem>	
(74)	ZINC23458989	<chem>COC(=O)c1cccc(CSc2nnc(COc3ccccc3F)n2c2ccccc2)c1</chem>	
(75)	ZINC23459999	<chem>CCN(CC)C(=O)c1ccc(cc1)NC(=O)CSc1nnc2sc(c3ccc(F)cc3)c12</chem>	
(76)	ZINC23460333	<chem>Fe1ccc(F)c(c1)C(=O)CSc1nc2ccc(Br)cc2c(=O)n1c1ccccc1</chem>	
(77)	ZINC23460338	<chem>Brc1ccc2nc(SC(C)C(=O)NC3CCC(C3)n(c3ccccc3)c(=O)c2c1</chem>	
(78)	ZINC23461483	<chem>Fe1ccc(F)c(c1)C(=O)COC(=O)C(=Cc1cccs1)n1nnnc1c1ccccc1</chem>	
(79)	ZINC23462655	<chem>O=C(CSc1nnc(o1)c1ccco1)OCc1cc(=O)oc2cc(C)c(cc12)C(C)C</chem>	
(80)	ZINC23462702	<chem>CC(=O)N=c1ccc2c(CSc3nnnc3ccc3C)cc(O)oc2c1</chem>	
(81)	ZINC23462933	<chem>COC(=O)c1ccc2c(c1)nc(SCC(=O)c1cc(F)ccc1F)n(c1ccccc1)c2=O</chem>	
(82)	ZINC23463873	<chem>O=C(Nc1ccnn1C(C)C)C(C)OC(=O)c1ccc(s1)c1nc2ccccc2s1</chem>	
(83)	ZINC23463963	<chem>CC(Sc1nc2ccccc2c(=O)n1c1ccccc1)C(=O)Nc1ccnn1C(C)C</chem>	
(84)	ZINC23464636	<chem>C=CCn1c(SC(C)C(=O)Nc2ccnn2C(C)C)nc2sc(cc2c1=O)c1ccccc1</chem>	
(85)	ZINC23464666	<chem>Cc1nc(SC(C)C(=O)Nc2ccnn2C(C)C)c2cc(sc2n1)c1ccccc1</chem>	
(86)	ZINC23465102	<chem>CCn1c(SCC(=O)NC2(C#N)CCCC2)nc2sc3CC(C)CCc3c2c1=O</chem>	N-(1-cyanocyclopentyl)-2-[(3-ethyl-7-methyl-4-oxo-5,6,7,8-tetrahydrobenzothiopheno[2,3-d]pyrimidin-2-yl)sulfanyl]acetamide
(87)	ZINC23465220	<chem>CC(Sc1nc2seccc2c(=O)n1c1ccccc1)C(=O)Nc1ccnn1C(C)C</chem>	
(88)	ZINC23465302	<chem>N#CC1(CCCC1)NC(=O)CSc1nc2sc(cc2c(=O)n1C)c1ccccc1</chem>	

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(89)	ZINC23465304	<chem>CC(Sc1nc2sc(cc2c(=O)n1C)c1cccc1)C(=O)Nc1ccnn1C(C)C</chem>	
(90)	ZINC23466190	<chem>O=C(NC1CCOCC1)CC1C(=O)NCN1Cc1ccc(cc1)c1cccc1</chem>	2-[3-oxo-1-[(4-phenylphenyl)methyl]piperazin-2-yl]-N-tetrahydropyran-4-yl-acetamide
(91)	ZINC23505966	<chem>O=C(NCC[C@@]1(CCOC(C)(C)C1)c1cccc1)Nc1nnn[nH]1</chem>	1-[2-(2,2-dimethyl-4-phenyl-tetrahydropyran-4-yl)ethyl]-3-(1H-tetrazol-5-yl)urea
(92)	ZINC23712292	<chem>COc1cccc1C(CNC(=O)C=Cc1ccco1)N1CCCC1</chem>	
(93)	ZINC23738831	<chem>CC(Oc1cccc1)C(=O)NCC(N1CCC1)c1cccc1</chem>	
(94)	ZINC23925507	<chem>COc1ccc(cc1)CN(C1CC1)C(=O)c1cccc(c1)n1cnm1</chem>	N-cyclopropyl-N-[(4-methoxyphenyl)methyl]-3-(tetrazol-1-yl)benzamide
(95)	ZINC23961594	<chem>COc1ccc(cc1)CN(C1CC1)C(=O)c1cccc(c1)n1cccc1</chem>	
(96)	ZINC11569796	<chem>Nc1ccc(cc1)N1CCN(CC1)C(=O)CCc1cccc1Cl</chem>	
(97)	ZINC20515967	<chem>Fc1ccc(cc1)[C@@]1(CNCCNc2ncc(c(C)c2)COCC1</chem>	N'-[[3-(4-fluorophenyl)tetrahydrofuran-3-yl]methyl]-N-(4-methyl-2-pyridyl)ethane-1,2-diamine
(98)	ZINC23441724	<chem>N#Cc1ccc(cc1)C(=O)Oc1cccc2C(=O)c3cccc(OC(=O)c4ccc(C#N)cc4)c3C(=O)c12</chem>	[8-(4-cyanobenzoyl)oxy-9,10-dioxo-1-anthryl] 4-cyanobenzoate
(99)	ZINC23442925	<chem>O=c1cc(CN2CCN(CC2)c2cccn2)c2c(ccc3cccc23)o1</chem>	1-[[4-(2-pyridyl)piperazin-1-yl]methyl]benzo[f]chromen-3-one
(100)	ZINC23442938	<chem>CCOC(=O)N=c1ccc2c(CN3CCN(C3)S(=O)(=O)c3ccc(cc3)C(C)C)cc(O)c2c1</chem>	ethyl N-[4-[[4-(4-isopropylphenyl)sulfonyl]piperazin-1-yl]methyl]-2-oxo-chromen-7-yl]carbamate
(101)	ZINC23443168	<chem>ClC1=CC2N=C(CN(CCCc3cccc3)Cc3nc4cc(Cl)ccc4c(=O)[nH]3)NC(=O)C2C=C1</chem>	7-chloro-2-[[[(7-chloro-4-oxo-4a,8a-dihydro-3H-quinazolin-2-yl)methyl-(3-phenylpropyl)amino]methyl]-1H-quinazolin-4-one
(102)	ZINC23447450	<chem>Clc1ccc(cc1)C(=O)C=c1sc(=Cc2cc(c(o2)c2ccc(cc2)[N](=O)O)c(O)n1</chem>	
(103)	ZINC23447555	<chem>Clc1ccc2c(=O)nc([nH]c2c1)C(=Cc1ccc(o1)c1ccc(cc1)[N](=O)O)Cl</chem>	
(104)	ZINC23447616	<chem>CC1CC(C)CN(C1)S(=O)(=O)c1ccc(c(c1)C(=O)N(Cc1nncc(o1)c1cccc1Cl)C1CC1</chem>	N-[[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl]methyl]-N-cyclopropyl-3-[(3,5-dimethyl-1-piperidyl)sulfonyl]benzamide
(105)	ZINC23447633	<chem>Clc1ccc(s1)CN(C)c1nc(CN2CCOC2)nc2sc(c3cccc3)c12</chem>	N-[(5-chloro-2-thienyl)methyl]-N-methyl-2-(morpholinomethyl)-5-phenyl-thieno[3,2-e]pyrimidin-4-amine
(106)	ZINC23447635	<chem>Clc1cccc(c1)c1nnn(n1)c1nc(CN2CCOCC2)nc2sc(c3cccc3)c12</chem>	4-[5-(3-chlorophenyl)tetrazol-2-yl]-2-(morpholinomethyl)-5-phenyl-thieno[2,3-d]pyrimidine
(107)	ZINC23448111	<chem>Cc1cc(C)c(c(C)c1)C(=O)CN1C(=O)N[C@@]2(CCCCc3cccc23)C1=O</chem>	
(108)	ZINC23448208	<chem>Cc1cccc(Oc2ccc(cc2)NC(=O)CN2C(=O)N[C@@]3(CCCCc4cccc34)C2=O)c1</chem>	
(109)	ZINC23448432	<chem>N#Cc1ccc(cc1)[C@@]1(C)NC(=O)N(CC(=O)c2c3cccc3n(C)c2c2cccc2)C1=O</chem>	

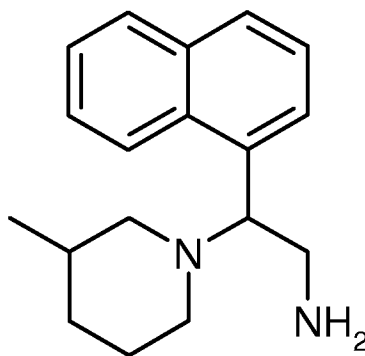
	ZINC ID ¹	SMILES ²	Name
(110)	ZINC23448450	<chem>N#Cc1ccc(cc1)[C@@]1(C)NC(=O)N(CC(=O)c2cc(C)n(c3ccc(C)c(C)c3)c2C)C1=O</chem>	
(111)	ZINC23448468	<chem>N#Cc1ccc(cc1)[C@@]1(C)NC(=O)N(CC(=O)c2cc(C)n(Cc3ccc(Cl)cc3)c2C)C1=O</chem>	
(112)	ZINC23448474	<chem>N#Cc1ccc(cc1)[C@@]1(C)NC(=O)N(CC(=O)c2cc(C)n(CCC3=CCCCC3)c2C)C1=O</chem>	
(113)	ZINC23448509	<chem>N#Cc1ccc(cc1)[C@@]1(C)NC(=O)N(CC(=O)Nc2ccc(cc2)Sc2cc(C)ccc2C)C1=O</chem>	
(114)	ZINC23448551	<chem>N#Cc1ccc(cc1)[C@@]1(C)NC(=O)N(CC(=O)c2cc(C)n(c3ccc(cc3)C(C)C)c2C)C1=O</chem>	
(115)	ZINC23448560	<chem>N#Cc1ccc(cc1)[C@@]1(C)NC(=O)N(CC(=O)c2cc(C)n(c3ccc(F)c(Cl)c3)c2C)C1=O</chem>	
(116)	ZINC23449314	<chem>O=C(CSc1nnc(c2cccs2)n1Cc1cccc1)Nc1cc(C)nn1c1cccc1</chem>	
(117)	ZINC23449370	<chem>O=C(NCc1ccc(cc1)S(=O)(=O)N)CSc1nnc(c2cccs2)n1Cc1cccc1</chem>	
(118)	ZINC23449802	<chem>O=c1cc(CSc2[nH]c(=O)c3enn(c4cccc4)c3n2)c2c(ccc3cccc23)o1</chem>	
(119)	ZINC23449810	<chem>O=C(Nc1ccc(cc1)N1CCCCC1)C(C)Sc1[nH]c(=O)c2enn(c3cccc3)c2n1</chem>	
(120)	ZINC23449819	<chem>CC(Sc1[nH]c(=O)c2enn(c3cccc3)c2n1)C(=O)NC(c1cccc1)c1cccc1</chem>	
(121)	ZINC23449873	<chem>CCOc1cccc1NC(=O)C(OC(=O)C1CC2CCCC(C1)C2=O)c1cccc1</chem>	
(122)	ZINC23449884	<chem>Fc1ccc(cc1)CN(C(=O)COC(=O)C1CC2CCCC(C1)C2=O)C12CC3CC(C1)C3)C2)C1</chem>	
(123)	ZINC23449903	<chem>Clc1ccc2Sc3cccc3N(C(=O)COC(=O)C3CC4CCCC(C3)C4=O)c2c1</chem>	
(124)	ZINC23449909	<chem>CCOC(=O)c1c(NC(=O)C(C)OC(=O)C2CC3CCCC(C2)C3=O)sc2CC(C)CCc12</chem>	
(125)	ZINC23450215	<chem>O=C(OCn1nnc2cccc2c1=O)C1CCC1C(=O)N1CCc2cccc12</chem>	
(126)	ZINC23450296	<chem>O=C(OCc1cc2ccc(C)cc2nc1Cl)CNC(=O)C12CC3CC(C1)C3)C2)C1</chem>	
(127)	ZINC23450311	<chem>COc1ccc(C)cc1NC(=O)C(OC(=O)CNC(=O)C12CC3CC(C1)C3)C2)C1)c1cccc1</chem>	[2-(2-methoxy-5-methyl-anilino)-2-oxo-1-phenyl-ethyl] 2-(adamantane-1-carbonylamino)acetate
(128)	ZINC23450317	<chem>CCOc1cccc1NC(=O)C(OC(=O)CNC(=O)C12CC3CC(C1)C3)C2)C1)c1cccc1</chem>	[2-(2-ethoxyanilino)-2-oxo-1-phenyl-ethyl] 2-(adamantane-1-carbonylamino)acetate
(129)	ZINC23450484	<chem>COc1cccc(c1)CN(C)C(=O)CSc1nc2cccc2c(=O)n1c1cccc(Cl)c1</chem>	
(130)	ZINC23450495	<chem>N#Cc1oc2cccc2c1NC(=O)CSc1nc2cccc2c(=O)n1c1cccc(Cl)c1</chem>	

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(140)	ZINC23451794	<chem>Cc1cc(C)cc(c1)NC(=S)N=C(Nc1nc(C)cc(C)n1)N1CCN(CC1)Cc1ccc2OCOC2c1</chem>	(1E)-1-[[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-[(4,6-dimethylpyrimidin-2-yl)amino]methylene]-3-(3,5-dimethylphenyl)thiourea
(141)	ZINC23451800	<chem>Clc1cccc(c1)NC(=O)N=C(Nc1nc(C)cc(C)n1)N1CCN(CC1)Cc1ccc2OCOC2c1</chem>	
(142)	ZINC23451845	<chem>O=C(N1CCC(CC1)Cc1cccc1)c1cc(c(c1)CN1CCc2ccccc2C1</chem>	(4-benzyl-1-piperidyl)-[4-(3,4-dihydro-1H-isoquinolin-2-ylmethyl)phenyl]methanone
(143)	ZINC23451928	<chem>O=C(CN1CCN(CC1)C1C2CC3CC(C2)CC1C3)Nc1cc(c(c1Cl)[N](=O)O</chem>	
(144)	ZINC23452519	<chem>Clc1ccc2c(c1)sc(C(=O)N1CCN(CC1)Cc1csc(n1)c1ccccc1C)c2Cl</chem>	(3,6-dichlorobenzothiophen-2-yl)-[4-[[2-(o-tolyl)thiazol-4-yl]methyl]piperazin-1-yl]methanone
(145)	ZINC23452588	<chem>O[N](=O)c1ccc2c(c1)sc(C(=O)N1CCN(CC1)Cc1csc(n1)c1ccccc1)c2Cl</chem>	
(146)	ZINC23452591	<chem>Cc1ccccc1c1sc(CN2CCN(CC2)C(=O)c2sc3cc(c(c3c2Cl)[N](=O)O)n1</chem>	
(147)	ZINC23452594	<chem>Cc1ccccc1c1sc(CN2CCN(CC2)C(=O)c2sc3cc(c(c3c2Cl)[N](=O)O)n1</chem>	
(148)	ZINC23452597	<chem>Cc1ccc(cc1)c1sc(CN2CCN(CC2)C(=O)c2sc3cc(c(c3c2Cl)[N](=O)O)n1</chem>	
(149)	ZINC23452601	<chem>BrC1CCCC(CN2CCN(CC2)C(=O)c2sc3cc(c(c3c2Cl)[N](=O)O)c1</chem>	
(150)	ZINC23452884	<chem>BrC1CCC(CC1)c1csc(N=C(O)CN(Cc2ccccc2)Cc2ccccc2)n1</chem>	N-[4-(4-bromophenyl)thiazol-2-yl]-2-(dibenzylamino)acetamide
(151)	ZINC23452893	<chem>OC(=Nc1sc(c(n1)c1ccc(C)c(C)c1)CN(Cc1ccccc1)Cc1ccccc1</chem>	2-(dibenzylamino)-N-[4-(3,4-dimethylphenyl)thiazol-2-yl]acetamide
(152)	ZINC23454847	<chem>O=C(OCC(=O)Nc1ccccc1Oc1ccccc1)CNC(=O)C12CC3CC(C(C1)(C3)C2)C1</chem>	
(153)	ZINC23458310	<chem>Cc1cc(C)n2nc(nc2n1)C(=O)OCC(=O)c1cc(C)n(c2ccc(Br)c(C)c2)c1C</chem>	
(154)	ZINC23458761	<chem>Cc1cc(C)c(C)c(C(=O)CSc2nnc3n(c4ccccc4)c(=O)c4ccccc4n23)c1C</chem>	
(155)	ZINC23458767	<chem>Clc1ccccc1C(C)Sc1nnc2n(c3ccccc3)c(=O)c3ccccc3n12</chem>	
(156)	ZINC23458843	<chem>O=C(CSc1nnc(o1)c1ccccc1)c1cc(C)n(c2ccc(Br)c(C)c2)c1C</chem>	
(157)	ZINC23459157	<chem>O=C(CSc1nnc(c2ccccc2)n1Cc1ccccc1)NC(C)c1ccc(Cl)c(Cl)c1</chem>	
(158)	ZINC23459165	<chem>CCCc1cc(NC(=O)CSc2nnc(C)n2Cc2ccccc2)n(n1)c1ccccc1</chem>	
(159)	ZINC23459342	<chem>CCCc1nn(c2ccccc2)c(NC(=O)CSc2nnnn2c2cccc(C)c2)c1</chem>	
(160)	ZINC23459653	<chem>CCCc1nn(c2ccccc2)c(NC(=O)CSc2nnc(Cc3ccccc3F)n2N)c1</chem>	
(161)	ZINC23460512	<chem>CC(=O)Nc1ccc2c(COC(=O)c3ccc4c(c3)C(=O)N(Cc3ccccc3)C4=O)cc(=O)oc2c1</chem>	

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(162)	ZINC23461019	<chem>CCC1CCc2sc(cc2C1)c1nnc(SCc2cc(=O)oc3cc(ccc23)NC(=O)C)n1C</chem>	
(163)	ZINC23461995	<chem>CCCCn1c2nnc(SCc3cc(=O)oc4cc(ccc34)NC(=O)C)n2c2ccccc2c1=O</chem>	
(164)	ZINC23463355	<chem>O=C(NCC(=O)Nc1c(C)cc(C)cc1C)COC(=O)c1c2ccccc2cc2ccccc12</chem>	
(165)	ZINC23463441	<chem>COc1ccc(C)cc1NC(=O)CNC(=O)COC(=O)c1cc(nc2ccccc12)c1cccs1</chem>	
(166)	ZINC23464262	<chem>Cc1cccc(c1)n1c(nnc1c1c[nH])c2ccc(cc12)SC(C)C(=O)Nc1ccnn1C(C)C</chem>	
(167)	ZINC23464289	<chem>COc1ccc(C)cc1NC(=O)CNC(=O)COC(=O)C12CC3CC(C1)CC(C3)(C2)c1ccccc1</chem>	
(168)	ZINC23464293	<chem>O=C(NCC(=O)Nc1c(C)cc(C)cc1C)COC(=O)C12CC3CC(C1)CC(C3)(C2)c1ccccc1</chem>	
(169)	ZINC23464887	<chem>O=C(CSc1nnc2n(c3ccccc3)c(=O)c3ccccc3n12)c1ccc(cc1)C(C)C</chem>	
(170)	ZINC23464891	<chem>CC(Sc1nnc2n1c1ccccc1c(=O)n2c1ccccc1)C(=O)Nc1ccnn1C(C)C</chem>	
(171)	ZINC23465350	<chem>CCc1cc2c(s1)nc(SCC(=O)NC1(C#N)CCCC1)n(CCc1ccccc1)c2=O</chem>	
(172)	ZINC23465585	<chem>CC(Sc1nnc2n1c1ccccc1c(=O)n2c1ccccc1)C(=O)Nc1ccnn1C(C)C</chem>	
(173)	ZINC23465836	<chem>O=C1NCCN(CC1)C1CCN(CC1)Cc1nc(oc1C)c1ccc(cc1)c1ccccc1</chem>	1-[1-[[5-methyl-2-(4-phenylphenyl)oxazol-4-yl]methyl]-4-piperidyl]-1,4-diazepan-5-one
(174)	ZINC23465874	<chem>NC1CCN(C1)Cc1nnn(c1)C1CCN(CC1)C(=O)C=Cc1ccccc1F</chem>	(E)-1-[4-[4-[[[(3R)-3-aminopyrrolidin-1-yl]methyl]triazol-1-yl]-1-piperidyl]-3-(2-fluorophenyl)prop-2-en-1-one

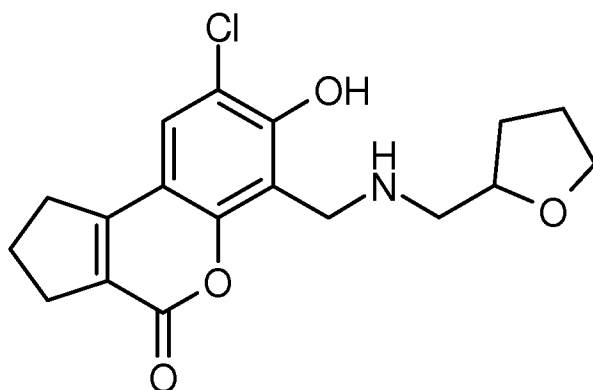
[0086] In one embodiment, preferred 7TM receptor binding compounds include

(i) 2-(3-methylpiperidin-1-yl)-2-(naphthalene-1-yl)ethan-1-amine



Compound K

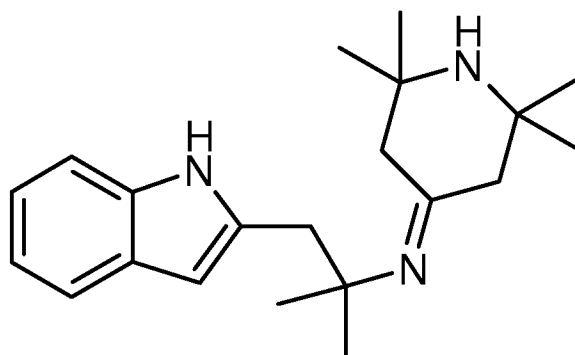
(ii) 8-chloro-7-hydroxy-6[(tetrahydrofuran-2-ylmethylamino)methyl]-2,3-dihydro-1H-cyclopenta[c]chromen-4-one



