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(71) Applicant (for all designated States except US): N.V. ORGANON [NL/NL]; Kloosterstraat 6, NL-5349 Ab Oss (NL).

(72) Inventors; and

(75) Inventors/Applicants (for US only): DASSE, Olivier [FR/US]; 24 Carillon Place, Foothill Ranch, CA 92610 (US). PARROTT, Jeff, A. [US/US]; 52 Reunion, Irvine,

CA 92603 (US). PUTMAN, David [US/US]; 26 Silveroak, Irvine, CA 92620 (US). ADAM, Julia [GB/GB]; 57 Hailes Gardens, Edinburgh EH13 OJH (GB).

(74) Agent: HESS, Susan; Organon International Inc., Patent Department, 56 Livingston Avenue, Roseland, NJ 07068 (US).

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[Continued on next page]

(54) Title: THERAPEUTIC RELEASE AGENTS

FIGURE 1

 Drug Name 5-Hydroxytryptamine, Serotonin, 5-HT Chemical Name 3-(2-Aminoethyl)-5-hydroxy-1H-indole	 Drug Name Morphine Chemical Name (Salpha,6alpha)-4,5-Epoxy-7,8-didehydro-17-methylmorphinan-3,6-diol	 Drug Name Isoproterenol hydrochloride, Isoprenaline hydrochloride, Isuprel hydrochloride, Vapo-Iso, Norisodrine Chemical Name 4-[1-Hydroxy-2-(isopropylamino)ethyl]benzene-1,2-diol hydrochloride
 Drug Name Dopamine Chemical Name 4-(2-Aminoethyl)-1,2-benzenediol	 Drug Name Norepinephrine, Noradrenaline Chemical Name (-)-4-[2-Amino-1(R)-hydroxyethyl]-1,2-benzenediol	 Drug Name Aurintricarboxylic acid Chemical Name 5-[(3-Carboxy-4-hydroxyphenyl)(3-carboxy-4-oxo-2,5-cyclohexadien-1-ylidene)methyl]-2-hydroxybenzoic acid
 Drug Name Amodiaquine, SN-10751, Camoquin, Flavoquin Chemical Name 4-(7-Chloroquinolin-4-ylamino)-2-(diethylaminomethyl)phenol	 Drug Name Cannabidiol, CBD, Nabidiol Chemical Name 2-[6(R)-Isopropenyl-3-methyl-2-cyclohexen-1(R)-yl]-5-pentyl-1,3-benzenediol	 Drug Name Phenylephrine hydrochloride, SLV-325, Biomydrin, Alcon Efrin, Mydrin, Nostril, Neo-Synephrine hydrochloride, Incostop Chemical Name (-)-3-[1(R)-Hydroxy-2-(methylamino)ethyl]phenol hydrochloride
 Drug Name Acetaminophen, Paracetamol, Efferalgan, Febrectal, Dolgesic, Tylenol, Perfalgan, Feverall, Fensum, Melabon, Calonal Chemical Name N-(4-Hydroxyphenyl)acetamide	 Drug Name SN-38 Chemical Name 7-Ethyl-10-hydroxycamptothecin; 4(S),11-Diethyl-4,9-dihydroxy-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14-dione	 Drug Name Estradiol, 17beta-Estradiol, NSC-9895, S-21400, SL-1100, Diogyn, Aerodiol, Bio-E-Gel, Estrace, Vagifem, Diogynets, Progyon, Aquadiol, Evorel, Estring Chemical Name (17beta)-Estra-1,3,5(10)-triene-3,17-diol

(57) Abstract: Pharmacological inhibition of fatty acid amide hydrolase (FAAH) activity leads to increased levels of fatty acid amides. Esters of alkylcarbamic acids are disclosed that are inhibitors of FAAH activity. Compounds disclosed herein inhibit FAAH activity. Described herein are processes for the preparation of esters of alkylcarbamic acid compounds, compositions that include them, and methods of use thereof.



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THERAPEUTIC RELEASE AGENTS

FIELD OF THE INVENTION

[0001] Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments containing such compounds, and methods of using such compounds and compositions that are inhibitors of amidases, such as, for example, fatty acid amide hydrolase (FAAH), and upon inhibition of the amidase, release a therapeutic agent.

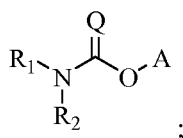
BACKGROUND OF THE INVENTION

[0002] Amidases are a class of enzymes that result in the hydrolysis of amide bonds. Amidases, such as fatty acid amide hydrolase (FAAH), hydrolyze the fatty acid amide (FAA) family of endogenous signaling lipids. General classes of FAAs include the N-acylethanolamines (NAEs) and fatty acid primary amides (FAPAs). Examples of NAEs include anandamide (AEA), palmitoylethanolamide (PEA) and oleoylethanolamide (OEA). Pharmacological inhibition of amidase activity, such as FAAH activity, results in increases in the levels of these fatty acid amides.