Compound L

and

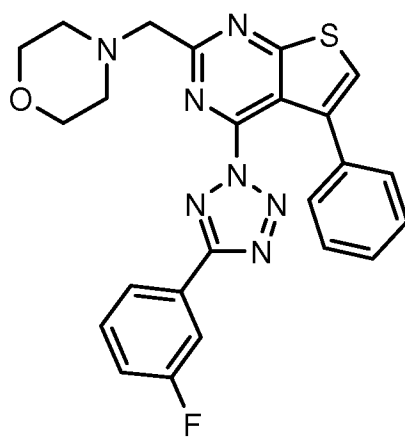
(iii) N-[2-(1H-indol-2-yl)-1,1-dimethylethyl]-2,2,6,6-tetramethyl-piperidin-4-imine



Compound M

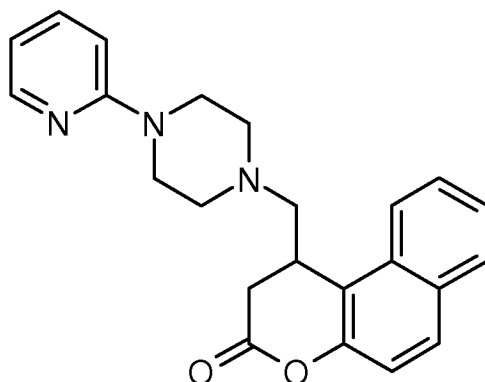
[0087] In another embodiment, preferred 6TM binding compounds include

(i) 4-(5-(3-fluorophenyl)-2H-tetrazol-2-yl)-2-(morpholinomethyl)-5-phenylthieno[2,3-d]pyrimidine



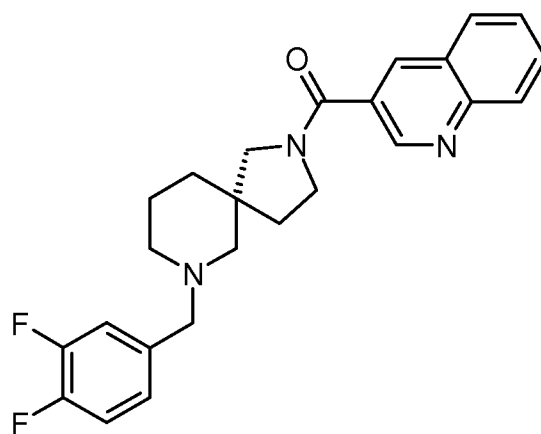
Compound A

(ii) 1-[[4-(2-pyridyl)piperazin-1-yl]mentyl]benzo[f]chromen-3-one



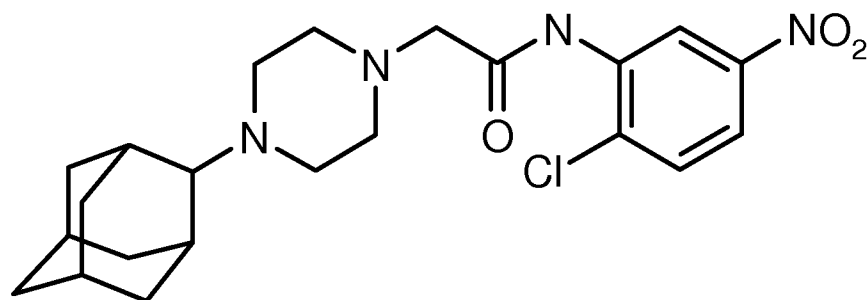
Compound B

(iii) [7-[(3,4-difluorophenyl)methyl]-2,7-diazaspiro[4.5]decan-2-yl]-(3-quinolyl)methanone



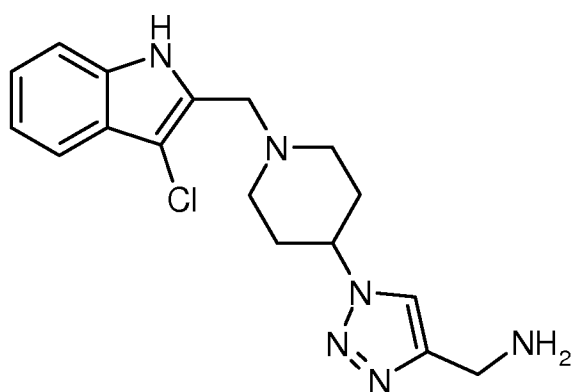
Compound C

(iv) 2-[4(adamantan-2-yl)piperazin-1-yl]-N-(2-chloro-5-nitrophenyl)acetamide



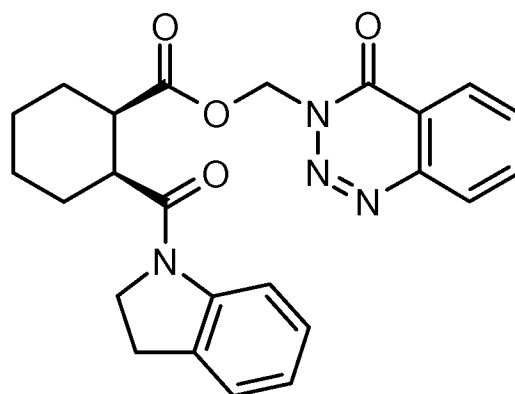
Compound D

(v) [1-[1[(3-chloro-1H-indol-2-yl)methyl]-4-piperidyl]triazol-4-yl]methanamine



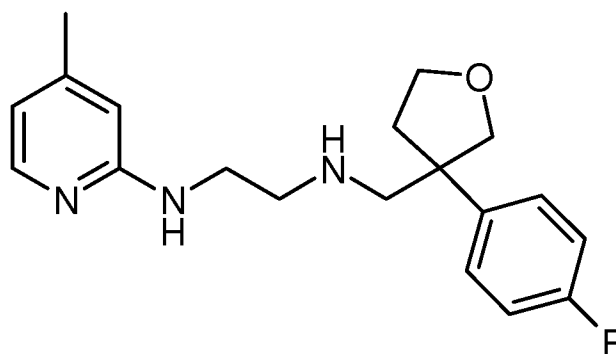
Compound E

(vi) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1R,2S)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



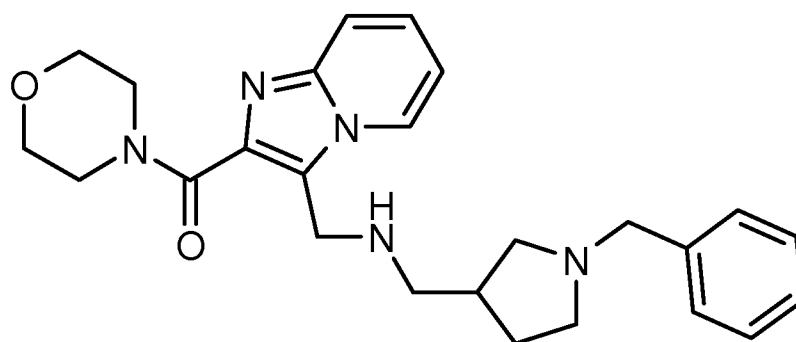
Compound F

(vii) N'-[[3-(4-fluorophenyl)tetrahydrofuran-3-yl]methyl]-N-(4-methyl-2-pyridyl)ethane-1,2-diamine



Compound G

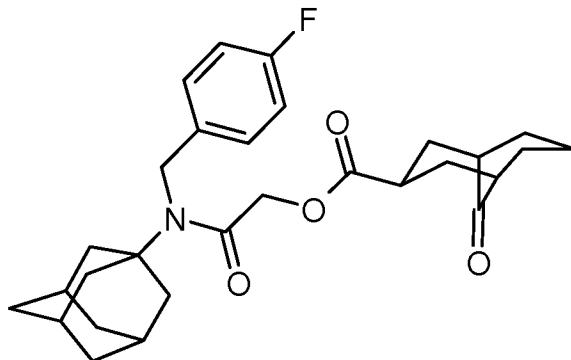
(viii) [(1-benzylpyrrolidin-3-yl)methyl({2-[(morpholin-4-yl)carbonyl]imidazo[1,2-a]pyridine-3-yl}methyl)amine



Compound I

and

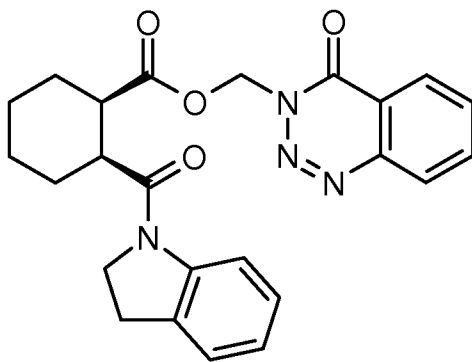
(ix) [(adamantan-1-yl)[(4-fluorophenyl)methyl]carbamoyl]methyl 9-oxobicyclo[3.3.1]nonane-3-carboxylate



Compound N

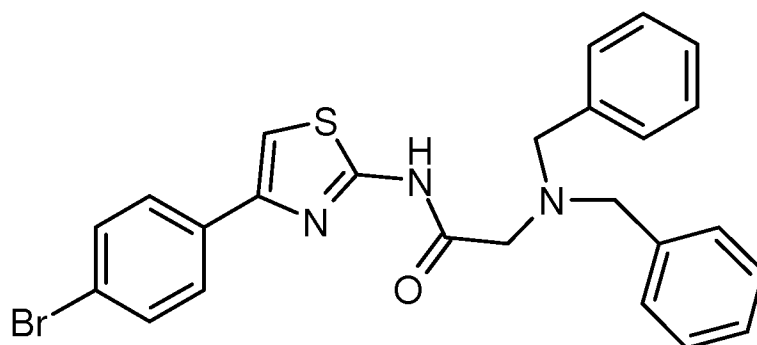
[0088] In a further embodiment, preferred promiscuous ligand compounds binding to both 6TM and 7TM structures of mu opioid receptor include

(i) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1R,2S)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



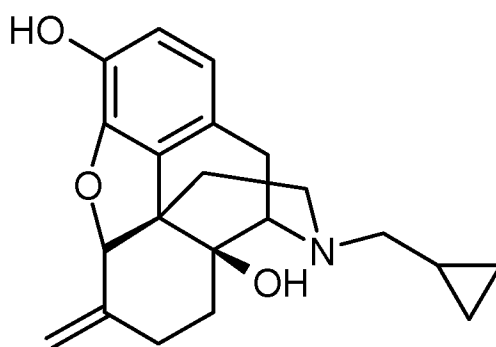
Compound F

(ii) N-[4-(4-bromophenyl)thiazol-2-yl]-2-(dibenzylamino)acetamide



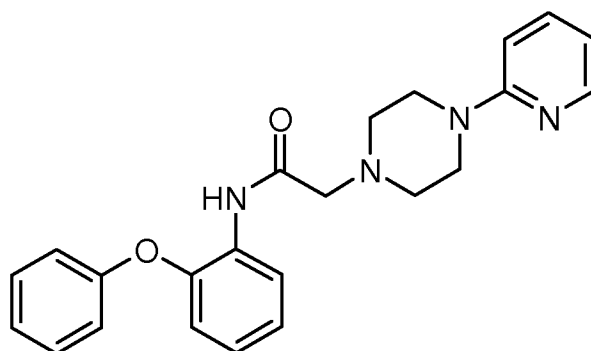
Compound H

(iii) 17-(cyclopropylmethyl)-4,5-epoxy-6-methylene-morphinan-3,14-diol



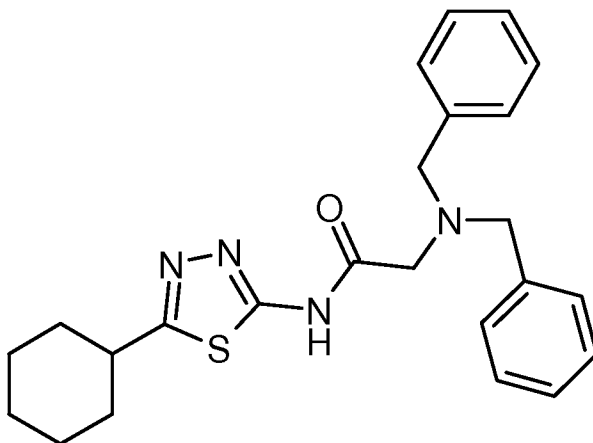
Compound J

(iv) N-(2-phenoxyphenyl)-2-[4-(2-pyridyl)piperazin-1-yl]acetamide



Compound O

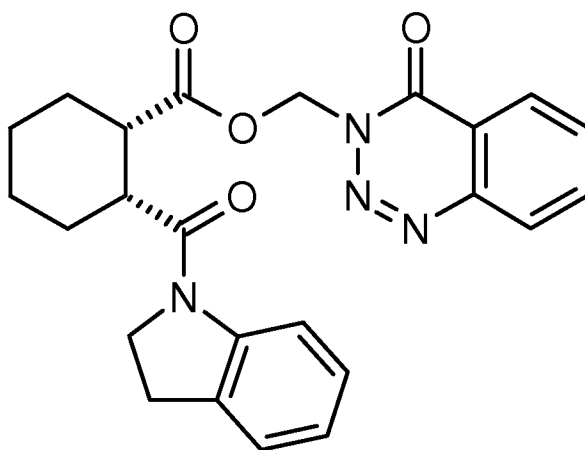
(v) N-(5-cyclohexyl-1,3,4-thiadiazol-2-yl)-2-(dibenzylamino)acetamide



Compound P

and

(vi) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1S,2R)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



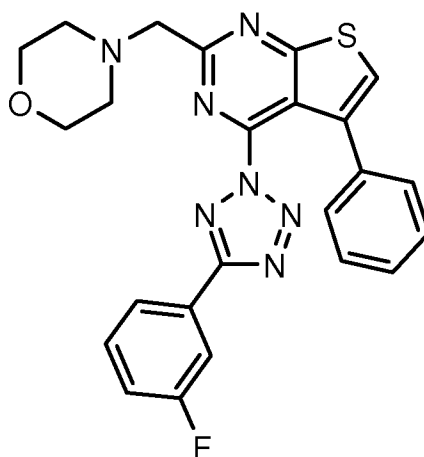
Compound Q

EXAMPLES

[0089] The advantages and features of the invention are more fully appreciated with reference to the following examples, which is not to be construed as in any way limiting the scope of the invention but rather as illustrative of various embodiments of the disclosure in specific applications thereof.

[0090] Example 1

4-(5-(3-fluorophenyl)-2H-tetrazol-2-yl)-2-(morpholinomethyl)-5-phenylthieno[2,3-d]pyrimidine



Compound A

[0091] Compound A is prepared beginning with condensation of 2-amino-4-phenyl-3-thiophenecarboxylic acid and chloroacetonitrile using dry HCl gas in anhydrous 1,4-dioxane to provide an intermediate 2-(chloromethyl)-5-phenylthieno[2,3-d]pyrimidin-4-one.

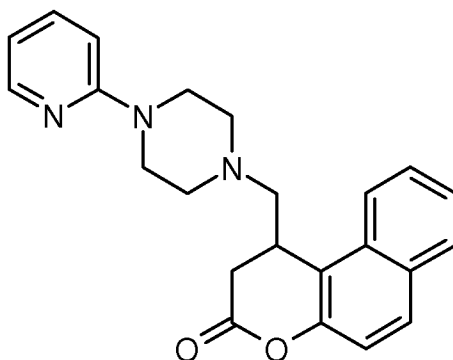
[0092] The resulting intermediate chloride is reacted with morpholine in a dry organic solvent such as DMF in the presence of an organic base such as triethylamine or an inorganic base such as sodium carbonate or the like, to provide intermediate 2-(morpholinomethyl)-5-phenylthieno[2,3-d]pyrimidin-4-one.

[0093] The pyrimidin-4-one is further reacted to provide a 4-chloropyrimidine. For example, reaction of 2-(morpholinomethyl)-5-phenylthieno[2,3-d]pyrimidin-4-one with phosphorus oxychloride in DMF yields 4-chloro-2-(morpholinomethyl)-5-phenylthieno[2,3-d]pyrimidine.

[0094] Compound A is produced by reaction of the 4-chlorothieno[2,3-d]pyrimidine with 5-(3-fluorophenyl)-1H-1,2,3,4-tetrazole in a polar solvent such as DMF, in the presence of a base, e.g., an organic base such as triethyl amine, or, more preferably, an inorganic base such as sodium carbonate or cesium carbonate.

[0095] Example 2

1-[[4-(2-pyridyl)piperazin-1-yl]menthyl]benzo[f]chromen-3-one



Compound B

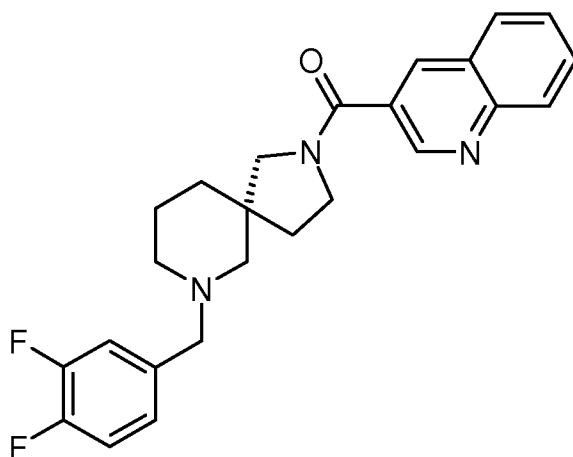
[0096] Compound B is synthesized through the condensation of 2-naphthol and dimethyl acetylenedicarboxylate mediated by triethyl phosphite in DCM, to provide methyl 3-oxo-1H,2H,3H-naphtho[2,1-b]pyran-1-carboxylate.

[0097] The methyl ester can be selectively reduced with diisobutyl aluminum hydride (DIBAL) at -78°C to provide the 3-oxo-1H,2H,3H-naphtho[2,1-b]pyran-1-methyl alcohol.

[0098] The alcohol can be further subjected to an activation/displacement sequence using any number of activating agents known to the art, such as trifluoromethanesulfonyl chloride and DIPEA. The resulting triflate may, without isolation, be reacted *in situ* with 1-(2-pyridyl)piperazine to yield Compound B.

[0099] Example 3

[7-[(3,4-difluorophenyl)methyl]-2,7-diazaspiro[4.5]decan-2-yl]-(3-quinolyl)methanone



Compound C

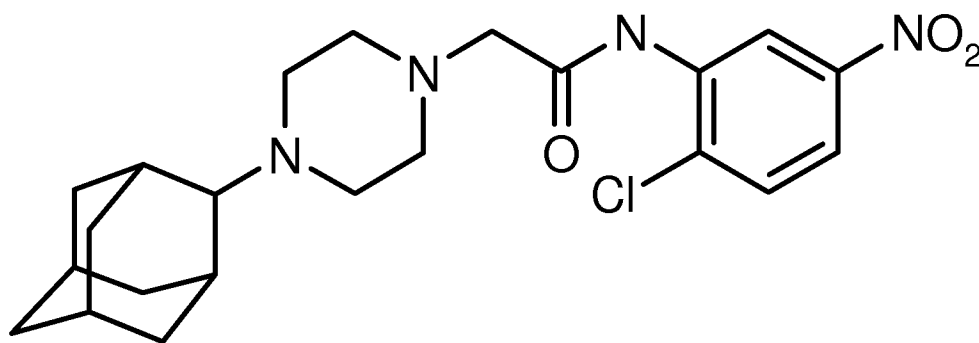
[00100] Compound C is synthesized from tert-butyl 2,7-diazaspiro[4.5]decane-7-carboxylate through reaction with 3,4-difluorobenzyl bromide in DMF with added Cs_2CO_3 to provide tert-butyl 2-[(3,4-difluorophenyl)methyl]-2,7-diazaspiro[4.5]decane-7-carboxylate.

[00101] The tert-butylcarboxy protecting group is subsequently removed through treatment with organic acid such as trifluoroacetic acid, or mineral acid such as HCl, to provide 2-[(3,4-difluorophenyl)methyl]-2,7-diazaspiro[4.5]decane.

[00102] Reaction of the free base of the diazaspiro[4.5]decane with quinoline 3-carboxylic acid in the presence of a dehydrating agent such as EDC and organic base DIPEA provides the Compound C.

[00103] Example 4

2-[4(adamantan-2-yl)piperazin-1-yl]-N-(2-chloro-5-nitrophenyl)acetamide



Compound D

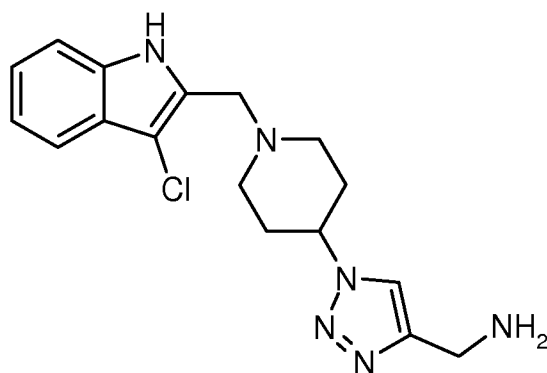
[00104] Compound D can be synthesized commencing with 1-adamantan-2-yl-piperazine through alkylation with ethyl bromoacetate in DMF, with Cs_2CO_3 or Na_2CO_3 added, yielding ethyl 2-[4-(adamantan-2-yl)piperazin-1-yl]acetate.

[00105] Hydrolysis of the ethyl ester with base, such as LiOH in THF/ H_2O , provides 2-[4-(adamantan-2-yl)piperazin-1-yl]acetic acid.

[00106] Condensation between the resulting carboxylic acid and 2-chloro-5-nitroaniline using a dehydrating agent such as EDC with added organic base DIPEA yields Compound D.

[00107] Example 5

[1-[1[(3-chloro-1H-indol-2-yl)methyl]-4-piperidyl]triazol-4-yl]methanamine



Compound E

[00108] Compound E is formed beginning with condensation between commercial 3-chloro-1H-indole-2-carboxylic acid and 4-hydroxy piperidine mediated by dehydrating agent such as HCTU in the presence of DIPEA to provide 1-[(3-chloro-1H-indol-2-yl)carbonyl]piperidin-4-ol.

[00109] The resulting amide is reduced with LAH in THF to provide the amine.

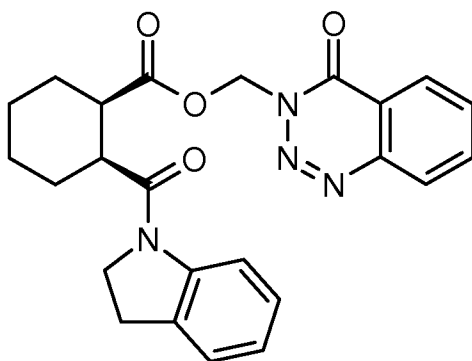
[00110] The alcohol functionality of the resulting 1-[(3-chloro-1H-indol-2-yl)methyl]piperidin-4-ol is converted to an azide using standard conditions employing triphenyl phosphine, diisopropylazodicarboxylate and diphenylphosphoryl azide.

[00111] Azide is then converted to a 1,2,3-triazole moiety through reaction with the alkyne propargylaldehyde diethyl acetal to produce 3-chloro-2-({4-[4-(diethoxymethyl)-1H-1,2,3-triazol-1-yl]piperidin-1-yl}methyl)1H-indol. The diethyl acetal can subsequently be hydrolyzed with dilute acid such as HCl in THF/H₂O to secure the corresponding aldehyde.

[00112] Reductive amination between the aldehyde and ammonia media by NaCNBH₃ in MeOH yields Compound E.

[00113] Example 6

(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1R,2S)-2-[(2,3-dihydro-1H-indol-1-yl)carbonyl]cyclohexane-1-carboxylate



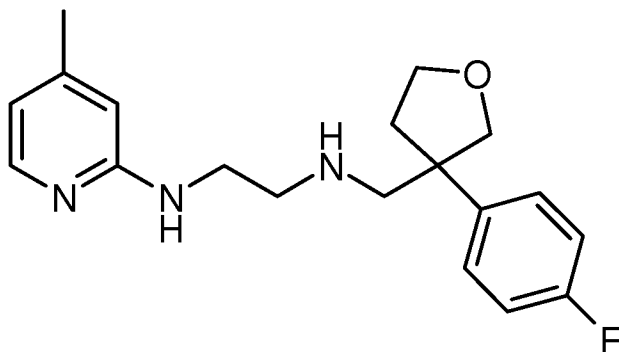
Compound F

[00114] Compound F can be synthesized starting with the condensation reaction between octahydro-2-benzofuran-1,3-dione and 2,3-dihydro-1H-indole to provide the carboxylic acid 2-[(2,3-dihydro-1H-indol-1-yl)carbonyl]cyclohexane-1-carboxylic acid.

[00115] Subsequent three component condensation between the carboxylic acid, 1,2,3-benzotriazin-4(3H)-one and formaldehyde methyl ethyl acetal, mediated by p-toluenesulfonic acid, provides compound of Formula F.

[00116] Example 7

N'-[[3-(4-fluorophenyl)tetrahydrofuran-3-yl]methyl]-N-(4-methyl-2-pyridyl)ethane-1,2-diamine



Compound G

[00117] Formula G compound can be synthesized starting with a double alkylation reaction between 4-fluorophenyl acetonitrile and 2-chloroethyl chloromethyl ether using a strong base such as NaH, in a polar solvent like DMF, or NMP, to provide 3-(4-fluorophenyl)oxolane-3-carbonitrile.

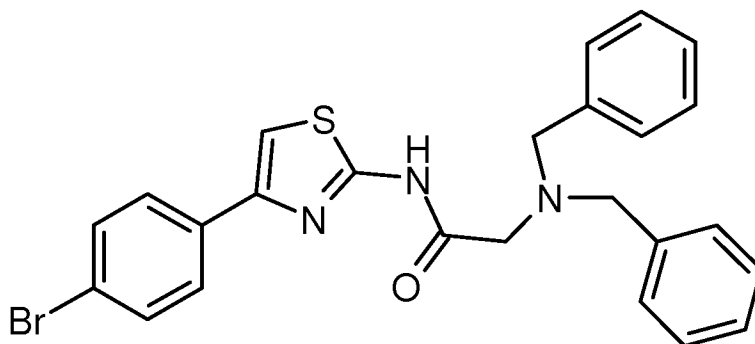
[00118] The nitrile functional group is subsequently hydrolyzed to a carboxylic acid using H₂SO₄.

[00119] The resulting 3-(4-fluorophenyl)oxolane-3-carboxylic acid is condensed with N-(2-aminoethyl)-4-methylpyridin-2-amine using a dehydrating agent such as EDC with added DIPEA to obtain amide 3-(4-fluorophenyl)N-{2-[(4-methylpyridin-2-yl)amino]ethyl}oxolane-3-carboxamide.

[00120] Subsequent reduction of the amide bond to an amine using lithium aluminum hydride (LAH) yields Compound G.

[00121] Example 8

N-[4-(4-bromophenyl)thiazol-2-yl]-2-(dibenzylamino)acetamide

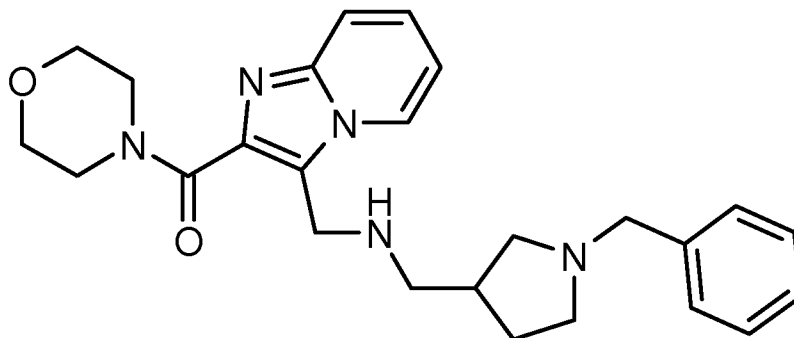


Compound H

[00122] Compound H can be obtained from commercial 4-(4-bromophenyl)-2-thiazolamine, utilizing condensation between the thiazolamine and bromoacetic acid mediated by EDC/DIPEA to yield 2-bromo-N-[4-(4-bromophenyl)-1,3-thiazol-2-yl]acetamide, followed by displacement of the bromide with dibenzyl amine using Cs_2CO_3 in dry DMF to yield Compound H.

[00123] Example 9

[(1-benzylpyrrolidin-3-yl)methyl({2-[(morpholin-4-yl)carbonyl]imidazo[1,2-a]pyridine-3-yl)methyl)amine



Compound I

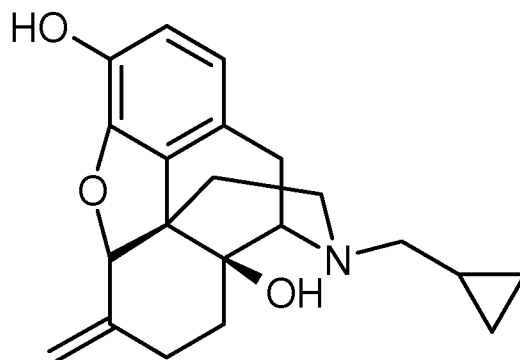
[00124] Compound I is synthesized starting from a condensation between 2-aminopyridine and ethyl bromopyruvate to provide ethyl imidazo[1,2-a]pyridine-2-carboxylate. Formylation at the 3 position of the imidazo[1,2-a]pyridine with phosphorus oxychloride in dimethyl sulfoxide (DMF) provides ethyl 3-formylimidazo[1,2-a]pyridine-2-carboxylate.

[00125] Reductive amination involving the formyl group and 3-aminomethyl-1-benzylpyrrolidine mediated by NaCNBH_3 provides [(1-benzylpyrrolidin-3-yl)methyl]({2-[ethoxycarbonyl]imidazo[1,2-a]pyridine-3-yl}methyl)amine.

[00126] Ester hydrolysis with LiOH followed by condensation between the resulting carboxylic acid and morpholine mediated by EDC/DIPEA yields Compound I.

[00127] Example 10

17-(cyclopropylmethyl)-4,5-epoxy-6-methylene-morphinan-3,14-diol

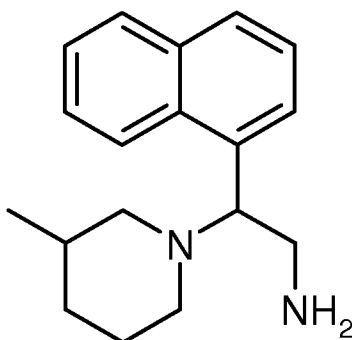


Compound J

[00128] Compound J is included for comparative basis. This compound is available as Nalmefene, CAS RN [55096-26-9], commercially available from Somaxon Pharmaceuticals, Inc. (San Diego, California, USA) and is a mu opioid antagonist having similar structure to naltrexone.

[00129] Example 11

2-(3-methylpiperidin-1-yl)-2-(naphthalene-1-yl)ethan-1-amine



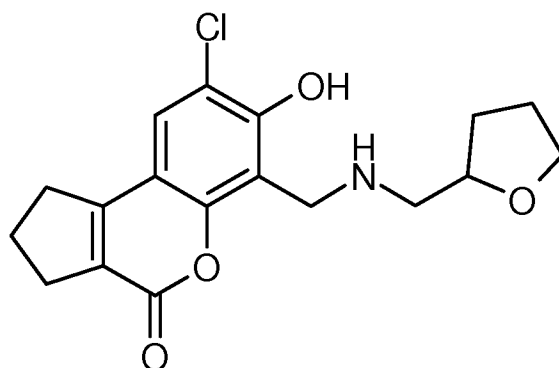
Compound K

[00130] Compound K can be synthesized starting with a three-component, one-pot, condensation involving naphthalene carboxyaldehyde, 3-methyl piperidine and sodium cyanide mediated by aqueous NaHSO_3 .

[00131] The resulting 2-(3-methylpiperidin-1-yl)-2-(naphthalene-1-yl)acetonitrile is then reduced to Compound K using lithium aluminum hydride (LAH).

[00132] Example 12

8-chloro-7-hydroxy-6[(tetrahydrofuran-2-ylmethylamino)methyl]-2,3-dihydro-1H-cyclopenta[c]chromen-4-one



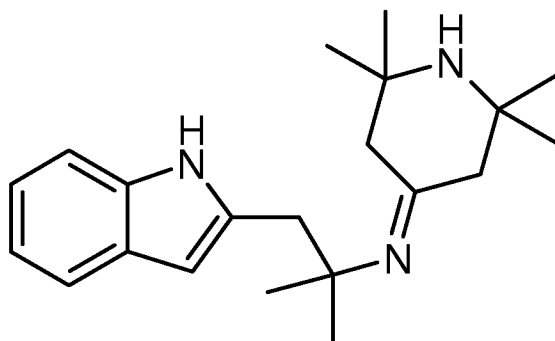
Compound L

[00133] Compound L can be synthesized starting from a condensation between 4-chlororesorcinol and ethyl 2-oxocyclopentanecarboxylate using dilute H_2SO_4 to yield 8-chloro-7-hydroxy-1H,2H,3H,4H-cyclopenta[c]chromen-4-one.

[00134] Aminomethylation at the 6-position occurs with dilute acid and the amination-dimer derived from (tetrahydrofuran-3-yl)methylamine to yield Compound L.

[00135] Example 13

N-[2-(1H-indol-2-yl)-1,1-dimethylethyl]-2,2,6,6-tetramethyl-piperidin-4-imine

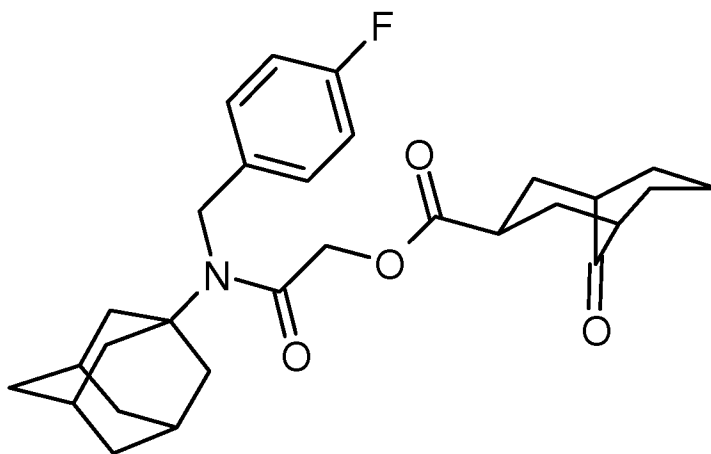


Compound M

[00136] Compound M can be synthesized from a one-step condensation between 1-(1H-indol-2-yl)-2-methyl-propan-2-amine and 2,2,6,6-tetramethylpiperidin-4-one using concentrated HCl in ethanol.

[00137] Example 14

[(adamantan-1-yl)[(4-fluorophenyl)methyl]carbamoyl]methyl 9-oxobicyclo[3.3.1]nonane-3-carboxylate



Compound N

[00138] Compound N can be synthesized commencing with a condensation between 1-adamantylamine and 2-(tert-butyldimethylsiloxy)acetic acid utilizing EDC as a dehydrating agent and

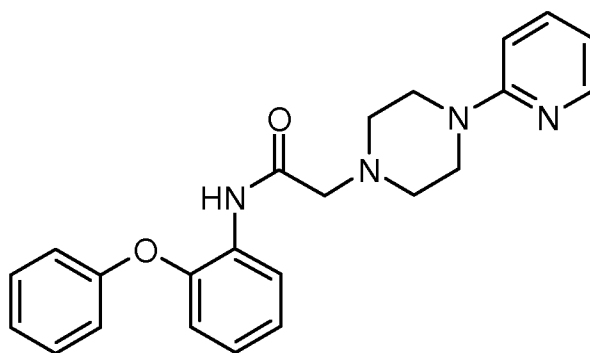
DIPEA as organic base. Subsequent removal of the silyl protecting group with tetra butyl ammonium fluoride (TBAF) in tetrahydrofuran (THF) provides intermediate N-(adaman-2-yl)-2-hydroxy acetamide.

[00139] Esterification of the 2-hydroxyl with 9-oxobicyclo[3.3.1]nonane-3-carboxylic acid mediated by EDC/DIPEA provides intermediate [(adaman-2-yl)-carbamoyl]methyl 9-oxobicyclo[3.3.1]nonane-3-carboxylate.

[00140] Alkylation of the acetamide nitrogen with 4-fluorobenzyl bromide and sodium hydride in anhydrous DMF yields Compound N.

[00141] Example 15

N-(2-phenoxyphenyl)-2-[4-(2-pyridyl)piperazin-1-yl]acetamide



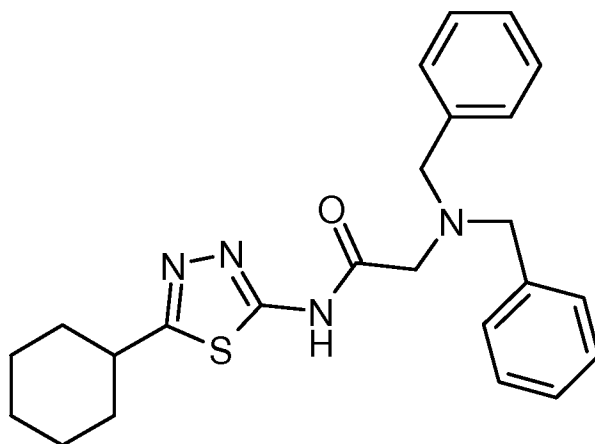
Compound O

[00142] Compound O is advantageously formed commencing with a condensation between 2-phenoxyaniline and bromoacetic acid mediated by a dehydrating agent such as EDC.

[00143] The resulting 2-bromo-N-(2-phenoxyphenyl)acetamide can be reacted with 1-(2-pyridyl)piperazine and Cs_2CO_3 in DMF to yield Compound O.

[00144] Example 16

N-(5-cyclohexyl-1,3,4-thiadiazol-2-yl)-2-(dibenzylamino)acetamide



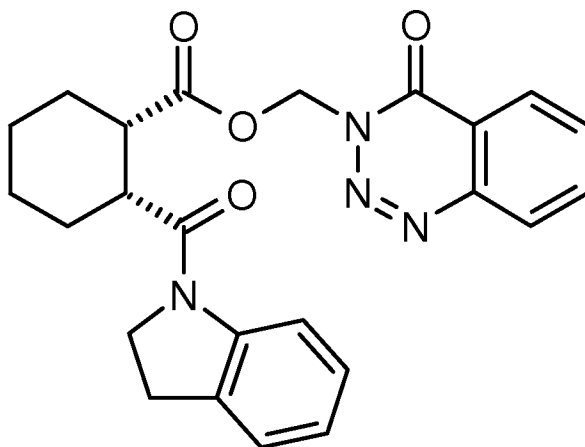
Compound P

[00145] Compound P is synthesized commencing with acylation of 2-amino-5-cyclohexyl-1,3,4-thiadiazole with bromoacetic acid with the use of EDC and DIPEA.

[00146] Compound P is obtained through the reaction of the resulting 2-bromo-N-(5-cyclohexyl-1,3,4-thiadiazole-2-yl)acetamide and dibenzylamine in the presence of Cs_2CO_3 in anhydrous DMF.

[00147] Example 17

(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1S,2R)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



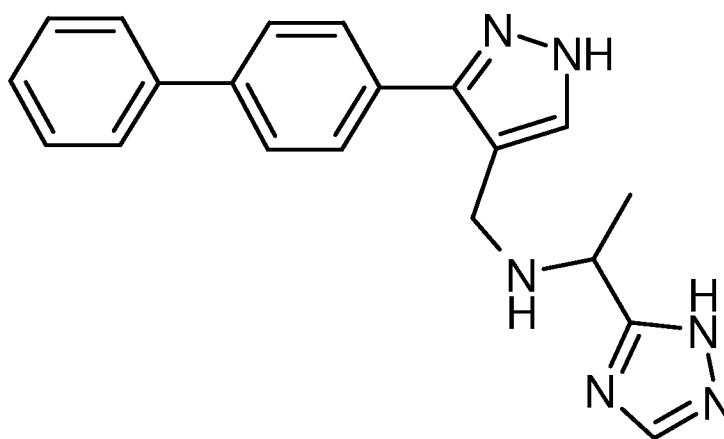
Compound Q

[00148] Compound Q can be synthesized starting with the condensation reaction between octahydro-2-benzofuran-1,3-dione and 2,3-dihydro-1H-indole to provide the carboxylic acid 2-[(2,3-dihydro-1H-indol-1-yl)carbonyl]cyclohexane-1-carboxylic acid.

[00149] Subsequent three component condensation between the carboxylic acid, 1,2,3-benzotriazin-4(3H)-one and formaldehyde methyl ethyl acetal mediated by p-toluenesulfonic acid yields Compound Q.

[00150] Example 18

N-[[3-(4-phenylphenyl)-1H-pyrazol-4-yl]methyl]-1-(1H-1,2,4-triazol-5-yl)ethanamine



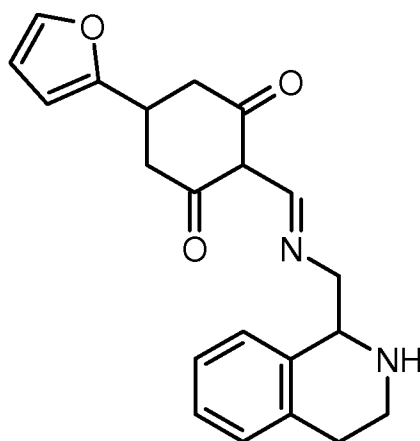
Compound R

[00151] The synthesis of Compound R can be carried out through a reductive amination between 3-[1,1'-biphenyl]-4-yl-1H-pyrazole-4-carboxaldehyde and 1-(1H-1,2,4-triazol-5-yl)ethyl amine using NaCNBH_3 .

[00152] 1-(1H-1,2,4-triazol-5-yl)ethyl amine can be synthesized through a three-component condensation involving Boc-alaninamide, dimethylformamide (DMF) dimethyl acetal and hydrazine hydrate. The resulting tert-butyl N-[1-(1H-1,2,4-triazol-5-yl)ethyl]carbamate can be deprotected with trifluoroacetic acid (TFA) in dichloromethane (DCM) then free-based with aqueous NaHCO_3 to provide free amine for condensation.

[00153] Example 19

5-(furan-2-yl)-2-[(1E)-[1,2,3,4-tetrahydroisoquinolin-1-methyl]imino]methyl]cyclohexane-1,3-dione



Compound S

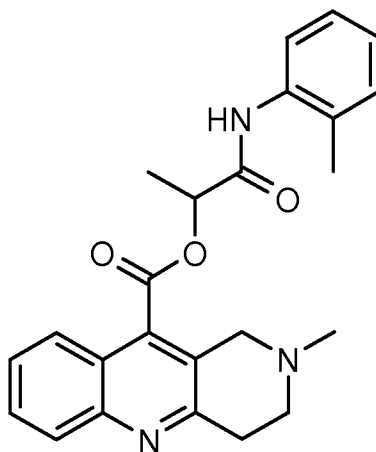
[00154] The synthesis of Compound S is carried out starting with the O-formylation of 5-furan-2-yl-cyclohexane-1,3-dione employing formyl chloride and pyridine in dichloromethane (DCM).

[00155] The resulting [5-(furan-2-yl)-3-oxocyclohex-1-en-1-yl]formate can be rearranged to 4-(furan-2-yl)-2,6-dioxocyclohexane-1-carbaldehyde with AlCl_3 in DCM.

[00156] Compound S can be generated through a dehydrative condensation between the carbaldehyde and 1,2,3,4-tetrahydro-1-isoquinolinemethanamine.

[00157] Example 20

1-[(2-methylphenyl)carbamoyl]ethyl-2-methyl-1,2,3,4-tetrahydro-benzo[b][1,6]-naphthyridine-10-carboxylate



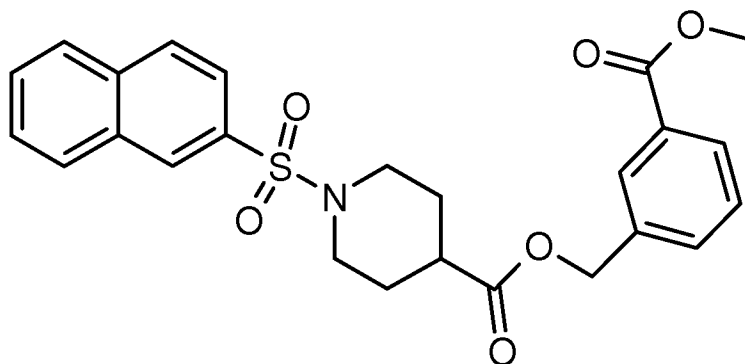
Compound T

[00158] The synthesis of Compound T can be achieved through the condensation between m-toluidine and 2-(tert-butyldimethylsiloxy)propionic acid in the presence of EDC and DIPEA. Removal of the silyl protecting group with TBAF/THF provides 2-hydroxy-N-(2-methylphenyl)propanamide.

[00159] Esterification of the resultant hydroxyl with commercial 2-methyl-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridine-10-carboxylic acid with EDC and DIPEA yields Compound T.