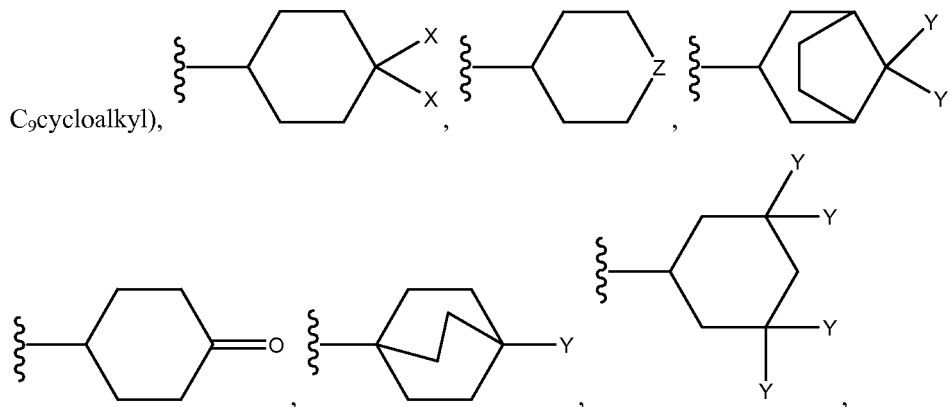
SUMMARY OF THE INVENTION

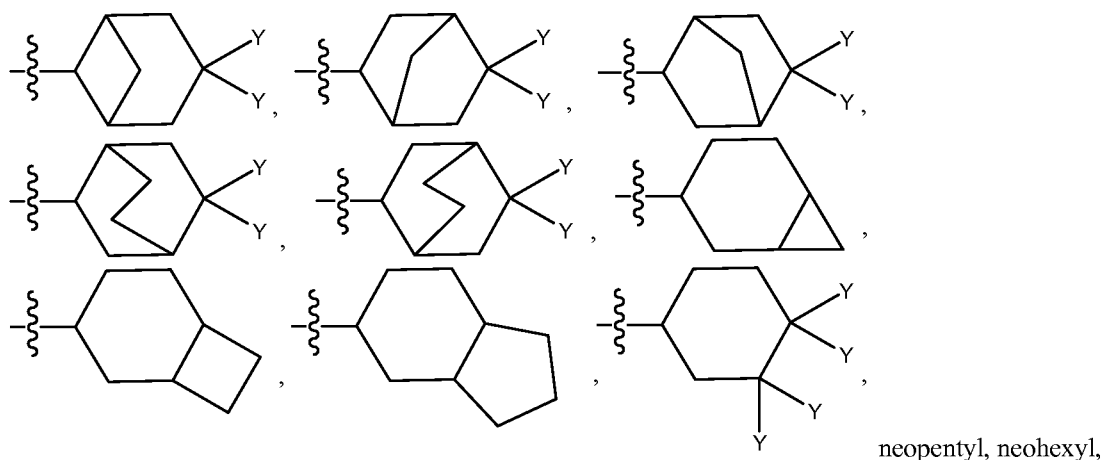
[0003] Compounds, compositions and methods for inhibiting the activity of amidases, such as for example, fatty acid amide hydrolase (FAAH) are provided. Compounds disclosed herein, upon inhibition of amidases, such as FAAH, release a therapeutic agent. Compounds, compositions and methods for inhibiting the activity of amidases, such as fatty acid amide hydrolase (FAAH) while concomitantly treating a disease, disorder, or condition related to FAAH inhibition are also provided. Among the compounds provided herein are FAAH inhibitors which release a therapeutic agent useful for treating a disease, disorder, or condition.

[0004] In one aspect is a compound having the formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-





methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R_2 is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C_1 - C_6 alkyl), or SO_2 ;

Q is O or S; and

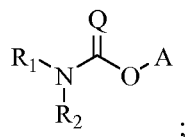
O-A is a deprotonated form of a hydroxy containing therapeutic agent; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

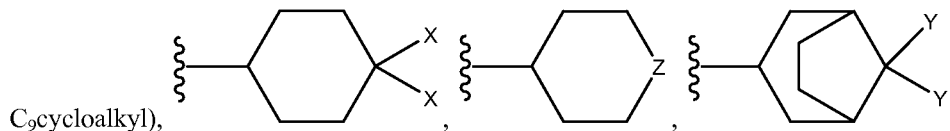
[0005] In one embodiment is a method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of formula (I).

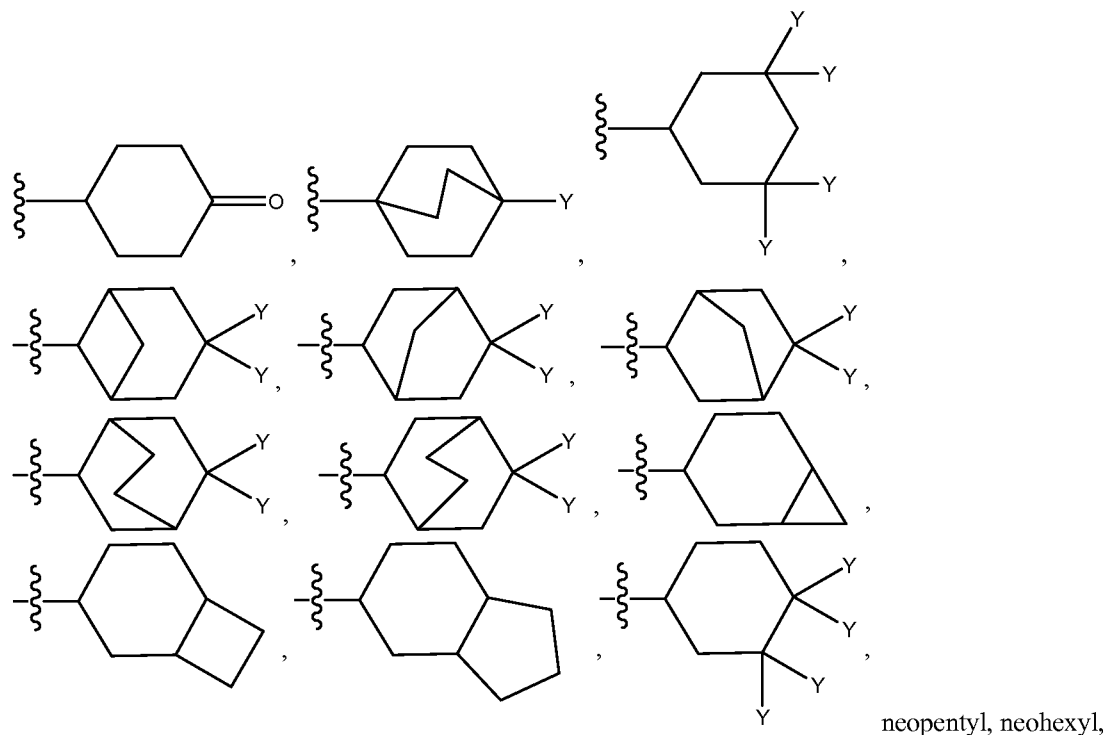
[0006] In another embodiment is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient.

[0007] In another embodiment is a compound having the formula (I):



wherein R_1 is an optionally substituted group selected from among C_1 - C_8 alkyl, C_3 - C_9 cycloalkyl, C_1 - C_4 alkyl-(C_3 -





methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

O-A is a deprotonated form of a hydroxy containing therapeutic agent; wherein the therapeutic agent is an

endocannabinoid, a hydroxy containing endocannabinoid derivative, a cannabinoid, a hydroxy containing cannabinoid derivative, a FAAH inhibitor, a hydroxy containing FAAH inhibitor derivative, an anandamide membrane transport inhibitor, a hydroxy containing anandamide membrane transport inhibitor derivative, a TRPV1 vanilloid receptor modulator, a hydroxy containing TRPV1 vanilloid receptor modulator derivative, serotonin or a serotonin-like compound, tyrosine or a tyrosine-like compound, acetaminophen or an acetaminophen-like compound, an NSAID, a hydroxy containing NSAID derivative, an anesthetic agent, a hydroxy containing anesthetic agent, a therapeutic agent used to treat metabolic disorders, a hydroxy containing derivative of a therapeutic agent used to treat metabolic disorders, an antihyperlipidemic agent, a hydroxy containing derivative of an antihyperlipidemic agent, a statin, a hydroxy containing statin derivative, a PPAR agonist, a hydroxy containing PPAR agonist derivative, a PPAR γ agonist, a hydroxy containing PPAR γ agonist derivative, a PPAR α agonist, a hydroxy containing PPAR α agonist derivative, a hypolipidemic agent, a hydroxy containing derivative of a hypolipidemic agent, an anti-diabetic agent, a hydroxy containing derivative

of an anti-diabetic agent, ezetimibe or ezetimibe-like compound, an anti-hypertensive agent, a hydroxy containing derivative of an anti-hypertensive agent, a decongestant agent, a hydroxy containing derivative of a decongestant agent, a phytochemical, a hydroxy containing phytochemical derivative, a phenethylamine, a hydroxy containing phenethylamine derivative, an anti-oxidant, a hydroxy containing derivative of an anti-oxidant, a vitamin, and a hydroxy containing derivative of a vitamin; and

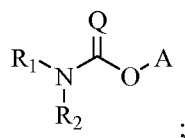
pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

[0008] In another embodiment is a method of treating a patient in need comprising administering to the patient a therapeutically effective amount of a compound of formula (I) wherein the therapeutic agent is an endocannabinoid, a hydroxy containing endocannabinoid derivative, a cannabinoid, a hydroxy containing cannabinoid derivative, a FAAH inhibitor, a hydroxy containing FAAH inhibitor derivative, an anandamide membrane transport inhibitor, a hydroxy containing anandamide membrane transport inhibitor derivative, a TRPV1 vanilloid receptor modulator, a hydroxy containing TRPV1 vanilloid receptor modulator derivative, serotonin or a serotonin-like compound, tyrosine or a tyrosine-like compound, acetaminophen or an acetaminophen-like compound, an NSAID, a hydroxy containing NSAID derivative, an anesthetic agent, a hydroxy containing anesthetic agent, a therapeutic agent used to treat metabolic disorders, a hydroxy containing derivative of a therapeutic agent used to treat metabolic disorders, an antihyperlipidemic agent, a hydroxy containing derivative of an antihyperlipidemic agent, a statin, a hydroxy containing statin derivative, a PPAR agonist, a hydroxy containing PPAR agonist derivative, a PPAR γ agonist, a hydroxy containing PPAR γ agonist derivative, a PPAR α agonist, a hydroxy containing PPAR α agonist derivative, a hypolipidemic agent, a hydroxy containing derivative of a hypolipidemic agent, an anti-diabetic agent, a hydroxy containing derivative of an anti-diabetic agent, ezetimibe or ezetimibe-like compound, an anti-hypertensive agent, a hydroxy containing derivative of an anti-hypertensive agent, a decongestant agent, a hydroxy containing derivative of a decongestant agent, a phytochemical, a hydroxy containing phytochemical derivative, a phenethylamine, a hydroxy containing phenethylamine derivative, an anti-oxidant, a hydroxy containing derivative of an anti-oxidant, a vitamin, and a hydroxy containing derivative of a vitamin.

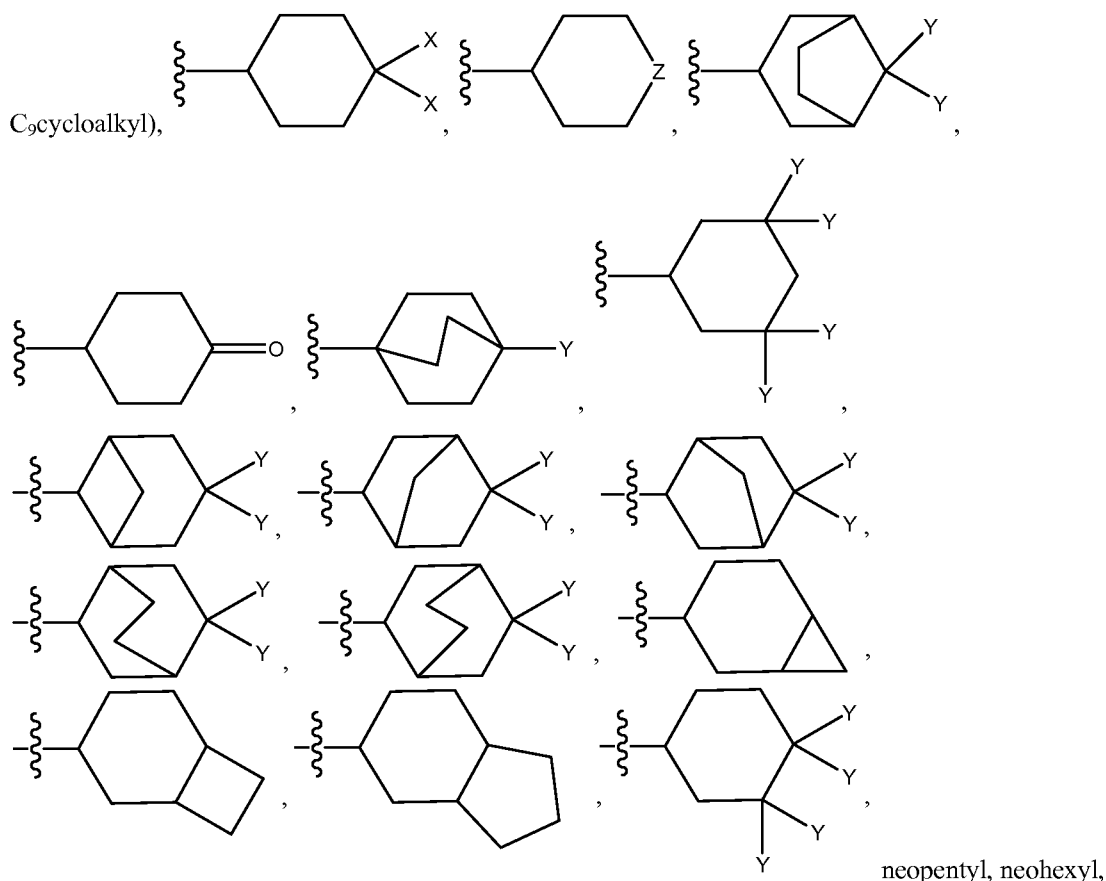
[0009] In another embodiment, is a pharmaceutical composition comprising a compound of formula (I) wherein the therapeutic agent is an endocannabinoid, a hydroxy containing endocannabinoid derivative, a cannabinoid, a hydroxy containing cannabinoid derivative, a FAAH inhibitor, a hydroxy containing FAAH inhibitor derivative, an anandamide membrane transport inhibitor, a hydroxy containing anandamide membrane transport inhibitor derivative, a TRPV1 vanilloid receptor modulator, a hydroxy containing TRPV1 vanilloid receptor modulator derivative, serotonin or a serotonin-like compound, tyrosine or a tyrosine-like compound, acetaminophen or an acetaminophen-like compound, an NSAID, a hydroxy containing NSAID derivative, an anesthetic agent, a hydroxy containing anesthetic agent, a therapeutic agent used to treat metabolic disorders, a hydroxy containing derivative of a therapeutic agent used to treat metabolic disorders, an antihyperlipidemic agent, a hydroxy containing derivative of an antihyperlipidemic agent, a statin, a hydroxy containing statin derivative, a PPAR agonist, a hydroxy containing PPAR agonist derivative, a PPAR γ agonist, a hydroxy