[00160] Example 21

[3-(methoxycarbonyl)phenyl]methyl 1-(naphthalene-2-sulfonyl)piperidine-4-carboxylate



Compound U

[00161] Compound U is produced through the sulfonylation of piperidine-4-carboxylic acid methyl ester using 2-naphthalenesulfonyl chloride in the presence of pyridine in dichloromethane (DCM) to provide methyl 1-(naphthalene-2-sulfonyl)piperidine-4-carboxylate.

[00162] Mild hydrolysis of the methyl ester with LiOH provides the corresponding carboxylic acid.

[00163] Esterification of the carboxylic acid with 3-(hydroxymethyl)benzoic acid methyl ester with 1-ethyl-3-(3'-dimethyl aminopropyl)carbodiimide hydrochloride (EDC) and N,N-diisopropylethylamine (DIPEA) in DCM yields Compound U.

[00164] Another aspect of the invention relates to mu opioid receptor binding compounds that fit the *in silico* model of the mu opioid receptor and the 6-transmembrane and 7-transmembrane structures of the mu opioid receptor, as described more fully hereinafter. Such compounds exhibiting ligand affinity in the *in silico* model, hereafter referred to as Matching Compounds as well as the

pharmaceutically acceptable derivatives of such compounds exhibiting such ligand affinity, constitute a further class of mu opioid receptor binding compounds contemplated by the invention. Matching Compounds can be derivatized as previously described herein, to form corresponding derivatives such as salts, esters, solvates, polymorphs, prodrugs, etc.

[00165] Thus, the invention contemplates a therapeutic composition comprising (i) a mu opioid receptor modulating compound selected from the group consisting of Matching Compounds and their pharmaceutically acceptable derivatives, (ii) a pharmaceutically acceptable carrier, and (iii) optionally, another therapeutic agent.

[00166] Such therapeutic composition can be employed in a method of modulating mu opioid receptor response in a subject in need thereof, comprising administering to the subject an effective amount for said response modulation of a mu opioid receptor modulating compound selected from the group consisting of Matching Compounds and their pharmaceutically acceptable derivatives.

[00167] The invention in a still further aspect relates to a therapeutic cocktail formulation, including (i) at least one Group I compound, Matching Compound, or pharmaceutically acceptable derivative thereof, and (ii) at least one compound selected from the group consisting of morphine, (+)-morphine, methadone, (+)-methadone, 3-methoxynaltrexone, etorphine, and naltrexone.

[00168] Referring now to the drawings, FIG. 1A depicts a human mu opioid receptor model exhibiting a seven-transmembrane-helix topology conserved among G-protein coupled receptors (GPCRs). N and C-termini are colored blue and red, respectively.

[00169] FIG. 1B is a Ramachandran plot mapping the Phi and Psi torsion angles of each residue. Regions bounded by dark blue are allowed conformations while those bounded by cyan are favored conformations.

[00170] For comparison, the quality of known GPCR crystal structures was evaluated, as set out in Table 1 below.

[00171] Table 1. Evaluation of Quality of the Transmembrane Regions of GPCR Structures

GPCR	Species	PDB ID	Ramachandran Analysis (Residues in favored conformation)	C β -Deviations (Fraction of residues with C β -deviation > 0.25 Å)*	Rotamer Analysis (Residues in unfavorable rotamer state)
μ opioid receptor	human		93.1 %	2/293	3.4 %
Rhodopsin	bovine	1u19	87.0 %	0/348	6.4 %
Rhodopsin	squid	2z73	92.2 %	0/350	4.7 %
b ₁ adrenergic receptor	turkey	2vt4	94.1 %	0/276	4.2 %
b ₂ adrenergic receptor	human	2rh1	98.6 %	0/282	0.4 %
A _{2A} adenosine receptor	human	3eml	98.6 %	0/288	1.6 %

* the distance from the modeled Cb position to the model ideal position calculated from the backbone coordinates.

[00172] Analysis showed that the geometry and quality of the human mu opioid receptor model is comparable to known structures of GPCR.

[00173] The Ramachandran analysis showed that 97.3% of the residues are in the allowed region. This human mu opioid receptor model is determined to exhibit a valid confirmation of character, comparable to known crystal structures of other GPCRs. Morphine docking in this model provided a lowest energy docking pose of -47 kcal/mol that predicts a protein binding affinity, pK_d , of approximately -11, as compared with an empirical morphine pK_d of approximately -13.5. Thus, the predicted lowest energy pose recapitulates the experimental binding affinity.

[00174] The ligand binding pocket of the OPRM1 model was also validated by testing its binding to a list of known OPRM1-binding ligands. The μ -opioid selective agonist morphine, the μ -opioid-selective antagonist β -funaltrexamine, and the non-selective opioid agonists diphrenorphine, naloxone, and naltrexone were docked to the human mu opioid receptor model, exhibiting similar docking poses in the binding pocket.

[00175] To validate the residues comprising the binding site, the sites whose mutations are known to affect or not affect morphine binding were mapped. This provided additional validation of the model from docking the morphine molecule to the mu opioid receptor model structure, and comparing the binding hot-spot residues with experiments.

[00176] FIG. 2A depicts the mapping of mutations in the mu opioid receptor model, showing sites where mutations significantly affect ligand binding. In particular, mutating D149 (TM III) to glutamic acid and Y326 (TM VII) to phenylalanine significantly reduces morphine binding by 100- to 1000-fold. A GPCR conserved disulfide bond is shown between C142/C219.

[00177] As shown in FIG. 2A, D149 and Y326 mediate morphine binding in the putative binding site. Substituting D116 (TM II) to either asparagine, glutamic acid, or alanine also shows a 100- to 1000-fold reduction in binding.

[00178] Although D116 faces the ligand-binding pocket, it does not directly interact with the ligand. Accordingly, mutations in this site may induce mu opioid receptor helix repacking.

[00179] There are also mutations that do not significantly affect ligand binding, as shown in FIG. 2B. These include V128A (TM II); T139E, I140L, I144A, I146L, and N152A (TM III); I200V and V204I (TM IV); K235 to R, A, H, and L (TM V); and H299 to Q and N (TM VI). In the mu opioid receptor model, these residues are either far or their side chains face away from the ligand-binding pocket.

[00180] Another way of validating the receptor structure is by evaluation of its surface charge distribution. Being a transmembrane protein, it is expected that the mu opioid receptor surfaces packing with the lipid bilayer should be hydrophobic while those that are exposed to solvent can be charged. Shown in FIG. 3 is a depiction of the calculated surface charge distribution of the mu opioid receptor model.

[00181] In FIG. 3, areas that are relatively positive, neutral or negative are rendered in blue, white, or red, respectively.

[00182] FIG. 4 is a depiction of the packing of a bilayer of the lipid DPPC (dipalmitoylphosphatidylcholine) around the mu opioid receptor. When the mu opioid receptor model is embedded in the DPPC bilayer, charged surfaces are solvent accessible, and the regions that pack with the membrane are hydrophilic. The membrane-embedded region of the protein is hydrophobic and the extra and intra-cellular surfaces exhibit polar or charged patches.

[00183] To determine if the structure is stable, equilibrium molecular dynamics simulation of the protein model embedded in a lipid bilayer was performed. This method can potentially detect major inaccuracies in the model such as steric clashes or incorrect core residue packing since these will cause the protein to be unstable during the simulation. A time series of the root-mean square deviation (RMSD) of the protein C α atoms was developed with respect to the starting conformation, showing that the protein becomes and remains stable after a few nanoseconds of molecular dynamics run.

[00184] FIG. 5 shows the conformational result of an equilibrium simulation performed on the mu opioid receptor model embedded in the DPPC bilayer for 8 ns, with the final structure (green) being ~3 Å root mean square deviation (RMSD) with respect to the starting conformation (cyan), suggesting no major conformational change occurred. As used in such context, RMSD is the average distance between the backbones of the respective superimposed structures, as determined from the C α atomic coordinates after superposition.

[00185] FIG. 6 is a graph of RMSD as a function of time in nanoseconds, for such molecular dynamics simulation of FIG. 5, showing that the model is stable during the molecular dynamics simulations.

[00186] In summary, the foregoing results show that the mu opioid receptor model exhibits valid conformations, comparable to known crystal structures of other GPCRs. The predicted morphine lowest energy pose recapitulates experimental binding affinity. Known mu opioid receptor binders exhibit similar docking poses. The GPCR conserved disulfide bond between C142/C219 is preserved in the mu opioid receptor model. The hydrophobic surface packs with lipid bilayer, and charged surfaces are exposed to water. The model is stable during molecular dynamics simulations.

[00187] In addition to the above-discussed model of the 7TM variant of the human mu opioid receptor, a corresponding in silico modeling effort was carried out to model the 6TM variant of the human mu opioid receptor.

[00188] The approach to modeling the human mu opioid receptor 6TM form included validation of the structural model using molecular dynamics simulation, comparison of the dynamics of the 7TM and 6TM variants, and comparison of morphine dynamics in the binding pockets of the 7TM and 6TM variants.

[00189] The 6TM form of the human mu opioid receptor is due to a splice variant containing exon 13 with a translation start at exon 2. This 6TM variant is missing the first transmembrane helix H1 in the canonical 7-transmembrane helix topology of G-protein coupled receptors (GPCRs). To arrive at a model of the 6TM variant, it is first noted that the helix H1 does not directly participate in the human mu opioid receptor binding pocket. FIG. 7 shows the structure of the 7TM variant, and the first transmembrane helix H1, which does not directly interact with bound morphine. Thus, it was surmised that a model of the 6TM can be constructed by excising the H1 helix. The viability of this model was then evaluated using molecular dynamics simulations. The putative binding pocket of the human mu opioid receptor 6TM variant is shown in FIG. 8.

[00190] Simulations of the human mu opioid receptor 6TM variant using explicit models of the protein, morphine, lipids, ions, and water were performed. Interactions between atoms used physical force fields. FIG. 9 shows the 6TM variant molecular dynamics simulation. The 6TM structure simulation used explicit models for the protein (shown embedded in the bilayer), morphine, lipids (shown as sticks), ions (spheres), and water (not shown).

[00191] To evaluate the stability of the 6TM structure, the root mean square deviation (RMSD) of the protein backbone with respect to the initial conformation was calculated. As shown in Figure 10, the RMSD value reached a steady state consistent with the stability of the 6TM structure in the lipid bilayer, at a value of ~ 3.5 Å.

[00192] Comparison of the 6TM structure before and after long (30 ns) equilibrium simulations shows rearrangements, although minor, of the transmembrane helices FIG. 11 shows the superposition of the human mu opioid receptor 6TM variant conformation before simulation (in cyan color) and after simulation (in green color). FIG. 12 shows a corresponding superposition view from the extracellular side of the superposition of the human mu opioid receptor 6TM variant conformation before simulation (in cyan color) and after simulation (in green color). Side chains shown in sticks are within 4 Å of the bound morphine.

[00193] These minor helical rearrangements are most prominent in helices H6, H7, and H2, which originally pack with the excised helix H1. The absence of global unfolding of the 6TM model is another indication that the structure is stable.

[00194] Next, a comparison was made of the dynamics of the 7TM and 6TM variants.

[00195] To evaluate the effect of the ligand on the dynamics of the human mu opioid receptor forms, simulations of the variants without and in the presence of morphine were performed. The average fluctuations of each residue, which is a measure of local flexibility, were calculated.

[00196] FIGS. 13-16 show the effect of ligand on human mu opioid receptor flexibility. Simulations of the 7TM and 6TM variants with and without ligands were performed. FIG. 13 is a plot of the root mean square fluctuations (RMSF), in Angstroms, for each residue during the simulation of the 7TM variant with and without morphine. FIG. 14 is a depiction of the 7TM variant with and without morphine, with the RMSF values mapped onto the protein structure. FIG. 15 is a plot of the root mean square fluctuations (RMSF), in Angstroms, for each residue during the simulation of the 6TM variant with and without morphine. FIG. 16 is a depiction of the 6TM variant with and without morphine, with the RMSF values mapped onto the protein structure. The backbone thickness and color are proportional to the RMSF values. Arrows indicate the regions that change flexibility in the presence of morphine.

[00197] It was seen that the extra- and intracellular loops exhibited greater flexibility than the transmembrane helices. Most flexible was the cytoplasmic loop CL3, which has been experimentally shown to be highly dynamic in other GPCR proteins. More importantly, in the 7TM variant, the bound morphine reduces the flexibility of the transmembrane region. However, in the 6TM variant, the structure with bound morphine exhibited greater flexibility than without morphine. The increased flexibility is most prominent in the transmembrane helices H5 and H7. In addition, while morphine increases the dynamics of the cytoplasmic loop CL3 in the 7TM variant, the opposite is true in the 6TM form. Considering that CL3 is directly engaged in G protein activation, the observed difference in dynamics affords a possible basis for the opposite inhibitory effects of the two human mu opioid receptor forms.

[00198] To identify the set of residues that mediate morphine binding in both 7TM and 6TM variants, the frequency a particular residue is in contact with morphine during the simulation was counted. It was defined that a residue is in contact with morphine if any of its heavy atoms is within 4.5 Å of the ligand. FIG. 17 shows the binding pocket residues with their calculated contact frequencies for the 7TM variant (left panel) and the 6TM variant (right panel), together with a contact probability scale shown at the far right for the 7TM and 6TM panels. Residues within the 4.5 Å of the bound morphine are illustrated. Side-chains are colored according to their contact probability, which is

defined as the likelihood of interacting with morphine during the simulation run. A contact probability of 1 indicates that the specific residue is always within 4.5 Å of morphine, while a contact probability of 0 indicates that the residue is always beyond 4.5 Å of morphine.

[00199] In the 7TM variant, most of the binding pocket residues exhibit high contact frequencies, indicating that the morphine is essentially “caged” within the pocket. However, in the 6TM variant, several residues show intermediate contact frequency values suggesting a more flexible binding pocket region.

[00200] Considering now the morphine dynamics in the binding pockets of 7TM and 6TM variants, specific sets of residues are critical in the morphine binding in both the 7TM and 6TM variants. FIG. 18 shows residues specific to both 6TM and 7TM variant binding pockets. Mutations in these sites affect ligand binding to both variants. Nonetheless, some other sites are specific only to one of such forms. For example, mutations in these sites, e.g., to alanine, adversely affect ligand binding in one form more than the other. FIG. 19 shows mutation sites that affect binding to the 7TM variant more than to the 6TM variant. FIG. 20 shows mutation sites that affect binding to the 6TM variant more than to the 7TM variant.

[00201] In summary of the foregoing discussion of the dynamics of the binding pockets of the 6TM and 7TM variants, the model structure of human mu opioid receptor 6TM variant is stable in molecular dynamics simulations. Morphine binding induces different effects on the flexibility of the 7TM and 6TM variants. Morphine is more dynamic in the 6TM form than in the 7TM form. Groups of residues within the binding pocket are critical only in the 7TM form, only in the 6TM form, or in both.

[00202] To validate the structure models of the human mu opioid receptor, the specificity of some known mu opioid receptor binding drugs was investigated by docking them onto the 7TM and 6TM human mu opioid receptor models. The docking was performed using MedsuaDock (Molecules in Action, LLC, Carrboro, NC, USA), a docking program featuring superior sampling efficiency and full receptor and ligand flexibilities. To sufficiently sample the conformational space, 10 receptor conformations were selected from equilibrium molecular dynamics (MD) for both 7TM and 6TM MOR, and 1000 docking poses were generated for each conformation. In total, 10,000 poses were generated for each drug docking to either 7TM or 6TM, from which binding affinities were estimated.

[00203] Binding specificity of a molecule to human mu opioid receptor variants was measured by calculating its binding energy difference to 7TM and 6TM human mu opioid receptor ($\Delta\Delta G = \Delta G^{6TM} - \Delta G^{7TM}$). The higher the $\Delta\Delta G$, the greater the drug's binding specificity to the 7TM variant. As shown in Table 2, morphine, (+)-morphine, and 3-methoxynaltrexone demonstrate the greatest specificity for

7TM, while other drugs are more promiscuous in terms of their binding strength to 7TM and 6TM human mu opioid receptor variants.

[00204] Table 2 shows the predicted 7TM human mu opioid receptor binding specificities of some of the known MOR drugs. The specificity is measured using the difference between the binding energy difference between 6TM and 7TM ($\Delta\Delta G = \Delta G^{6TM} - \Delta G^{7TM}$).

[00205] Table 2

<u>Drug</u>	<u>$\Delta\Delta G$ (kcal/mol)</u>
Morphine	2.8
(+)-morphine	3.0
Methadone	0.9
(+)-methadone	1.1
3-methoxynaltrexone	2.1
Etorphine	-1.1
Naltrexone	0.6

[00206] Using the human mu opioid receptor structure models, two chemical compound libraries were computationally screened for novel binding ligands for both 7TM and 6TM human mu opioid receptors. The two compound libraries include a lead-like library that contains 1,296,388 compounds, and a drug-like focused library containing 55,227 compounds. Each compound was compositionally docked onto the human mu opioid receptor structures and its binding affinity was estimated based on the docking poses. For the large-scale docking, only one representative conformation for both 7TM and 6TM human mu opioid receptor was used, which was selected as the centroid structure of the largest clusters during the equilibrium MD simulation.

[00207] FIG. 21 is a schematic flow chart for the virtual screening process for identifying binding ligands to a protein target, as utilized to identify modulator compounds for 7TM and 6TM human mu opioid receptor variants.

[00208] For each virtual screening, all compounds were first ranked based on the predicted binding affinities, and then the top 100 compounds were visually inspected. The purpose of the visual inspection was to verify if a compound was located correctly in the pocket and formed proper electrostatic interactions such as salt bridges and hydrogen binding with the target. Beside high binding affinity and electrostatic matching, a search was made for a small number of rotatable bonds of the compounds and large cluster size of the docking pose, as parameters related to the entropic contribution to the binding free energy, which is not included in the calculated binding affinity.

[00209] Selection criteria thus included binding energy, electrostatic matching, salt-bridge considerations, hydrogen-bonding, number of rotatable bonds, and pose cluster size.

[00210] From the 1,296,388 compounds in the lead-like library, four compounds were identified that satisfied all criteria, as top hits for 7TM human mu opioid receptor binding ligands. Also selected were an additional 30 ligands that had the best electrostatic matching (20 ligands), the highest binding affinity (three ligands), or the smallest number of rotatable bonds (seven ligands). The average number of heavy atoms for these top 34 7TM Matching Compound “hits” was 27.8.

[00211] Table 3 below lists some known mu opioid receptor drugs and their binding score for 7TM and 6TM mu opioid receptor.

[00212] Table 3

Drug	Predicted Binding Energy (kcal/mol)	
	7TM	6TM
morphine	-36.37873	-33.59727
(+)-morphine	-35.36442	-32.37101
methadone	-42.90599	-41.81951
(+)-methadone	-43.44691	-42.46769
3-methoxynaltrexone	-43.61195	-41.55124
etorphine	-44.9	-46.01383
naltrexone	-39.5816	-39.04055

[00213] Table 4 below lists the top 100 compounds from the lead-like library that have the highest predicted binding energy for 7TM mu opioid receptor.

[00214] Table 4

Compound ID	Bind energy ranking	Binding free energy	Number of heavy atoms	Number Rotatabl e bonds	Cluster size
34 top hits selected by different criteria					
Best picks that satisfy all criteria					
ZINC22129845-1331	18	-12.3900	28	4	30
ZINC20081644-11923	32	-12.2200	24	4	30
ZINC20403482-4440	35	-12.2000	26	4	23
ZINC20551710-22800	73	-11.9000	27	3	28
Best electrostatic matching					
ZINC19671354-15601	49	-12.0400	24	5	24
ZINC20256570-27111	46	-12.0600	28	5	18
ZINC20123483-22322	51	-12.0200	23	6	13
ZINC20027815-19544	57	-11.9800	26	6	23
ZINC19793243-25040	26	-12.2800	28	4	29
ZINC12324222-8402	76	-11.8700	27	4	10
ZINC23465304-1490	21	-12.3400	32	5	23
ZINC23448074-18322	5	-13.2700	34	6	17
ZINC07602428-16249	16	-12.4400	29	6	13
ZINC17380409-17000	47	-12.0500	24	6	30
ZINC07492291-12922	78	-11.8600	25	6	10
ZINC20595810-8738	9	-12.8800	24	7	9
ZINC23452876-19689	12	-12.6900	31	7	29
ZINC23738835-17530	48	-12.0500	27	7	8
ZINC19750484-9190	65	-11.9300	29	7	11
ZINC23712292-16597	71	-11.9200	27	7	15
ZINC23738831-17529	74	-11.8900	27	7	8
ZINC20098540-24758	61	-11.9500	26	6	23
ZINC19741238-23968	94	-11.8100	29	4	29
ZINC23449497-18848	23	-12.3200	31	3	30

Least number of rotatable bonds					
ZINC22840489-23843	29	-12.2700	26	1	30
ZINC22527267-23883	17	-12.4300	27	3	30
ZINC08943315-13648	64	-11.9300	27	3	29

Best binding energy					
ZINC14173219-23075	1	-13.8500	25	6	4
ZINC11311718-19462	2	-13.5500	24	6	10
ZINC23448082-18326	3	-13.4400	35	7	15
ZINC23459999-21913	4	-13.4100	35	7	19
ZINC23464636-1116	6	-13.2700	34	7	27
ZINC23448069-18319	7	-13.0100	31	7	5
ZINC19848790-23133	8	-12.9700	27	4	23
Others compounds					
ZINC23055155-11891	42	-12.0900	27	3	30
ZINC13628053-2069	55	-12.0000	26	3	30
ZINC23055148-11887	60	-11.9600	27	3	30
ZINC23505966-4252	62	-11.9400	27	3	9
ZINC09470353-16508	69	-11.9200	25	3	15
ZINC08351587-19306	83	-11.8400	25	3	10
ZINC07911348-2425	88	-11.8200	26	3	28
ZINC13369793-20933	89	-11.8200	25	3	29
ZINC22527271-23884	95	-11.8100	27	3	30
ZINC12582679-977	99	-11.8000	28	3	30
ZINC14547613-9675	100	-11.8000	27	3	30

ZINC23460338-22045	19	-12.3600	30	4	19
ZINC16459982-17529	31	-12.2300	24	4	3
ZINC09809243-22089	34	-12.2000	31	4	25
ZINC23460333-22043	36	-12.1800	30	4	22
ZINC05037099-19033	79	-11.8500	27	4	8
ZINC07033908-22499	92	-11.8100	24	4	20
ZINC23465302-1489	96	-11.8100	30	4	24
ZINC06697480-2136	97	-11.8000	27	4	20
ZINC12096403-24483	98	-11.8000	25	4	22
ZINC23448071-18321	11	-12.7500	31	5	13
ZINC23463963-749	20	-12.3500	32	5	23
ZINC17483293-17768	22	-12.3200	26	5	13
ZINC05035394-6837	28	-12.2700	25	5	5
ZINC23448063-18316	33	-12.2200	30	5	11
ZINC23465306-1491	37	-12.1700	32	5	28
ZINC23450215-19085	38	-12.1400	32	5	17
ZINC06139335-8296	41	-12.1000	25	5	10
ZINC07693689-19348	43	-12.0800	24	5	11
ZINC23462702-67	44	-12.0800	31	5	10
ZINC23925507-2172	45	-12.0700	26	5	4
ZINC23449495-18846	50	-12.0300	30	5	12
ZINC23465220-1440	54	-12.0100	31	5	21
ZINC23961594-4094	58	-11.9700	26	5	7
ZINC07814689-24010	63	-11.9300	26	5	8
ZINC21782724-12409	66	-11.9300	26	5	8
ZINC09154410-19417	72	-11.9000	25	5	15
ZINC23466190-2147	75	-11.8800	33	5	30
ZINC23450092-19045	81	-11.8500	29	5	14
ZINC23464666-1133	82	-11.8500	31	5	15
ZINC05852245-20230	85	-11.8300	25	5	10
ZINC18991361-8342	86	-11.8300	25	5	28
ZINC23465102-1376	91	-11.8200	30	5	23
ZINC16290785-14823	93	-11.8100	25	5	7
ZINC23449458-18834	13	-12.6200	30	6	10
ZINC23448010-18295	24	-12.2900	32	6	22
ZINC09156590-13280	25	-12.2800	25	6	20
ZINC23463873-701	40	-12.1200	31	6	17
ZINC23449492-18845	52	-12.0100	34	6	13
ZINC23450183-19076	53	-12.0100	30	6	10
ZINC14805534-14597	56	-11.9800	26	6	6
ZINC21001129-10243	59	-11.9600	25	6	25
ZINC23457077-20845	68	-11.9300	31	6	23
ZINC23449461-18835	80	-11.8500	30	6	8
ZINC22508970-22761	87	-11.8300	27	6	5
ZINC23448013-18296	90	-11.8200	33	6	23
ZINC23464638-1117	15	-12.5000	34	7	30
ZINC23462655-42	27	-12.2800	27	7	5
ZINC23449884-18981	39	-12.1300	35	7	19
ZINC22014240-18970	67	-11.9300	26	7	6
ZINC23450156-19066	77	-11.8700	32	7	15
ZINC23461483-22489	84	-11.8400	32	7	9

[00215] Table 5 below lists the top 100 compounds from the lead-like library that have the highest predicted binding energy for 6TM mu opioid receptor.