containing PPAR γ agonist derivative, a PPAR α agonist, a hydroxy containing PPAR α agonist derivative, a hypolipidemic agent, a hydroxy containing derivative of a hypolipidemic agent, an anti-diabetic agent, a hydroxy containing derivative of an anti-diabetic agent, ezetimibe or ezetimibe-like compound, an anti-hypertensive agent, a hydroxy containing derivative of an anti-hypertensive agent, a decongestant agent, a hydroxy containing derivative of a decongestant agent, a phytochemical, a hydroxy containing phytochemical derivative, a phenethylamine, a hydroxy containing phenethylamine derivative, an anti-oxidant, a hydroxy containing derivative of an anti-oxidant, a vitamin, and a hydroxy containing derivative of a vitamin; and a pharmaceutically acceptable excipient.

[0010] In another embodiment are compounds of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

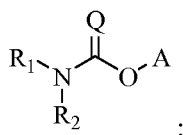
each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

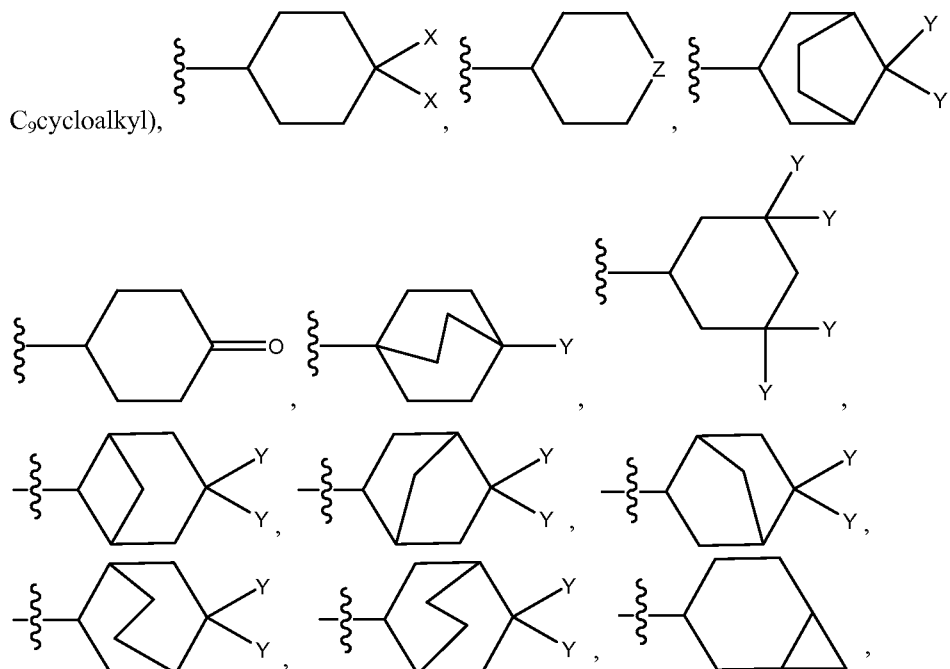
Q is O or S; and

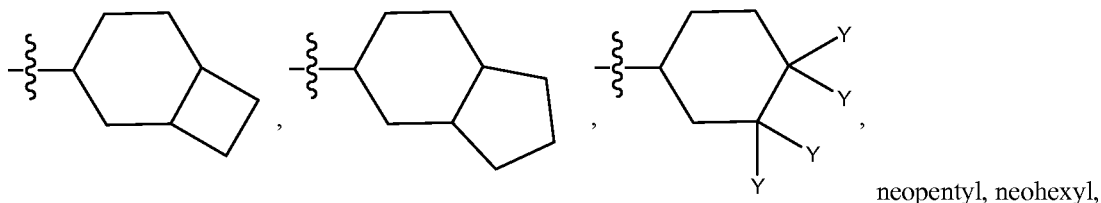
O-A is a deprotonated form of a hydroxy containing agent as provided in Section **aa** or a deprotonated form of a hydroxy containing derivative of a therapeutic agent as provided in Section **aa**; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof. In another embodiment is a method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of formula (I) wherein O-A is a deprotonated form of a hydroxy containing agent as provided in Section **aa** or a deprotonated form of a hydroxy containing derivative of a therapeutic agent as provided in Section **aa**. In another embodiment is a pharmaceutical composition comprising a compound of formula (I) wherein O-A is a deprotonated form of a hydroxy containing agent as provided in Section **aa** or a deprotonated form of a hydroxy containing derivative of a therapeutic agent as provided in Section **aa** and a pharmaceutically acceptable excipient. In another embodiment is a compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-





methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R_2 is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

O-A is a deprotonated form of a hydroxy containing agent as provided in Figures 1-4 or a deprotonated form of a hydroxy containing derivative of an agent as provided in Figures 1-4; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof. In a further embodiment is a method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of formula (I) wherein O-A is a deprotonated form of a hydroxy containing agent as provided in Figures 1-4 or a deprotonated form of a hydroxy containing derivative of an agent as provided in Figures 1-4. In another embodiment is a pharmaceutical composition comprising a compound of formula (I) wherein O-A is a deprotonated form of a hydroxy containing agent as provided in Figures 1-4 or a deprotonated form of a hydroxy containing derivative of an agent as provided in Figures 1-4 and a pharmaceutically acceptable excipient.

[0011] In some embodiments, compounds provided herein are administered to a human.

[0012] In some embodiments, compounds provided herein are orally administered.

[0013] In some embodiments, compounds provided herein are used for inhibiting fatty acid amide hydrolase (FAAH) activity. In some embodiments, compounds provided herein are used for inhibiting the activity of fatty acid amide hydrolase activity or for the treatment of a disease or condition that would benefit from inhibition of fatty acid amide hydrolase activity.

[0014] Articles of manufacture containing packaging material, a compound or composition or pharmaceutically acceptable derivative thereof provided herein, which is effective for inhibiting the activity of fatty acid amide hydrolase (FAAH), within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is used for inhibiting the activity of fatty acid amide hydrolase (FAAH), are provided.

[0015] Any of the combinations of the groups described above for the various variables is contemplated herein.

[0016] Other objects, features and advantages of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the present disclosure will become apparent to those skilled in the art from this detailed description. All references cited herein, including patents, patent applications, and publications, are hereby incorporated by reference in their entirety.

INCORPORATION BY REFERENCE

[0017] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE FIGURES

[0018] A better understanding of the features and advantages of the present compositions and methods may be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of our compositions, methods are utilized, and the accompanying drawings of which:

[0019] FIG. 1 presents illustrative, non-limiting examples of a deprotonated form of a hydroxy containing therapeutic agent.

[0020] FIG. 2 presents illustrative, non-limiting examples of a deprotonated form of a hydroxy containing therapeutic agent.

[0021] FIG. 3 presents illustrative, non-limiting examples of a deprotonated form of a hydroxy containing therapeutic agent.

[0022] FIG. 4 presents illustrative, non-limiting examples of a deprotonated form of a hydroxy containing therapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

[0023] Disclosed herein are carbamate compounds that inhibit the activity of amidases, such as for example, fatty acid amide hydrolase (FAAH), compositions that include the compounds, and methods of their use. Carbamate compounds disclosed herein are inhibitors of amidases, such as, for example, fatty acid amide hydrolase (FAAH), and are useful in the treatment of diseases, disorders, or conditions that would benefit from the inhibition of amidases, such as, for example, fatty acid amide hydrolase, and increases in endogenous fatty acid amides. Carbamate compounds disclosed herein, upon inhibition of amidases, such as, for example, fatty acid amide hydrolase (FAAH), release a therapeutic agent containing at least one aromatic moiety bearing at least one hydroxy moiety. In some embodiments, the therapeutic agent that is released upon inhibition of an amidase enzyme by the carbamate compounds described herein are hydroxy metabolites of therapeutic agents that: 1) contain at least one aromatic moiety bearing at least one hydroxy moiety; and 2) retain the same type of activity as the parent therapeutic agent.

[0024] The released therapeutic agents will be able to provide additional or alternatives modes of treatment for diseases, disorders, or conditions, as compared to treatment of diseases, disorders, or conditions that involve inhibition of amidase inhibition alone, such as, for example, FAAH inhibition alone.

[0025] In some embodiments, the compounds of Formula (I) provided herein are selectively metabolized by amidases, such as for example, the FAAH enzyme. In certain embodiments, the compounds provided herein are metabolized by amidases, such as, for example, FAAH, resulting in inhibition of the amidase enzyme. In some embodiments, compounds provided herein are metabolized by amidases, such as for example, the FAAH enzyme, resulting in the inhibition of amidase activity, such as, for example, FAAH activity, and formation of a therapeutic agent that contains at least one aromatic moiety bearing at least one hydroxy moiety. In other embodiments, compounds provided herein are metabolized by amidases, such as, for example, the FAAH enzyme, resulting in inhibition of the amidase activity, and formation of an hydroxy metabolite of a therapeutic agent, wherein the hydroxy metabolite of the therapeutic agent contains at least one aromatic moiety bearing at least one hydroxy moiety. Thus, the compounds provided herein can exhibit two different phases of activity when administered to a patient. In the initial stage, inhibition of amidase activity, such as for example, inhibition of FAAH enzyme activity, is observed. In the subsequent or concurrent stage, increasing levels of a therapeutic agent or hydroxy metabolite of a therapeutic agent is observed. In some embodiments, compounds provided herein are expected to have reduced renal toxicity compared to conventional treatments that include a therapeutic agent, which contains at least one aromatic moiety bearing at least one hydroxy moiety.

FAAH Belongs to the Amidase Family of Proteins

[0026] FAAH is a member of a family of enzymes that hydrolyze fatty acid amide bonds, named amidases. Amidases have a highly conserved central region rich in glycine, serine and alanine residues. This region was defined as the signature sequence (corresponding to amino acids 215–257 in mammalian FAAH proteins) and 17 other stable positions scattered throughout the sequence were noted. (Chebrou H., *et al.*, Study of the amidase signature group. *Biochim Biophys Acta* 1996; 1298: 285–293; Kobayashi M., *et al.* Identification of active sites in amidase: evolutionary relationship between amide bond- and peptide bond-cleaving enzymes. *Proc Natl Acad Sci USA* 1997; 94: 11986–11991).

[0027] The first mammalian amidase to be cloned was from rat and was called FAAH. The definition of the conserved regions has grown to include amino acids 134–257. More than 80 enzymes containing this region belong to the amidase signature family. (Patricelli M. P., Cravatt B. F. Proteins regulating the biosynthesis and inactivation of neuromodulatory fatty acid amides. *Vitam Horm* 2001; 62: 95–131).