[00216] Table 5

Compound ID	Bind energy ranking	Binding free energy	Number of heavy atoms	Number Rotatable bonds	Cluster size
34 top hits selected by different criteria					
Best picks that satisfy all criteria					
ZINC23447638-18160	6	-12.1900	34	2	10
ZINC23442925-2445	3	-12.0600	29	2	13
ZINC23466118-2079	13	-11.9400	32	3	13
ZINC23451928-19325	9	-12.0400	32	4	20
ZINC23505226-4178	8	-12.0100	29	4	26
ZINC23450215-19085	19	-12.2000	32	5	2
ZINC20515967-11216	25	-12.1900	27	6	6
ZINC23452884-19692	25	-12.1900	32	7	22
ZINC23466160-2118	30	-12.4100	35	7	8
Best electrostatic matching					
ZINC23464293-922	28	-12.9900	38	7	11
ZINC23466012-3111	29	-12.9400	33	5	2
ZINC23458761-21459	13	-12.7200	34	4	5
ZINC23465836-1810	6	-12.6100	35	2	6
ZINC23465963-1928	29	-12.5700	36	7	6
ZINC23465587-1647	14	-12.4100	36	5	15
ZINC23443168-17389	30	-12.3100	38	8	1
ZINC23465962-1927	29	-12.3100	36	7	3
ZINC23466155-2113	17	-12.2300	33	5	13
ZINC23465963-3090	30	-12.2200	35	7	4
ZINC23465882-1853	10	-12.2000	31	2	22
ZINC23459653-21789	29	-12.0800	36	9	3
ZINC23465874-1845	11	-12.0700	32	5	1
ZINC23466159-2117	27	-12.0300	35	7	5
ZINC23505996-4258	10	-11.9400	27	4	26
ZINC11569796-8878	4	-11.9300	27	4	30
Least number of rotatable bonds					
ZINC23447635-18158	6	-12.5600	34	2	23
ZINC23448111-18335	3	-12.2900	30	3	29
ZINC23448432-18455	12	-12.5500	36	3	8
ZINC23448450-18461	8	-12.0800	35	3	3
ZINC23448560-18508	4	-11.9600	35	3	4
ZINC23449802-18954	11	-12.8200	34	3	3
ZINC23451800-19307	7	-12.4800	39	3	19
ZINC23452519-19549	15	-12.0200	32	3	1
ZINC23458767-21461	11	-12.0200	30	3	13
Best binding energy					
ZINC23466380-2329	30	-12.9700	37	8	5
ZINC23451794-19305	22	-12.8200	40	5	8
ZINC23452588-19576	13	-12.8100	33	4	16
ZINC23441724-17178	29	-12.6900	38	6	2
ZINC23449884-18981	27	-12.6800	35	7	6
Others compounds					
ZINC23458843-21490	23	-12.5300	30	4	4
ZINC23447633-18157	17	-12.4700	31	5	12
ZINC23450495-19185	22	-12.4700	35	4	2
ZINC23466011-3109	21	-12.4700	33	5	7
ZINC23448468-18467	22	-12.4600	36	6	4
ZINC23448474-18470	25	-12.4500	35	6	8

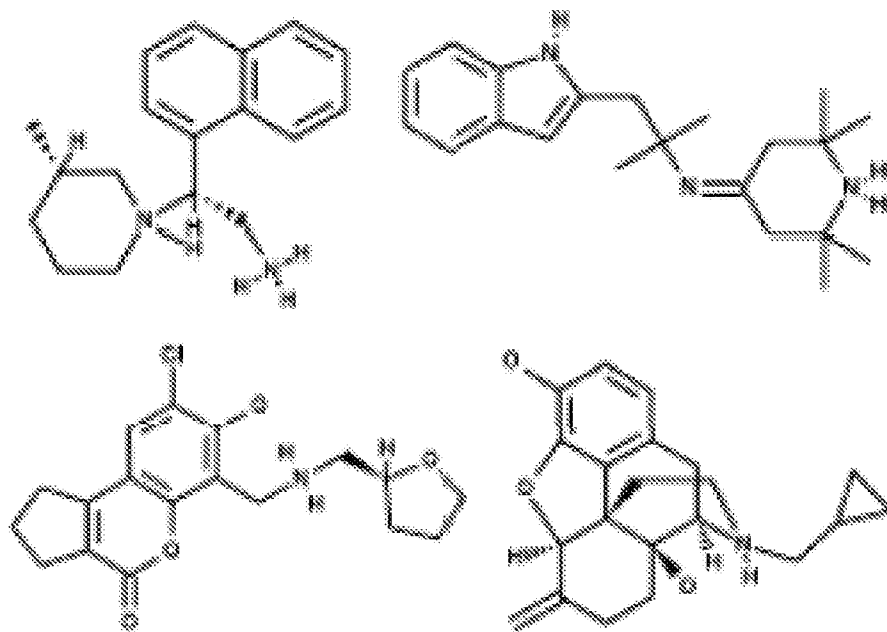
ZINC23448554-18506	8	-12.4300	36	4	2
ZINC23449909-18989	24	-12.4300	34	8	13
ZINC23450296-19111	28	-12.4300	31	6	2
ZINC23450317-19119	30	-12.4300	38	10	2
ZINC23461019-2784	15	-12.4000	35	5	5
ZINC23452591-19577	18	-12.3900	34	4	7
ZINC23464295-923	30	-12.3700	38	7	15
ZINC23459342-21670	18	-12.3600	32	6	13
ZINC23450314-19118	30	-12.3400	38	9	16
ZINC23449810-18957	22	-12.3300	36	4	8
ZINC23449813-18958	13	-12.3300	36	4	5
ZINC23454847-20050	29	-12.3100	37	9	14
ZINC23449819-18960	25	-12.2900	37	6	4
ZINC23452597-19579	12	-12.2900	34	4	4
ZINC23465962-3089	30	-12.2900	35	7	5
ZINC23448509-18484	10	-12.2700	37	5	4
ZINC23464291-921	30	-12.2700	38	8	10
ZINC23464893-1247	15	-12.2500	35	5	15
ZINC23464887-1244	11	-12.2300	33	5	21
ZINC23451845-19316	18	-12.2200	32	5	2
ZINC23452893-19695	25	-12.2200	33	7	2
ZINC23466072-3144	20	-12.1900	31	5	8
ZINC23449370-18804	30	-12.1800	36	9	1
ZINC23461995-2818	18	-12.1800	36	7	8
ZINC23443172-17390	29	-12.1500	38	8	1
ZINC23449873-18977	28	-12.1500	33	8	7
ZINC23450484-19180	24	-12.1500	33	6	1
ZINC23449314-18784	29	-12.1300	35	6	6
ZINC23450221-19087	27	-12.1100	32	5	1
ZINC23447450-18084	22	-12.1000	31	5	5
ZINC23447616-18149	25	-12.1000	36	6	8
ZINC23459157-21608	28	-12.1000	34	7	1
ZINC23464891-1246	15	-12.1000	35	5	16
ZINC23464262-906	16	-12.0800	37	5	16
ZINC23449912-18990	25	-12.0700	34	8	10
ZINC23452601-19581	6	-12.0500	29	4	17
ZINC23452594-19578	14	-12.0400	34	4	8
ZINC23463441-459	29	-12.0400	37	8	6
ZINC23442938-17326	23	-12.0300	38	9	13
ZINC23447555-2625	12	-12.0300	30	4	20
ZINC23448208-18377	15	-12.0200	37	5	3
ZINC23448551-18505	8	-12.0100	36	4	7
ZINC23449903-18987	14	-12.0100	31	4	21
ZINC23442938-2447	27	-12.0000	39	9	5
ZINC23450218-19086	22	-12.0000	32	5	2
ZINC23458310-21296	20	-12.0000	32	5	2
ZINC23450224-19088	23	-11.9800	32	5	6
ZINC23450311-19117	28	-11.9700	38	9	16
ZINC23463355-415	27	-11.9700	36	7	5
ZINC23465350-1513	30	-11.9700	33	8	6
ZINC23459165-21611	29	-11.9500	33	8	4
ZINC23460512-2769	29	-11.9500	38	7	2
ZINC23464289-919	30	-11.9500	38	8	11
ZINC23466160-3194	27	-11.9400	34	7	4
ZINC23465585-1645	23	-11.9300	36	5	10

[00217] Table 6 below lists the top 10 compounds from the lead-like library that have the highest predicted binding energy for 6TM and 7TM mu opioid receptor.

[00218] Table 6

Compound ID	6TM ranking	6TM Binding free energy (kcal/mol)	7TM ranking	7TM Binding free energy (kcal/mol)
ZINC23449884-18981	9	-12.6800	39	-12.1300
ZINC23450215-19085	49	-12.2000	38	-12.1400
ZINC23443293-17415	120	-11.8600	110	-11.7900
ZINC23452876-19689	220	-11.6400	12	-12.6900
ZINC22129845-1331	217	-11.6400	18	-12.3900
ZINC23450224-19088	88	-11.9800	204	-11.6200
ZINC19741238-23968	199	-11.6700	94	-11.8100
ZINC19848788-23131	223	-11.6300	107	-11.7900
ZINC23443991-17643	248	-11.6000	195	-11.6300
ZINC23462786-108	432	-11.3700	152	-11.7000

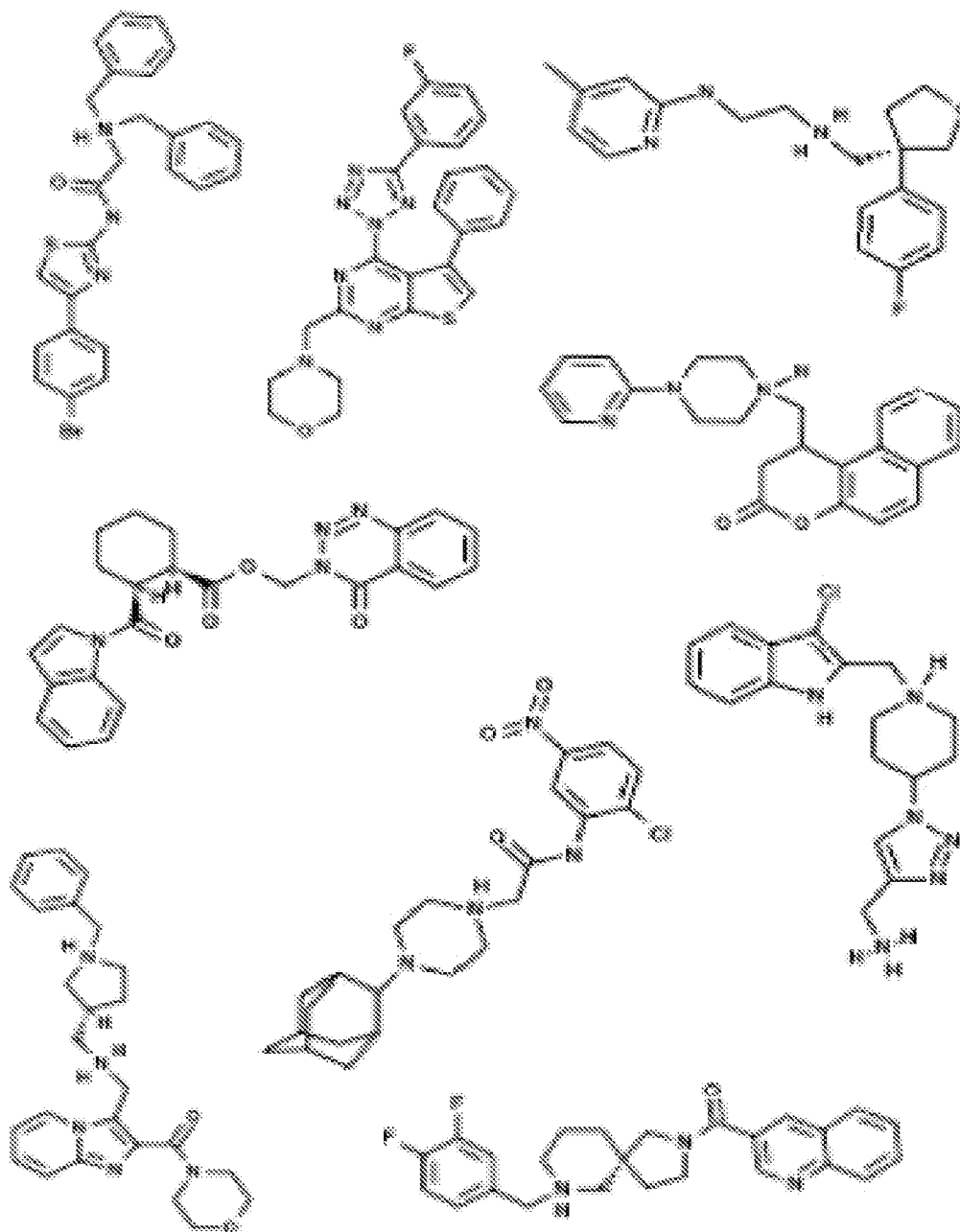
[00219] The top four Matching Compound 7TM human mu opioid receptor binding ligands identified from the ZINC lead-like library were



[00220] Interestingly, a morphine-like compound, nalmefene, an opioid receptor antagonist, was determined among the top four hits from 7TM MOR screening, as a further cross-validation of the screening results, consistent with the finding that the predicted docking pose of nalmefene is similar to that of morphine.

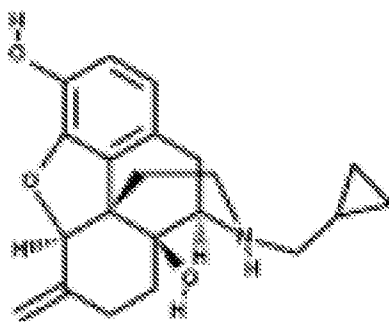
[00221] Thirty-nine Matching Compound 6TM mu opioid receptor ligands were identified, including nine Matching Compound “hits” that satisfied all the selection criteria. None of the nine compounds corresponded to known drugs. In average, the ligand sizes for the 6TM mu opioid receptor hits are slightly larger than those for 7TM mu opioid receptor hits. The average number of heavy atoms for the top 39 6TM Matching Compound binding ligands was 33.6, slightly larger than that for the 7TM. The larger ligand size distribution was consistent with the observation that the 6TM mu opioid receptor has a larger pocket and the character that the 6TM mu opioid receptor is more promiscuous in terms of ligand binding.

[00222] The top nine 6TM MOR Matching Compound binding ligands identified from the ZINC lead-like library that satisfied all selection criteria were the following:



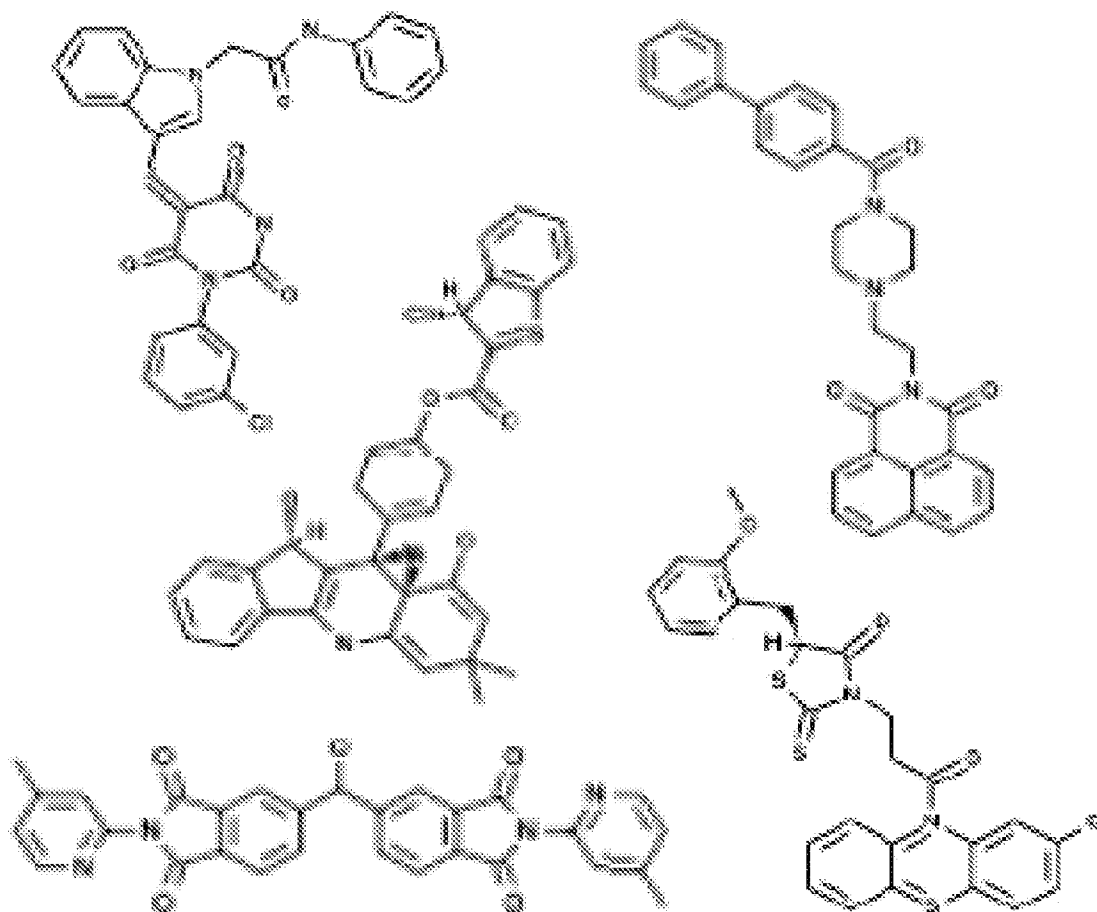
[00223] Combining the 7TM and 6TM screening results, compounds were identified that bind to 7TM and 6TM MOR promiscuously. In this case, all the 1,296,388 compounds were ranked by combining their binding affinity ranking in both 7TM and 6TM screening, to specify the top 10 Matching Compound hits for promiscuous binding.

[00224] Nalmefene



was ranked 5th in this promiscuous binding list, ranking 18th for 7TM binding and 217th for 6TM binding.

[00225] Screening was also performed using a focused library, but the large sizes prevented most compounds from fitting into the 7TM mu opioid receptor pocket. As a result, the following compounds binding to 6TM mu opioid receptor were identified as Matching Compounds from the drug-like focused library:



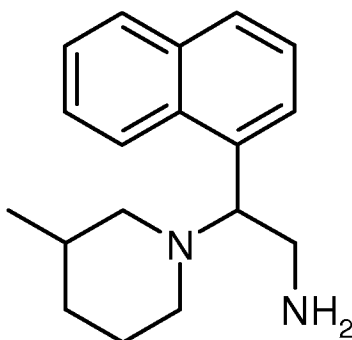
[00226] Any of the foregoing compounds exhibiting mu opioid receptor binding affinity and therapeutic or diagnostic effect can be utilized in compositions and formulations of the invention, and in the methods and techniques herein disclosed.

[00227] While the invention has been described herein in reference to specific aspects, features and illustrative embodiments of the invention, it will be appreciated that the utility of the invention is not thus limited, but rather extends to and encompasses numerous other variations, modifications and alternative embodiments, as will suggest themselves to those of ordinary skill in the field of the present invention, based on the disclosure herein. Correspondingly, the invention as hereinafter claimed is intended to be broadly construed and interpreted, as including all such variations, modifications and alternative embodiments, within its spirit and scope.