[0028] Domains in human FAAH, mouse FAAH (Giang D. K., Cravatt B. F. Molecular characterization of human and mouse fatty acid amide hydrolases. *Proc Natl Acad Sci USA* 1997; 94: 2238–2242.), rat (Cravatt B. F., *et al.* Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. *Nature* 1996; 384:83–87), and porcine (Goparaju S. K., *et al.* Enzymes of porcine brain hydrolyzing 2-arachidonoylglycerol, an endogenous ligand of cannabinoid receptors. *Biochem Pharmacol* 1999; 57: 417–423) FAAH enzymes are 73% identical at the amino acid level overall and 90% identical in the amidase signature sequence between amino acids 215–257. While the mRNAs differ in size across species, the FAAH proteins are all 579 amino acids in length. In the amino terminus there is a predicted transmembrane domain (Cravatt B. F., *et al.* Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. *Nature* 1996; 384: 83–87).

[0029] Anandamide and certain other fatty acid amides (e.g., N-palmitoyl ethanolamine, N-oleoyl ethanolamide, oleamide, 2-arachidonoylglycerol) are cleaved and inactivated by amidases, such as fatty acid amide hydrolase (FAAH)

(Deutsch et al. 2003 *Prostaglandins Leukot Essent Fatty Acids* 66:201; and Cravatt and Lichtman 2003 *Current Opinion in Chemical Biology* 7:469). Inhibition of FAAH is expected to lead to an increase in the level of anandamide and other fatty acid amides. This increase in fatty acid amides may lead to an increase in the nociceptive threshold. Thus, inhibitors of FAAH are useful in the treatment of pain. Such inhibitors might also be useful in the treatment of other disorders that can be treated using fatty acid amides or modulators of cannabinoid receptors (e.g., anxiety, eating disorders, and cardiovascular disorders).

[0030] NPAA (N-palmitoylethanolamine acid anhydrolase) is a hydrolase that breaks down N-palmitoyl ethanolamine (PEA), a fatty acid amide. Inhibition of NPAA may lead to increased PEA levels. Accordingly, NPAA inhibitors may be useful in, but not limited to, the treatment of inflammation and nociceptive pain control.

[0031] N-palmitoylethanolamine hydrolase is 1.5 times more active with N-palmitoylethanolamine than anandamide. The enzyme is most active at lower pH (about pH 5), and almost inactive at the alkaline optimum pH of FAAH. In the brain, mice lacking FAAH (FAAH^{-/-}) have very low levels of anandamide hydrolytic activity. It is possible that in some tissues this remaining activity results from N-palmitoylethanolamine hydrolase.

[0032] In addition, there is evidence (see, e.g., Weber *et al.* 2004 *J. Lipid Res.* 45:757) that when FAAH activity is reduced or absent, one of its substrates, anandamide, acts as a substrate for COX-2 that can be converted to a prostamide. Thus, certain prostamides may be elevated in the presence of an FAAH inhibitor. Given that certain prostamides are associated with reduced intraocular pressure and ocular hypotensivity, FAAH inhibitors may be useful agents for treating glaucoma.

[0033] Ethanolamides of long-chain fatty acids (collectively referred to as N-acylethanolamines) exist ubiquitously in animal tissues (Hansen, *et al.* (2000) N-Acylethanolamines and precursor phospholipids – relation to injury. *Chem. Phys. Lipids* 108, 135–150; Schmid, *et al.* (2002) Cell signaling by endocannabinoids and their congeners: questions of selectivity and other challenges. *Chem. Phys. Lipids* 121, 111–134; Sugiura, *et al.*, (2002) Biosynthesis and degradation of anandamide and 2-arachidonoylglycerol and their possible physiological significance. *Prostaglandins Leukotrienes Essential Fatty Acids* 66, 173–192). This class of lipids includes several bioactive compounds. N-Arachidonoylethanolamine (anandamide) is well known to be an agonist of cannabinoid receptors (CB1 and CB2) and the vanilloid receptor (VR1) (Devane, *et al.*, (1992) Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 258, 1946–1949; Di Marzo, *et al.*, (2002) Anandamide receptors. *Prostaglandins Leukotrienes Essential Fatty Acids* 66, 377–391). N-Palmitoylethanolamine does not activate cannabinoid receptors, but shows anti-inflammatory and analgesic effects (Calignano, A., *et al.*, (1998) Control of pain initiation by endogenous cannabinoids. *Nature* (London) 394, 277–281; Lambert, *et al.*, (2002). The palmitoylethanolamide family: a new class of anti-inflammatory agents? *Curr. Med. Chem.* 9, 663–674). N-Oleoylethanolamine has been reported to have an anorexic effect (Rodríguez de Fonseca, *et al.*, (2001) An anorexic lipid mediator regulated by feeding. *Nature* (London) **414**, 209–212) through activation of the nuclear receptor PPAR-alpha (peroxisome proliferator-activated receptor-alpha) (Fu, *et al.*, (2003) Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR- α . *Nature* (London) **425**, 90–93). N-Stearoylethanolamine has an apoptosis-inducing effect (Maccarrone, *et al.*, (2002) Binding, degradation and apoptotic activity of stearoylethanolamide in rat C6 glioma cells. *Biochem. J.* **366**, 137–144).

The Endocannabinoid System

[0034] The endocannabinoid signaling system is composed of three elements (Lambert *et al. J. Med. Chem.* 2005, vol. 48, no. 16, 5059-5087). The first is represented by the G protein-coupled receptors that bind endogenous and exogenous cannabinoid ligands. Two such receptors have been identified, the CB₁ receptor, which is found almost everywhere in the body, but is most abundant in the central nervous system (CNS) (Freund *et al. Physiol. Rev.* 2003; 83:1017-1066); and the CB₂ receptor, which is primarily expressed in immune cells and in hematopoietic cells, but is also present at low levels in the brain (Munro *et al. Nature*, 1993; 365:61-65; Van Sickle *et al. Science* 2005; 310:329-332; Hanus *et al., Proc. Nat. Acad. Sci., U.S.A.*, 1999; 96:14228-14233).

[0035] The second element is represented by the endocannabinoids, naturally occurring lipid molecules that bind to and activate cannabinoid receptors (Devane *et al. Science* 1992;258:1946-1949; Mechoulam *et al. Biochem. Pharmacol.* 1995;50:83-90; Sugria *et al. Biochem. Biophys. Res. Commun.* 1995; 215:89-97), are generated on demand by neurons and other cells (Di Marzo *et al. Nature* 1994; 372: 686-691; Giuffrida *et al. Nat. Neurosci.* 1999; 2:358-363; Stella *et al. Nature* 2001; 388:773-778), and are rapidly eliminated (Beltramo *et al. FEBS Lett.* 1997; 403:263-267; Stella *et al. Nature* 2001; 388:773-778).

[0036] The third element is represented by the proteins involved in the formation and elimination of the various endocannabinoid ligands (Piomelli, D. *Nat Rev. Neurosci.* 2003;4:873-884).

[0037] Cannabinoid receptors can be activated by endocannabinoids, as well as synthetic ligands.

[0038] Anandamide (arachidonylethanolamide) was the first endocannabinoid substance to be discovered (Devane *et al. Science* 1992;258:1946-1949; Piomelli, D. *Nat Rev. Neurosci.* 2003;4:873-884). Current evidence indicates that this lipid-derived mediator is released upon demand by stimulated neurons (Di Marzo *et al. Nature*, 1994;372:686-691; Giuffrida *et al. Nat. Neurosci.* 1999, 2:358-363); activates cannabinoid receptors with high potency (Devane *et al. Science* 1992;258:1946-1949), and is rapidly eliminated through a two-step process consisting of carrier-mediated internalization followed by intracellular hydrolysis (metabolism) (Beltramo *et al. Science* 1997; 277:1094-1097; Di Marzo *et al. Nature* 1994; 372:686-691; Hillard *et al. J. Lipid Res.* 1997; 38:2383-2398).

[0039] The endocannabinoids anandamide and 2-arachidonylglycerol (2-AG), both of which produce most of their effects by binding to the CB₁ receptor, have been shown to be tonically released and can control basal nociceptive thresholds (Meng *et al., Nature* 1998;Sep 24;395(6700):381-3). In particular, anandamide acts as a CB₁ agonist and exhibits pharmacological activity in mice comparable to other synthetic cannabinoids.

Fatty Acid Amide Hydrolase (FAAH)

[0040] Fatty acid amide hydrolase (FAAH) is an enzyme that hydrolyzes the fatty acid amide (FAA) family of endogenous signaling lipids. General classes of fatty acid amides include the N-acylethanolamines (NAEs) and fatty acid primary amides (FAPAs). Examples of NAEs include anandamide (AEA), palmitoylethanolamide (PEA) and oleoylethanolamide (OEA). An example of FAPAs includes 9-Z-octadecenamide or oleamide. (McKinney MK, Cravatt BF. 2005. *Annu Rev Biochem* 74:411-32)]. FAAH can act as a hydrolytic enzyme not only for fatty acid ethanolamides and primary amides, but also for esters, such as, for example, 2-arachidonylglycerol (2-AG) (Mechoulam *et al. Biochem. Pharmacol.* 1995; 50:83-90; Stella *et al. Nature*, 1997; 388:773-778; Sugria *et al. Biochem. Biophys. Res. Commun.* 1995; 215:89-97).

[0041] FAAH is abundantly expressed throughout the CNS (Freund *et al. Physiol. Rev.* 2003; 83:1017-1066) as well as in peripheral tissues, such as, for example, in the pancreas, brain, kidney, skeletal muscle, placenta, and liver (Giang, D.K. *et al. Molecular Characterization of Human and Mouse Fatty Acid Amide Hydrolases. Proc. Natl. Acad. Sci. U.S.A.* 1997, 94, 2238-2242; Cravatt *et al. PNAS*, 2004, vol. 101, no. 29, 10821-10826.).

[0042] Anandamide, or arachidonylethanolamide, is a NAE that acts as an endogenous ligand for the cannabinoid type 1 (CB₁) receptor (Devane WA, *et al.* 1992. *Science* 25 8:1946-49). Anandamide is rapidly eliminated through a two-step process consisting of carrier-mediated transport followed by intracellular hydrolysis by FAAH. The hydrolysis of anandamide by FAAH results in the formation of arachidonic acid and ethanolamine. The current postulated catalytic mechanism for hydrolysis of anandamide by FAAH involves nucleophilic attack of amino acid residue Serine 241 of FAAH on the amide moiety of anandamide, resulting in the formation of arachidonic acid and ethanolamine (Deutsch *et al. The fatty acid amide hydrolase (FAAH) Prostaglandins, Leukotrienes and Essential Fatty Acids* (2002) 66 (2&3), 201-210; Alexander *et al. Chemistry & Biology*, vol. 12, 1179-1187; 2005).

[0043] Mutant mice lacking the gene encoding for FAAH display a profound reduction in hydrolysis activity for anandamide and other fatty acid amides and show signs of enhanced anandamide activity at cannabinoid receptors, leading to observable physiological phenomena such as reduced pain sensation (Cravatt BF, *et al.* 2001. *Proc Nat Acad Sci USA* 98: 9371-9376). This suggests that therapeutic agents that alter the activity of the FAAH enzyme can increase the actions of anandamide and other fatty acid amides in the body. Such agents may also avoid the multiple, often undesirable effects produced by indiscriminant activation of cannabinoid receptors by administration of Δ^9 -THC (the active ingredient in marijuana) and other direct-acting cannabinoids.