THE CLAIMS

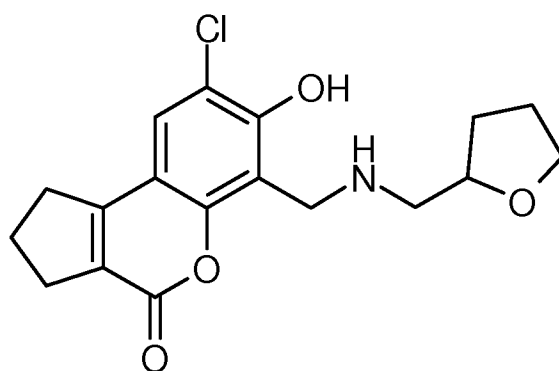
What is claimed is:

1. A pharmaceutical composition, comprising (i) a mu opioid receptor modulating compound selected from the group consisting of Group I compounds and their pharmaceutically acceptable derivatives, (ii) a pharmaceutically acceptable carrier, and (iii) optionally, another therapeutic agent.
2. The pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable derivatives comprise salts, esters, solvates, polymorphs, racemic mixtures, enantiomers, and prodrugs of the Group I compounds.
3. The pharmaceutical composition of claim 1, in an oral dose form.
4. The pharmaceutical composition of claim 1, wherein the mu opioid receptor modulating compound comprises a 6TM agonist.
5. The pharmaceutical composition of claim 1, wherein the mu opioid receptor modulating compound comprises a 6TM antagonist.
6. The pharmaceutical composition of claim 1, wherein the mu opioid receptor modulating compound comprises a 7TM agonist.
7. The pharmaceutical composition of claim 1, wherein the mu opioid receptor modulating compound comprises a 7TM antagonist.
8. A pharmaceutical composition, comprising (i) a mu opioid receptor modulating compound binding a 7TM structure of said receptor, selected from the group consisting of
 - (i) 2-(3-methylpiperidin-1-yl)-2-(naphthalene-1-yl)ethan-1-amine



Compound K

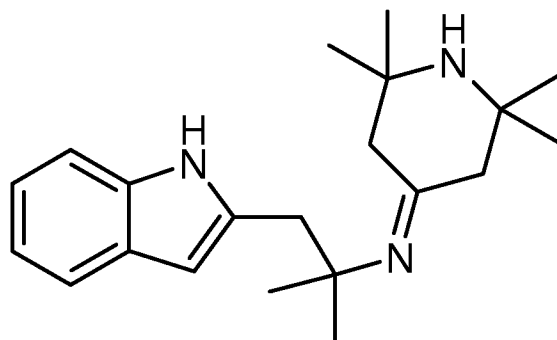
- (ii) 8-chloro-7-hydroxy-6[(tetrahydrofuran-2-ylmethylamino)methyl]-2,3-dihydro-1H-cyclopenta[c]chromen-4-one



Compound L

and

- (iii) N-[2-(1H-indol-2-yl)-1,1-dimethylethyl]-2,2,6,6-tetramethyl-piperidin-4-imine



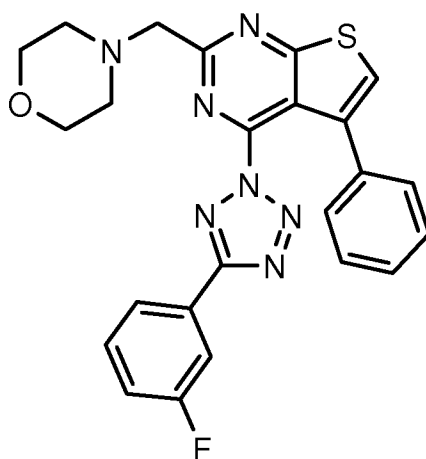
Compound M

and their pharmaceutically acceptable derivatives, and

(ii) a pharmaceutically acceptable carrier.

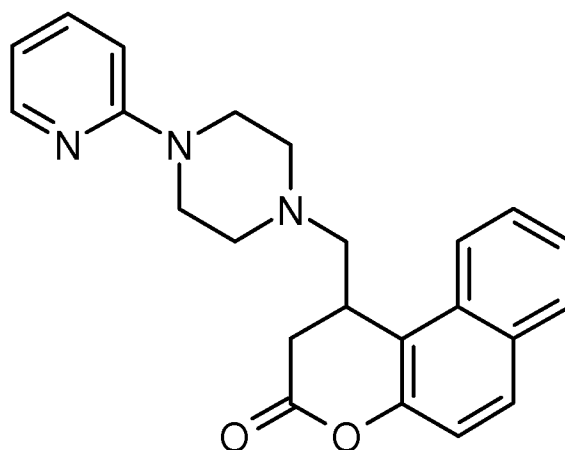
9. A pharmaceutical composition, comprising (i) a mu opioid receptor modulating compound binding a 6TM structure of said receptor, selected from the group consisting of

(i) 4-(5-(3-fluorophenyl)-2H-tetrazol-2-yl)-2-(morpholinomethyl)-5-phenylthieno[2,3-d]pyrimidine



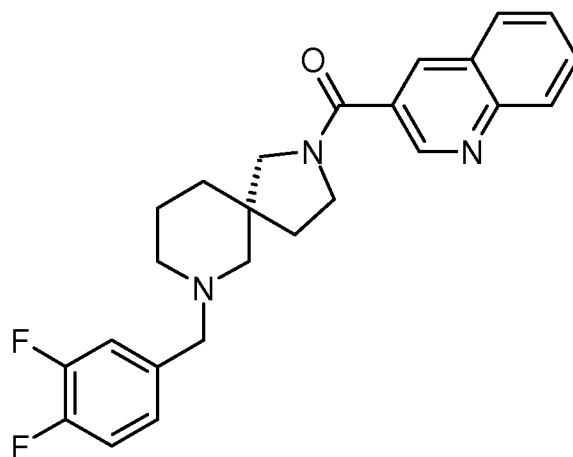
Compound A

(ii) 1-[[4-(2-pyridyl)piperazin-1-yl]mentyl]benzo[f]chromen-3-one



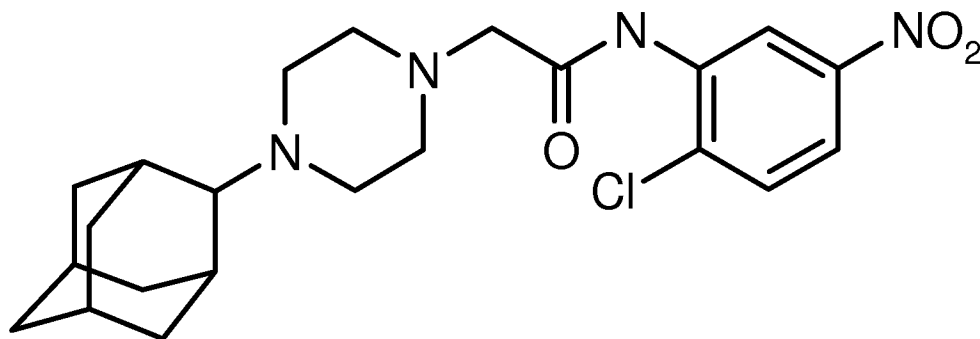
Compound B

(iii) [7-[(3,4-difluorophenyl)methyl]-2,7-diazaspiro[4.5]decan-2-yl]-(3-quinolyl)methanone



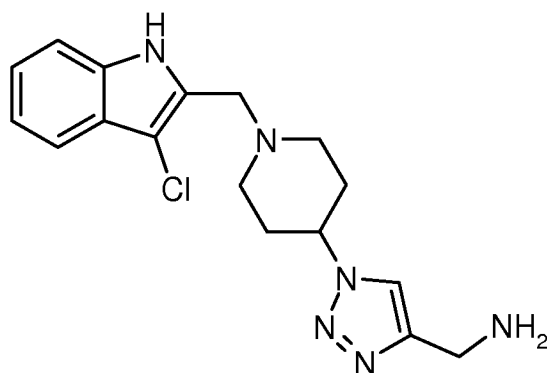
Compound C

(iv) 2-[4(adamantan-2-yl)piperazin-1-yl]-N-(2-chloro-5-nitrophenyl)acetamide



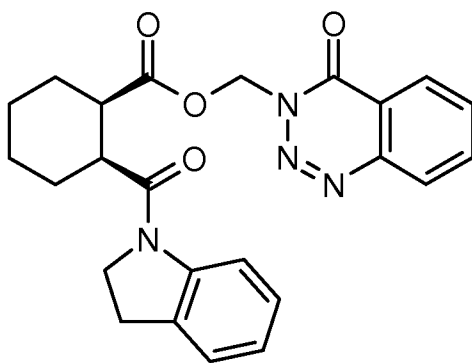
Compound D

(v) [1-[1[(3-chloro-1H-indol-2-yl)methyl]-4-piperidyl]triazol-4-yl]methanamine



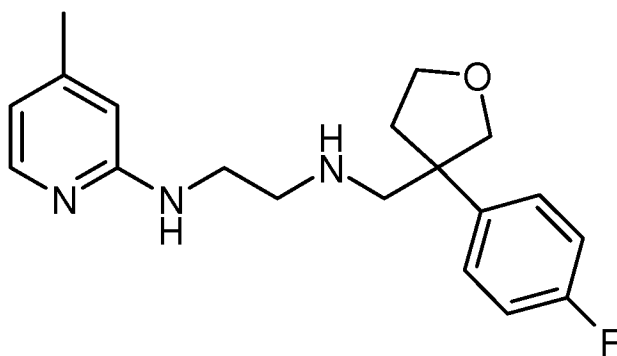
Compound E

(vi) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1R,2S)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



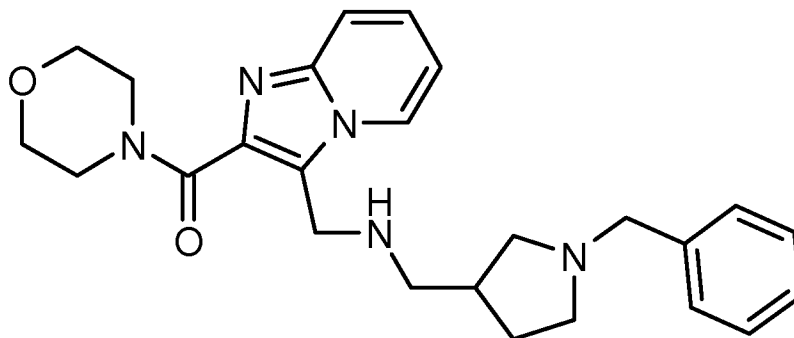
Compound F

(vii) N'-[[3-(4-fluorophenyl)tetrahydrofuran-3-yl]methyl]-N-(4-methyl-2-pyridyl)ethane-1,2-diamine



Compound G

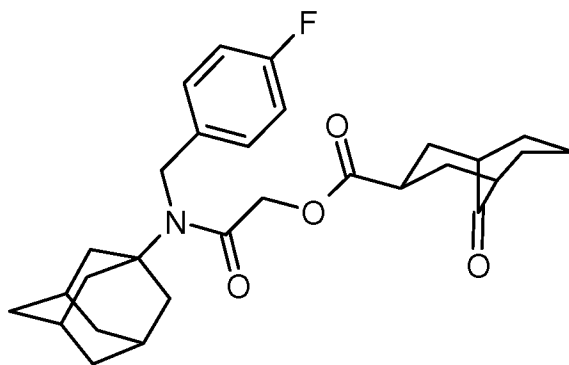
(viii) [(1-benzylpyrrolidin-3-yl)methyl]({2-[(morpholin-4-yl)carbonyl]imidazo[1,2-a]pyridine-3-yl}methyl)amine



Compound I

and

(ix) [(adamantan-1-yl)[(4-fluorophenyl)methyl]carbamoyl]methyl 9-oxobicyclo[3.3.1]nonane-3-carboxylate



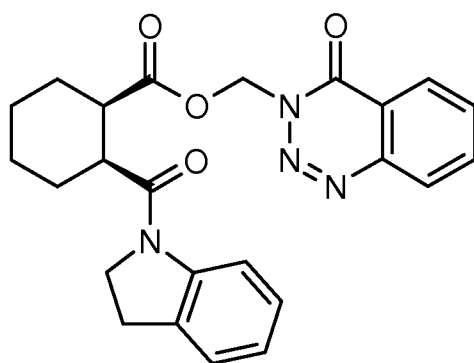
Compound N

and their pharmaceutically acceptable derivatives, and

(ii) a pharmaceutically acceptable carrier.

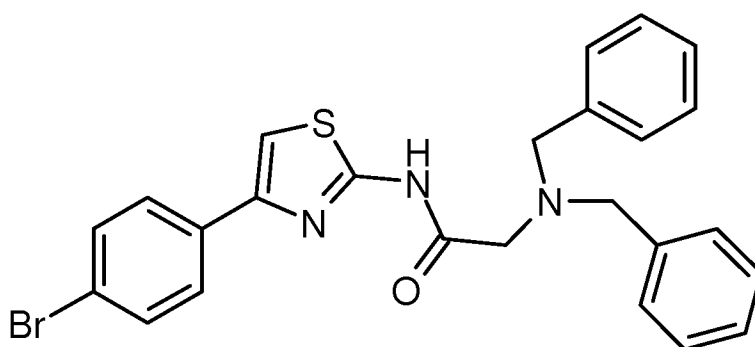
10. A pharmaceutical composition, comprising (i) a mu opioid receptor modulating compound binding both 6TM and 7TM structures of said receptor, selected from the group consisting of

(i) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1R,2S)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



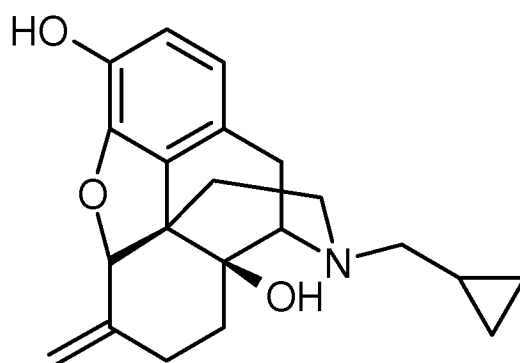
Compound F

(ii) N-[4-(4-bromophenyl)thiazol-2-yl]-2-(dibenzylamino)acetamide



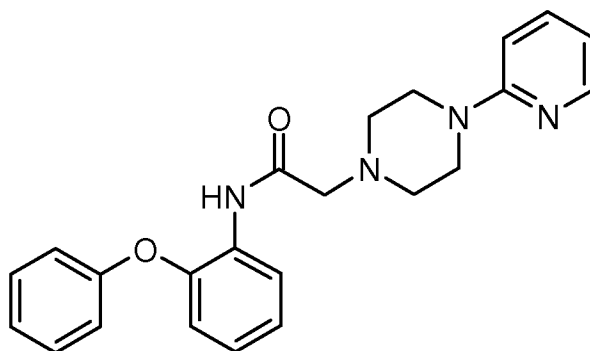
Compound H

(iii) 17-(cyclopropylmethyl)-4,5-epoxy-6-methylene-morphinan-3,14-diol



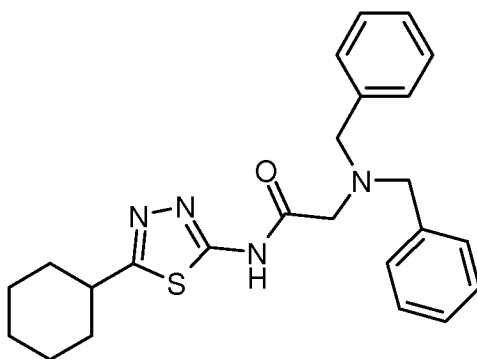
Compound J

(iv) N-(2-phenoxyphenyl)-2-[4-(2-pyridyl)piperazin-1-yl]acetamide



Compound O

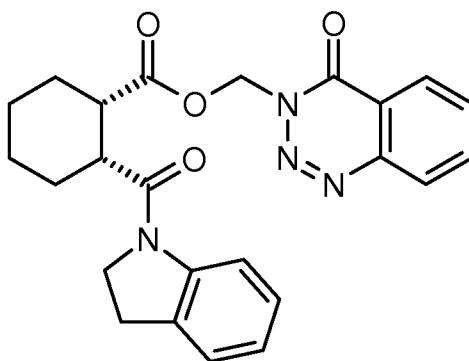
(v) N-(5-cyclohexyl-1,3,4-thiadiazol-2-yl)-2-(dibenzylamino)acetamide



Compound P

and

(vi) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1S,2R)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



Compound Q

and their pharmaceutically acceptable derivatives, and

(ii) a pharmaceutically acceptable carrier.

11. A method of modulating mu opioid receptor response in a subject in need thereof, comprising administering to the subject an effective amount for said response modulation of a mu opioid receptor modulating compound selected from the group consisting of Group I compounds, and their pharmaceutically acceptable derivatives.

12. The method of claim 11, wherein the pharmaceutically acceptable derivatives comprise salts, esters, solvates, polymorphs, racemic mixtures, enantiomers, and prodrugs of the Group I compounds.

13. The method of claim 11, wherein the mu opioid receptor modulating compound is in an oral dose form.

14. The method of claim 11, wherein the mu opioid receptor modulating compound comprises a 6TM agonist.

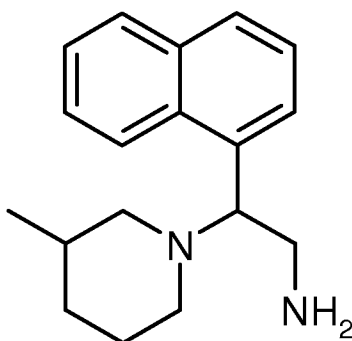
15. The method of claim 11, wherein the mu opioid receptor modulating compound comprises a 6TM antagonist.

16. The method of claim 11, wherein the mu opioid receptor modulating compound comprises a 7TM agonist.

17. The method of claim 11, wherein the mu opioid receptor modulating compound comprises a 7TM antagonist.

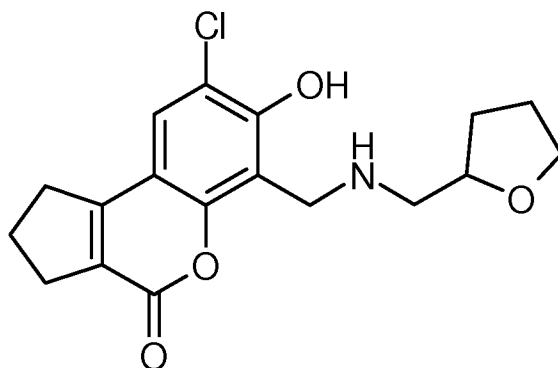
18. A method of modulating mu opioid receptor response in a subject in need thereof, comprising administering to the subject an effective amount for said response modulation of a mu opioid receptor modulating compound binding a 7TM structure of said receptor, selected from the group consisting of

(i) 2-(3-methylpiperidin-1-yl)-2-(naphthalene-1-yl)ethan-1-amine



Compound K

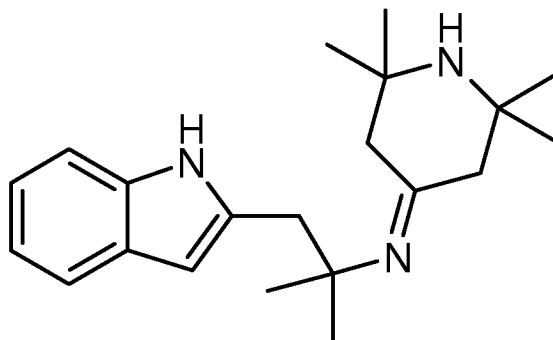
(ii) 8-chloro-7-hydroxy-6-[(tetrahydrofuran-2-ylmethylamino)methyl]-2,3-dihydro-1H-cyclopenta-[c]chromen-4-one



Compound L

and

(iii) N-[2-(1H-indol-2-yl)-1,1-dimethylethyl]-2,2,6,6-tetramethyl-piperidin-4-imine

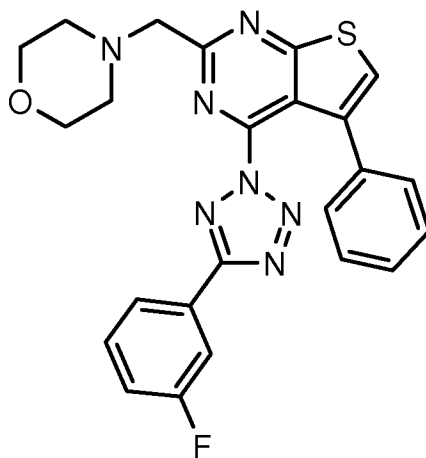


Compound M

and their pharmaceutically acceptable derivatives.

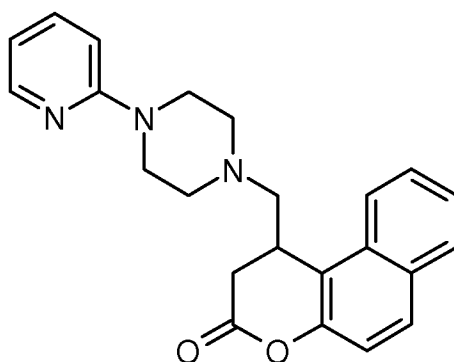
19. A method of modulating mu opioid receptor response in a subject in need thereof, comprising administering to the subject an effective amount for said response modulation of a mu opioid receptor modulating compound binding a 6TM structure of said receptor, selected from the group consisting of

(i) 4-(5-(3-fluorophenyl)-2H-tetrazol-2-yl)-2-(morpholinomethyl)-5-phenylthieno[2,3-d]pyrimidine



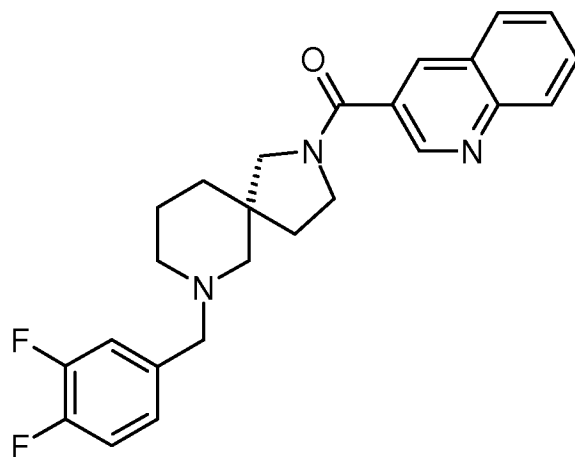
Compound A

(ii) 1-[[4-(2-pyridyl)piperazin-1-yl]menthyl]benzo[f]chromen-3-one



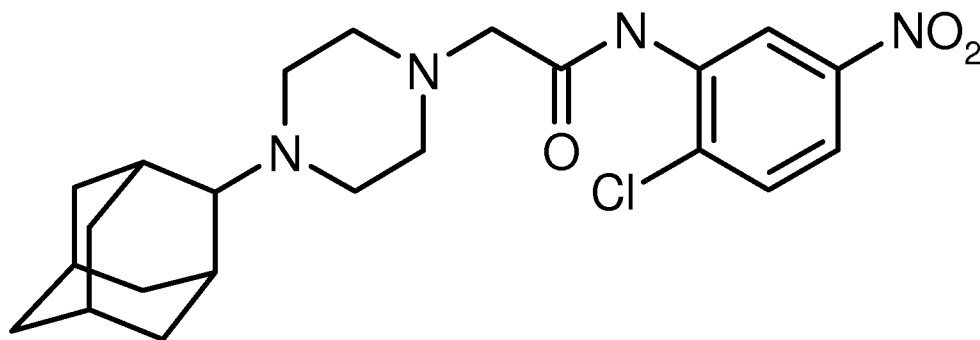
Compound B

(iii) [7-[(3,4-difluorophenyl)methyl]-2,7-diazaspiro[4.5]decan-2-yl]-(3-quinolyl)methanone



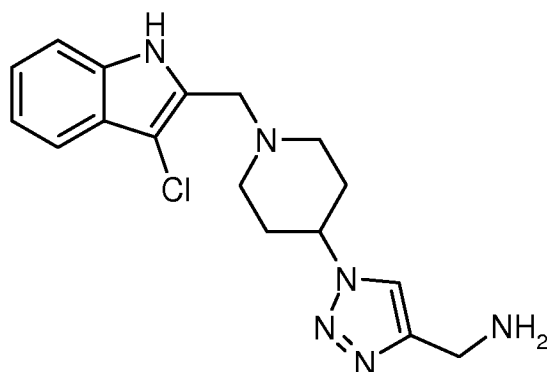
Compound C

(iv) 2-[4(adamantan-2-yl)piperazin-1-yl]-N-(2-chloro-5-nitrophenyl)acetamide



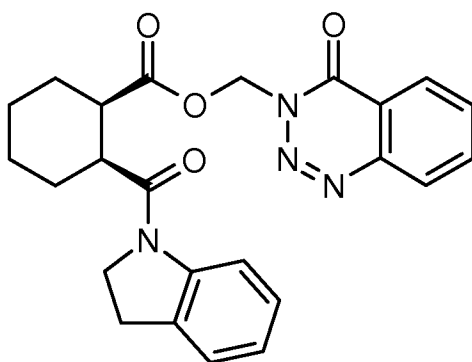
Compound D

(v) [1-[1[(3-chloro-1H-indol-2-yl)methyl]-4-piperidyl]triazol-4-yl]methanamine



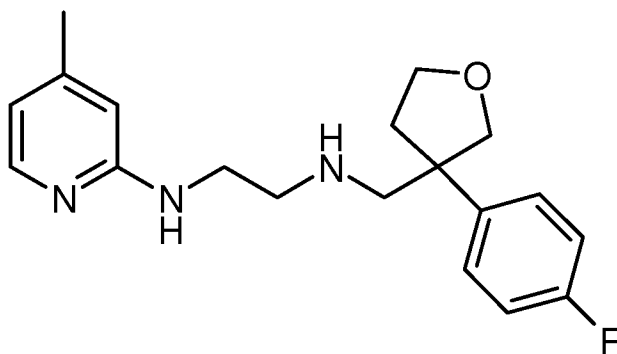
Compound E

(vi) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1R,2S)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



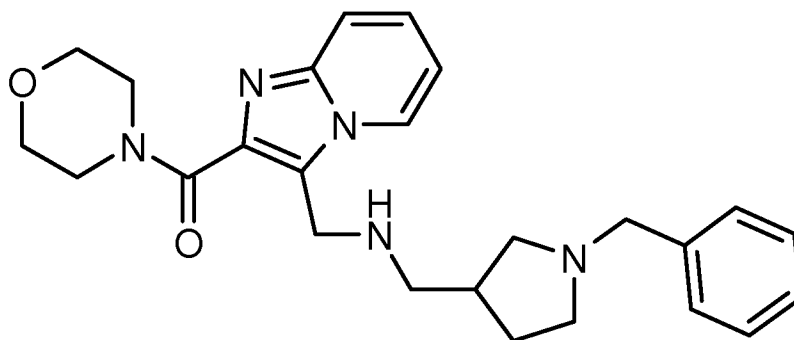
Compound F

(vii) N'-[[3-(4-fluorophenyl)tetrahydrofuran-3-yl]methyl]-N-(4-methyl-2-pyridyl)ethane-1,2-diamine



Compound G

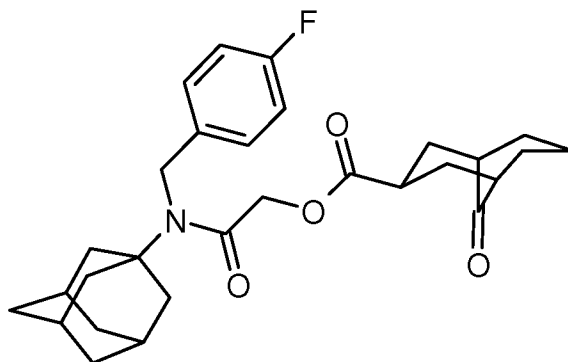
(viii) [(1-benzylpyrrolidin-3-yl)methyl({2-[(morpholin-4-yl)carbonyl]imidazo[1,2-a]pyridine-3-yl}methyl)amine



Compound I

and

(ix) [(adamantan-1-yl)[(4-fluorophenyl)methyl]carbamoyl]methyl 9-oxobicyclo[3.3.1]nonane-3-carboxylate

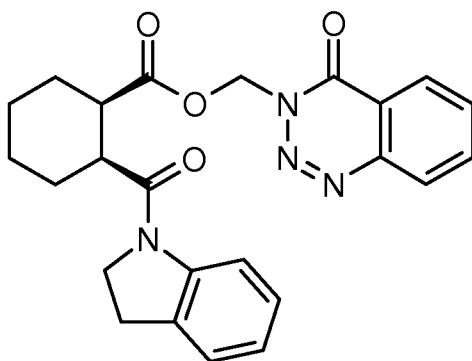


Compound N

and their pharmaceutically acceptable derivatives.

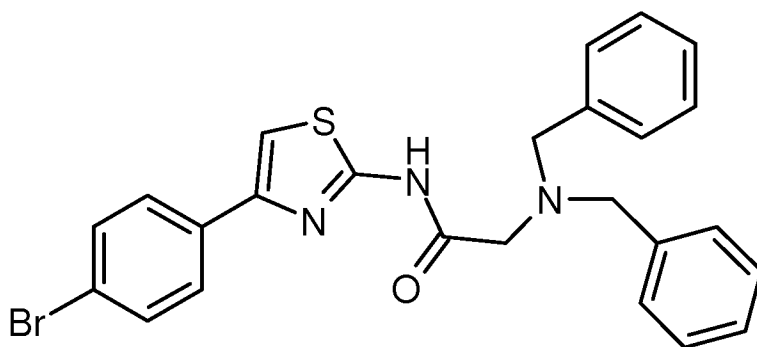
20. A method of modulating mu opioid receptor response in a subject in need thereof, comprising administering to the subject an effective amount for said response modulation of a mu opioid receptor modulating compound binding both 6TM and 7TM structures of said receptor, selected from the group consisting of

(i) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1R,2S)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



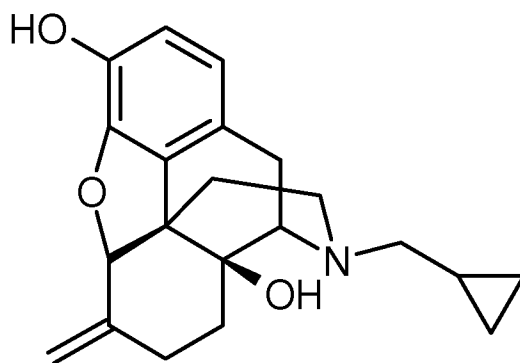
Compound F

(ii) N-[4-(4-bromophenyl)thiazol-2-yl]-2-(dibenzylamino)acetamide



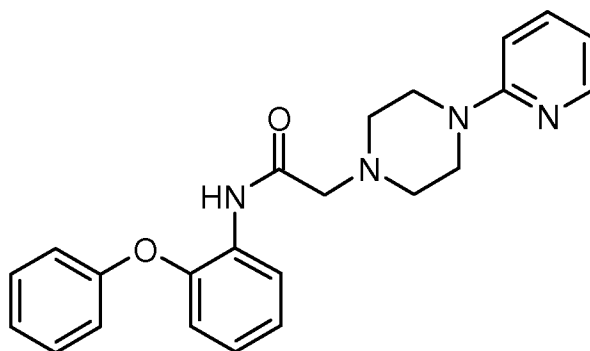
Compound H

(iii) 17-(cyclopropylmethyl)-4,5-epoxy-6-methylene-morphinan-3,14-diol



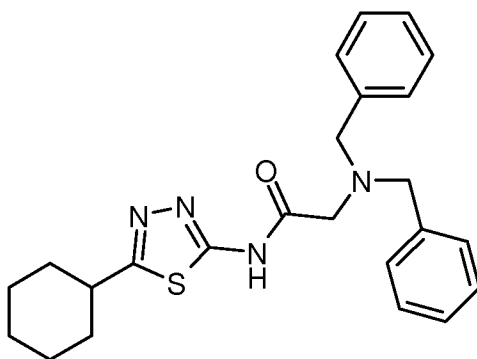
Compound J

(iv) N-(2-phenoxyphenyl)-2-[4-(2-pyridyl)piperazin-1-yl]acetamide



Compound O

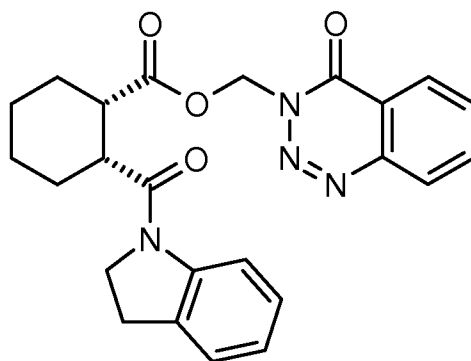
(v) N-(5-cyclohexyl-1,3,4-thiadiazol-2-yl)-2-(dibenzylamino)acetamide



Compound P

and

(vi) (4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)methyl (1S,2R)-2-[(2,3-dihydro-1H-indo-1-yl)carbonyl]cyclohexane-1-carboxylate



Compound Q

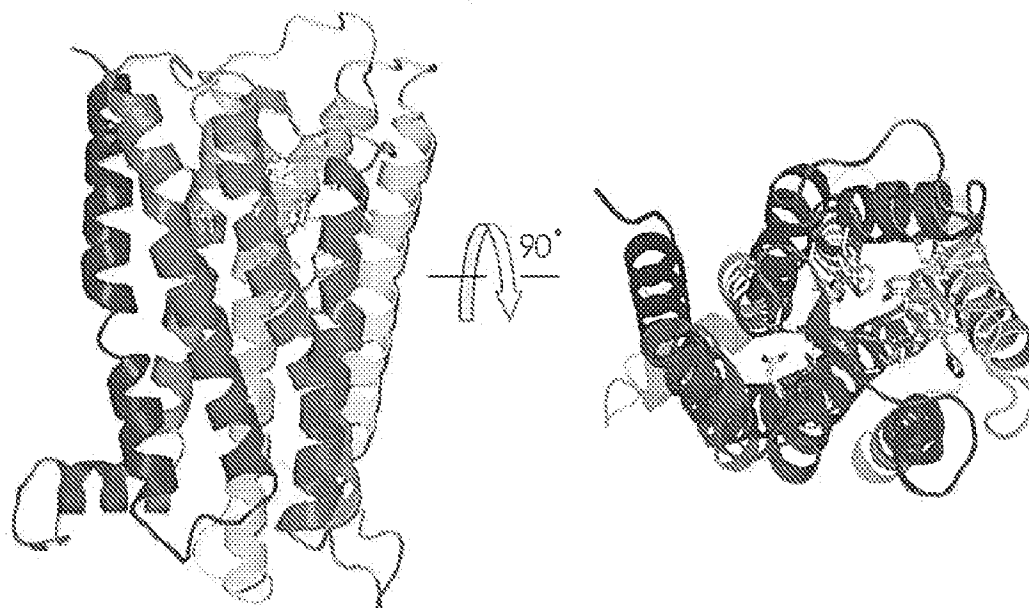
and their pharmaceutically acceptable derivatives.

21. A therapeutic composition comprising (i) a mu opioid receptor modulating compound selected from the group consisting of Matching Compounds and their pharmaceutically acceptable derivatives, (ii) a pharmaceutically acceptable carrier, and (iii) optionally, another therapeutic agent.

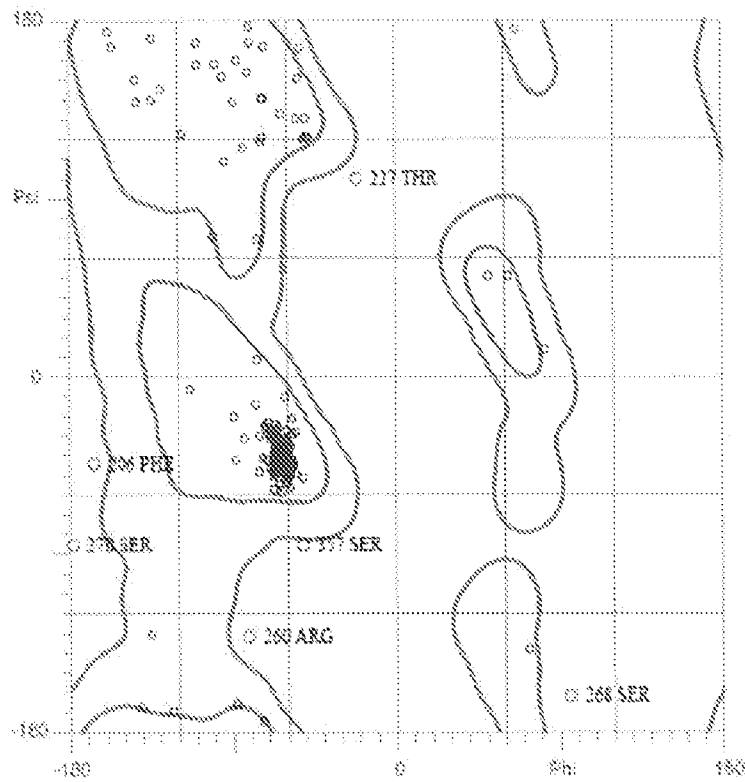
22. A method of modulating mu opioid receptor response in a subject in need thereof, comprising administering to the subject an effective amount for said response modulation of a mu opioid receptor modulating compound selected from the group consisting of Matching Compounds and their pharmaceutically acceptable derivatives.

23. A therapeutic cocktail formulation, including (i) at least one Group I compound, Matching Compound, or pharmaceutically acceptable derivative thereof, and (ii) at least one compound selected from the group consisting of morphine, (+)-morphine, methadone, (+)-methadone, 3-methoxynaltrexone, etorphine, and naltrexone.

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**FIG. 1A**

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**FIG. 1B**

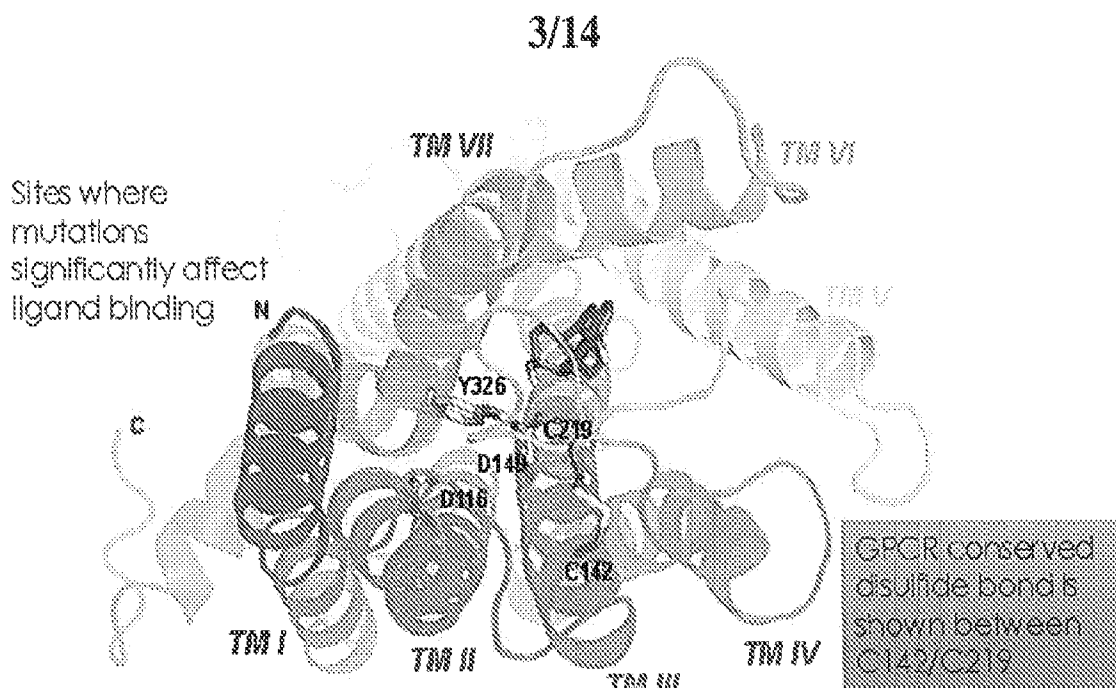


FIG. 2A

Sites where mutations do not significantly affect morphine binding.

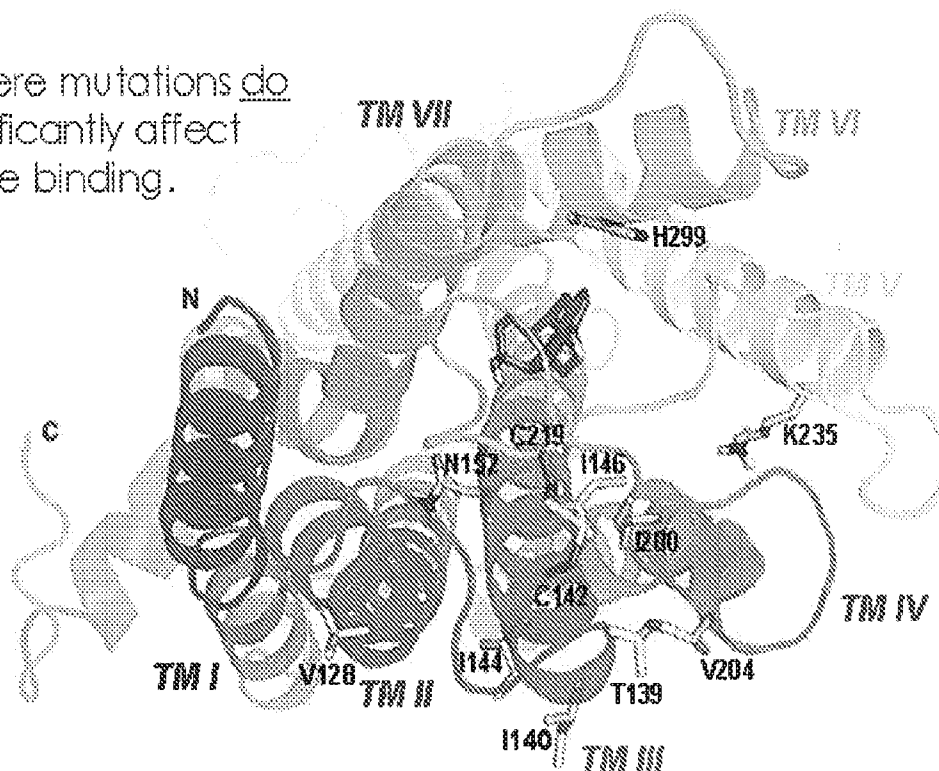


FIG. 2B

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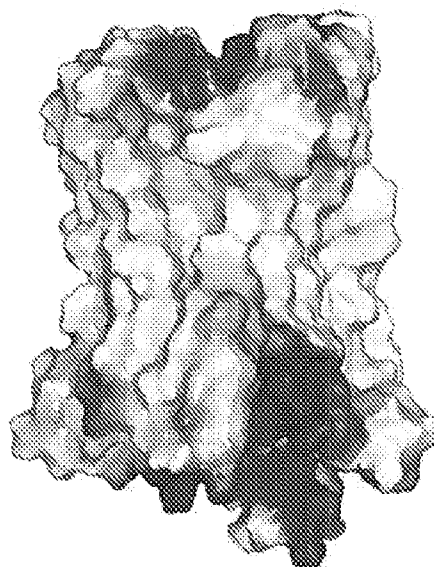


FIG. 3

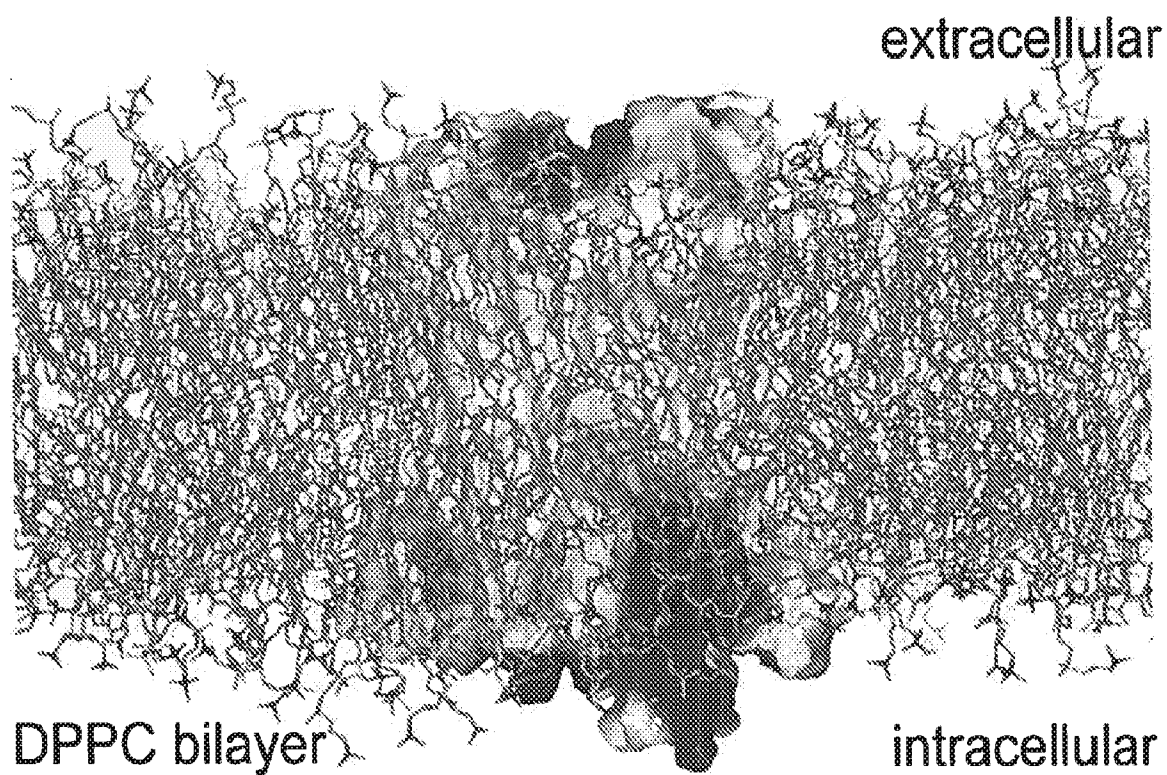
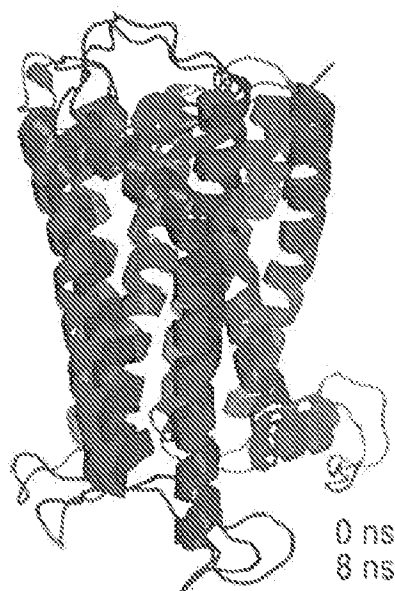
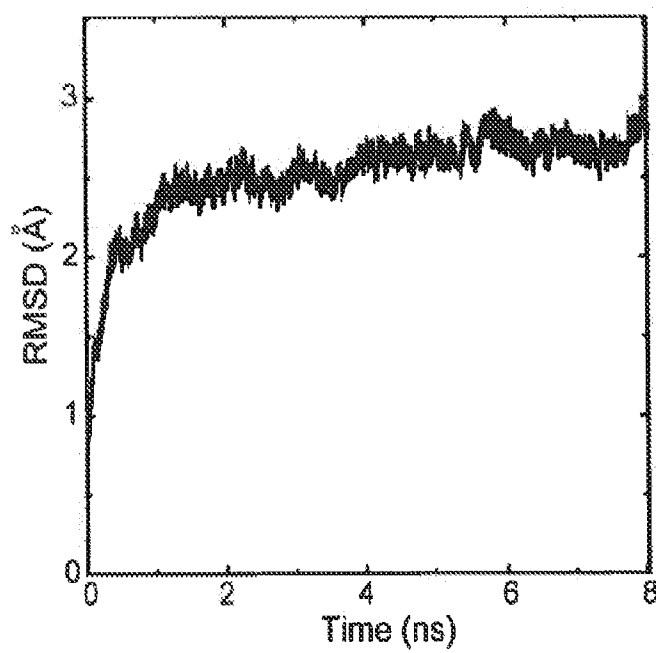


FIG. 4

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**FIG. 5****FIG. 6**

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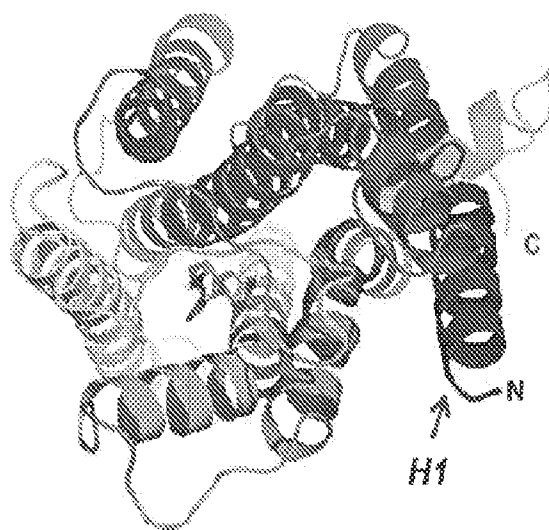


FIG. 7

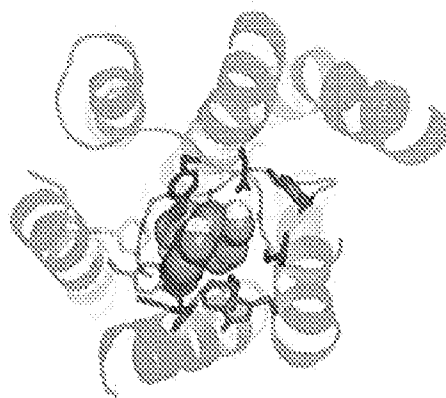
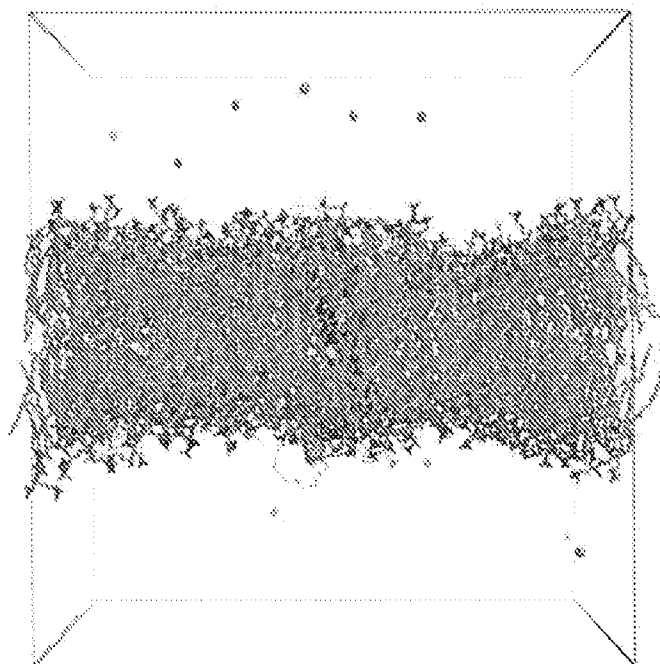
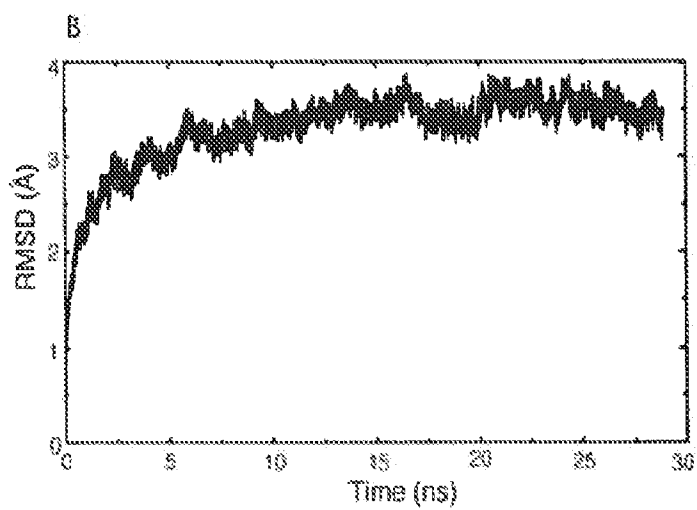


FIG. 8

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**FIG. 9****FIG. 10**

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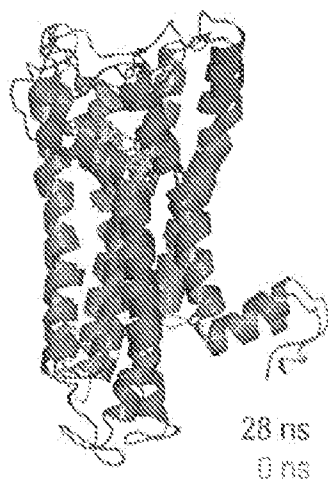


FIG. 11

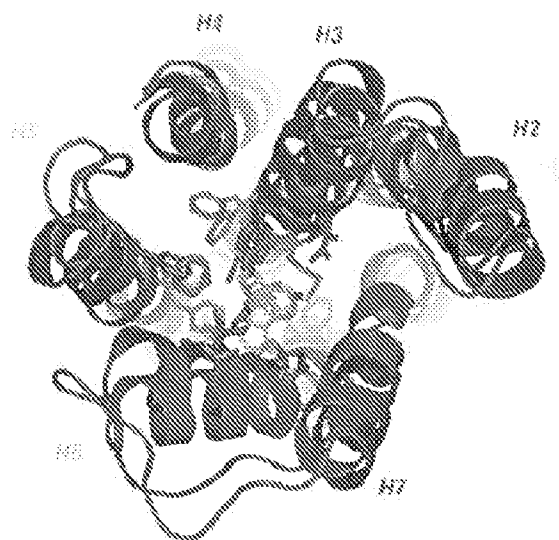


FIG. 12

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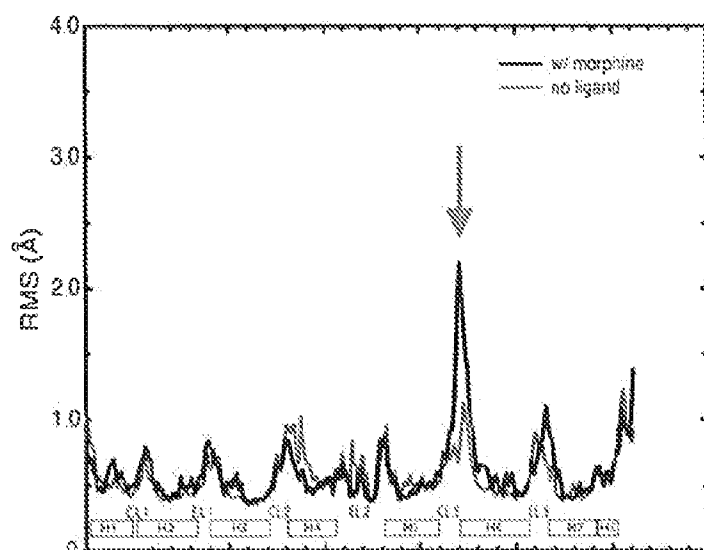


FIG. 13

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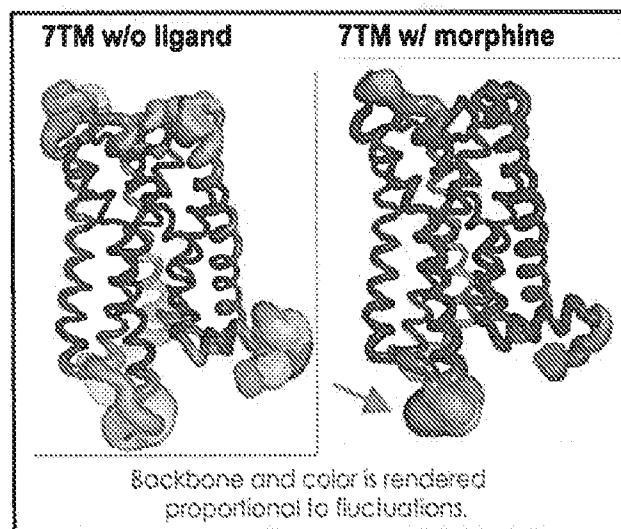


FIG. 14

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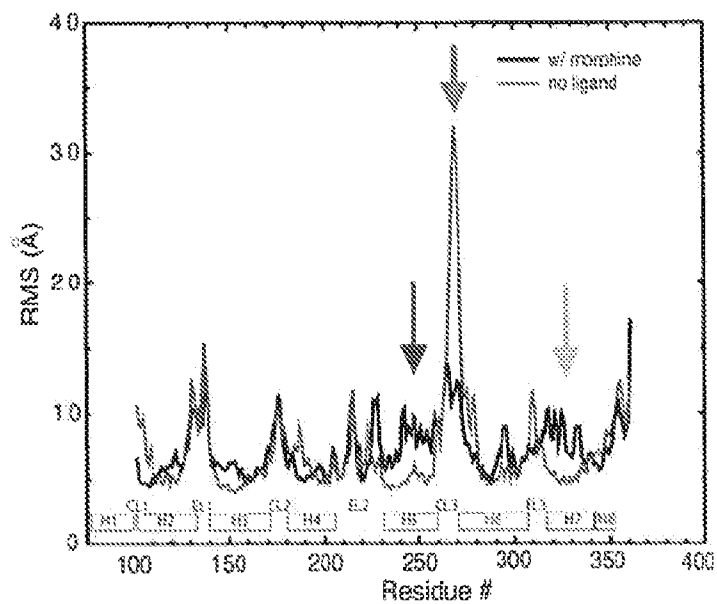


FIG. 15

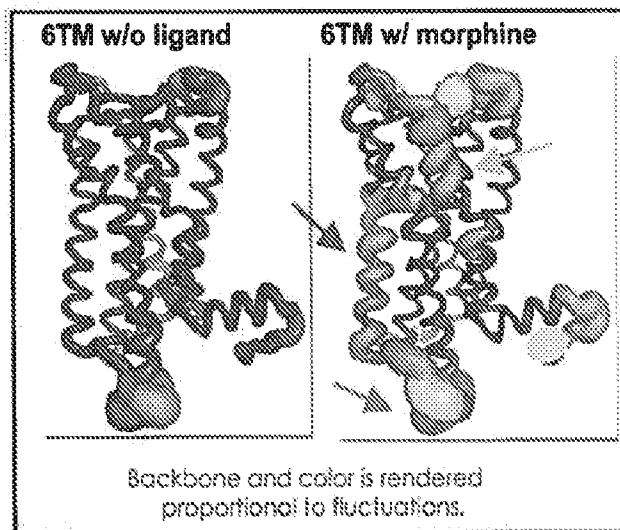


FIG. 16

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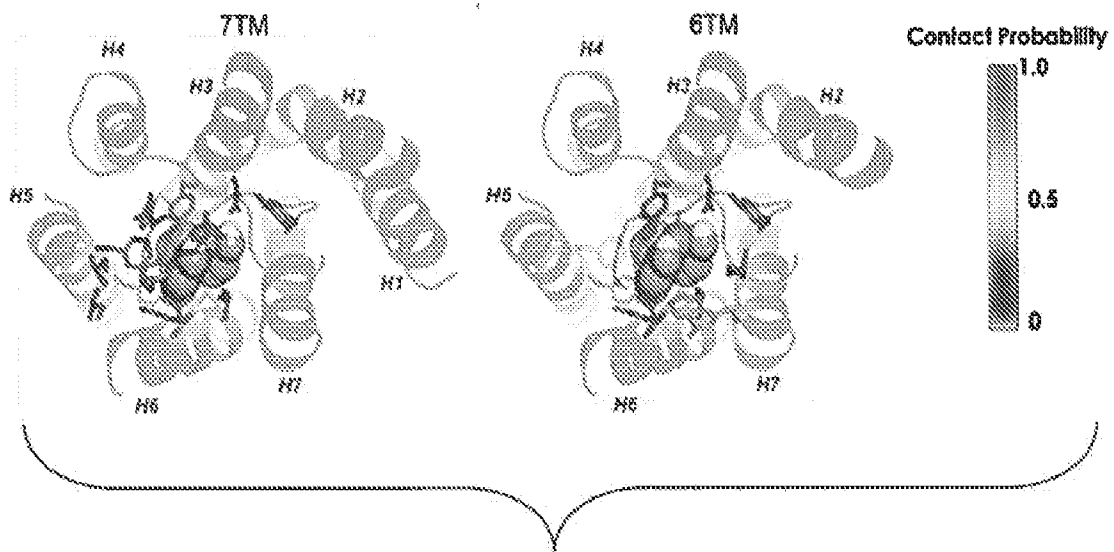


FIG. 17

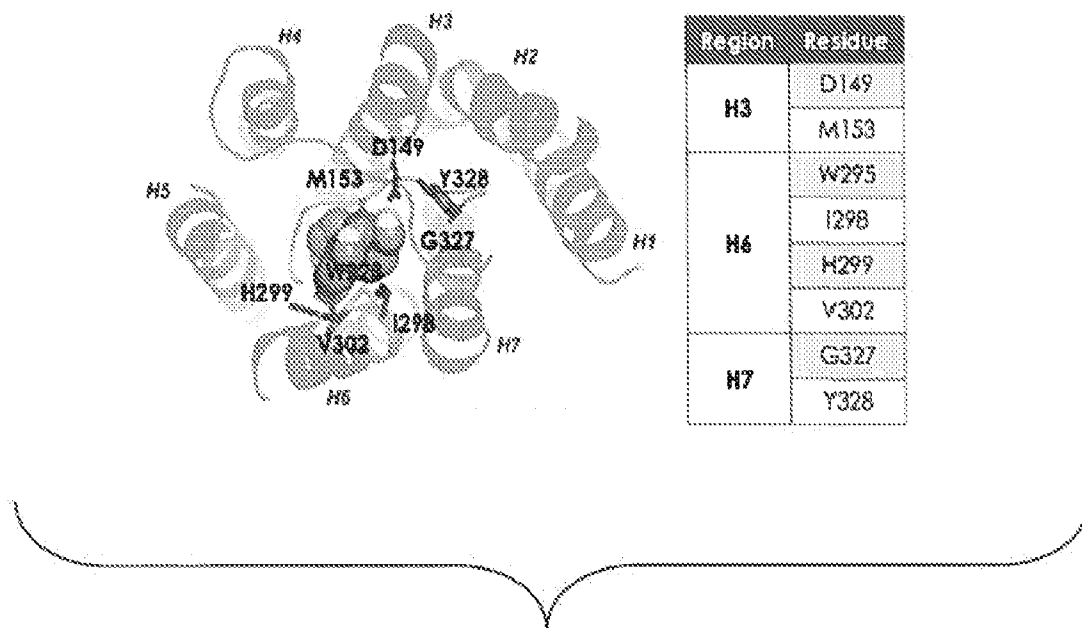


FIG. 18

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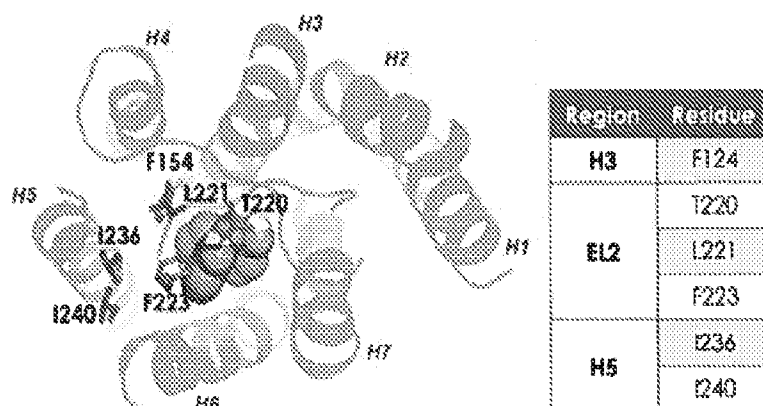


FIG. 19

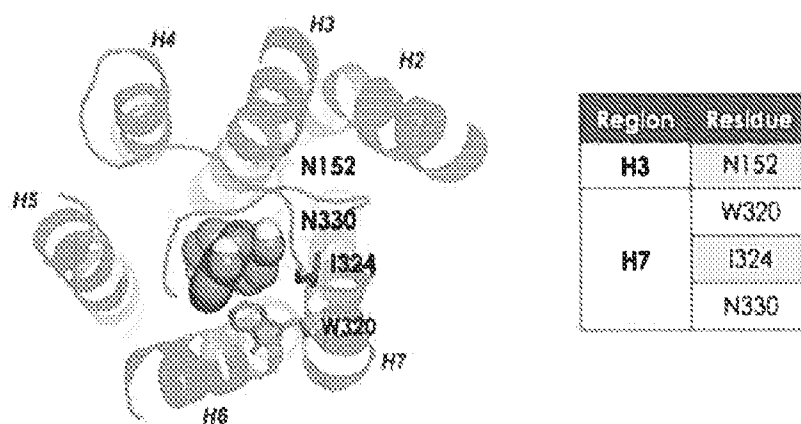


FIG. 20

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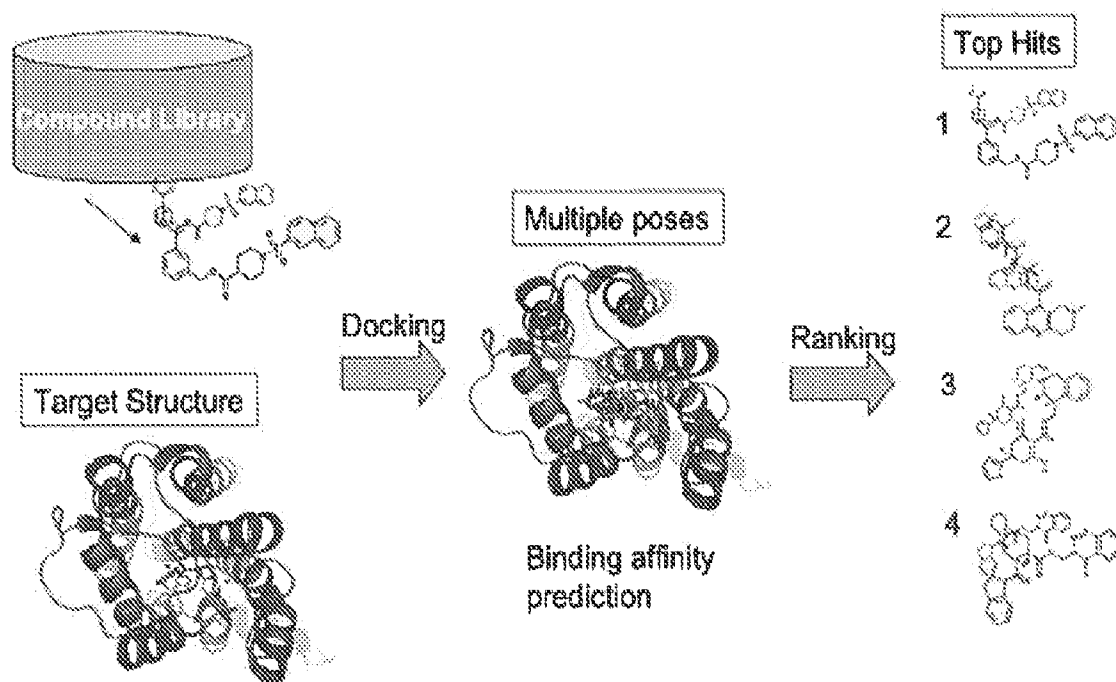


FIG. 21