[0044] Many endogenous fatty acid amides, other than anandamide, do not bind the CB₁ receptor. Several of these lipids have been shown to produce specific cellular and behavioral effects, and may represent a large family of endogenous signaling lipids that act *in vivo* on receptor systems distinct from CB₁. These include palmitoylethanolamide (PEA) (Calignano A, *et al.* 1998. *Nature* 394:277-8 1; Jaggar SI, *et al.* 1998. *Pain* 76:189-99; Franklin A, Parmentier-Batteur *et al.* 2003. *J Neurosci* 23: 7767-75), stearoylethanolamide (SEA) (Terrazino *et al.* 2004 FASEB J: 18:1580-82; Maccarrone M, *et al.* 2002. *Biochem J* 366:137-44), and oleoylethanolamide (OEA) (deFonseca FR, *et al.* 2001. *Nature* 414:209-12; Fu J, *et al.* 2003. *Nature* 425:90-93; Fu J, *et al.* 2005. *Neuropharmacology* 48(8):1 147-53). Both OEA and PEA have been shown to activate peroxisome proliferator-activated receptor alpha (PPAR-alpha) (Fu J, *et al.* 2003. *Nature* 425:90-93; Guzman M, *et al.* 2004, *J Biol Chem* 279(27): 27849-54; Lo Verme J, *et al.* 2005. *Cell Mol Life Sci* 62(6): 708-16; LoVerme J, *et al.* 2005. *Life Sci* 77(14): 1685-98; Lo Verme J, *et al.* 2005. *Mol Pharmacol* 67(1): 15-9). Through these actions, OEA and PEA can regulate several biological pathways including, but not limited to, feeding, metabolism, pain and inflammation. Therefore, agents that alter FAAH enzymatic activity can regulate the levels of a variety of fatty acid amides *in vivo* that, in turn, have therapeutic actions through a variety of targets.

[0045] Without being bound by theory, it is thought that certain fatty acid amides, such as, for example, OEA, act through the peroxisome proliferator-activated receptor α (PPAR- α) to regulate diverse physiological processes, including, e.g., feeding and lipolysis. Consistent with this, human adipose tissue has been shown to bind and metabolize endocannabinoids such as anandamide and 2-arachidonylglycerol. See Spoto *et al.*, August 22, 2006, *Biochimie* (E-publication ahead of print); and Matias *et al.* (2006), *J. Clin. Endocrin. & Met.*, 91(8):3171-3180. Thus, inhibiting

FAAH activity *in vivo* leads to reduced body fat, body weight, caloric intake, and liver triglyceride levels. However, unlike, other anti-lipidemic agents that act through PPAR- α , e.g., fibrates, FAAH inhibitors do not cause adverse side effects such as rash, fatigue, headache, erectile dysfunction, and, more rarely, anemia, leukopenia, angioedema, and hepatitis. See e.g., Muscari *et al.* (2002), *Cardiology*, 97:115-121. An additional therapeutic property of FAAH inhibitors is that due to their ability to elevate anandamide levels, they effectively alleviate depression and anxiety, conditions often associated with energy metabolism disorders (EMDs) such as obesity. See Simon *et al.* (2006), *Archives of Gen. Psychiatry*, 63(7):824-830. In some embodiments, FAAH inhibitor compounds may be peripherally restricted and may not substantially affect neural disorders, such as, for example, depression and anxiety. Finally, agonism of cannabinoid receptors has also been shown to reduce the progression of atherosclerosis in animal models. See Steffens *et al.* (2005), *Nature*, 434:782-786; and Steffens *et al.* (2006), *Curr. Opin. Lipid.*, 17:519-526. Thus, increasing the level of endogenous cannabinergic fatty acid amides (e.g., anandamide) is expected to effectively treat or reduce the risk of developing atherosclerosis.

[0046] Many fatty acid amides are produced on demand and rapidly degraded by FAAH. As a result, hydrolysis by FAAH is considered to be one of the essential steps in the regulation of fatty acid amide levels in the central nervous system as well as in peripheral tissues and fluids. The broad distribution of FAAH combined with the broad array of biological effects of fatty acid amides (both endocannabinoid and non-endocannabinoid mechanisms) suggests that inhibition of FAAH may lead to altered levels of fatty acid amides in many tissues and fluids and may be useful to treat many different conditions. FAAH inhibitors increase the levels of endogenous fatty acid amides. FAAH inhibitors block the degradation of endocannabinoids and increase the tissue levels of these endogenous substances. FAAH inhibitors can be used in this respect in the prevention and treatment of pathologies in which endogenous cannabinoids and or any other substrates metabolized by the FAAH enzyme are involved.

[0047] Inhibition of FAAH is expected to lead to an increase in the level of anandamide and other fatty acid amides. This increase in fatty acid amides may lead to an increase in the noiceptive threshold. Thus, in one embodiment, inhibitors of FAAH are useful in the treatment of pain. Such inhibitors might also be useful in the treatment of other disorders that can be treated using fatty acid amides or modulators of cannabinoid receptors, such as, for example, anxiety, eating disorders, metabolic disorders, cardiovascular disorders, and inflammation.

[0048] The various fatty acid ethanolamides have important and diverse physiological functions. As a result, inhibitor molecules that selectively inhibit FAAH enzymatic activity would allow a corresponding selective modulation of the cellular and extra-cellular concentrations of a FAAH substrate. FAAH inhibitors that are biologically compatible could be effective pharmaceutical compounds when formulated as therapeutic agents for any clinical indication where FAAH enzymatic inhibition is desired. In some embodiments, FAAH activity in peripheral tissues can be preferentially inhibited. In some embodiments, FAAH inhibitors that do substantially cross the blood-brain-barrier can be used to preferentially inhibit FAAH activity in peripheral tissues. In some embodiments, FAAH inhibitors that preferentially inhibit FAAH activity in peripheral tissues can minimize the effects of FAAH inhibition in the central nervous system. In some embodiments, it is preferred to inhibit FAAH activity in peripheral tissues and minimize FAAH inhibition in the central nervous system.

[0049] Diseases, disorders, syndromes and/or conditions, that would benefit from inhibition of FAAH enzymatic activity include, for example, Alzheimer's Disease, schizophrenia, depression, alcoholism, addiction, suicide, Parkinson's disease, Huntington's disease, stroke, emesis, miscarriage, embryo implantation, endotoxic shock, liver cirrhosis, atherosclerosis, cancer, traumatic head injury, glaucoma, and bone cement implantation syndrome.

[0050] Other diseases, disorders, syndromes and/or conditions that would benefit from inhibition of FAAH activity, include, for example, multiple sclerosis, retinitis, amyotrophic lateral sclerosis, immunodeficiency virus-induced encephalitis, attention-deficit hyperactivity disorder, pain, nociceptive pain, neuropathic pain, inflammatory pain, non-inflammatory pain, painful hemorrhagic cystitis, obesity, hyperlipidemia, metabolic disorders, feeding and fasting, alteration of appetite, stress, memory, aging, hypertension, septic shock, cardiogenic shock, intestinal inflammation and motility, irritable bowel syndrome, colitis, diarrhea, ileitis, ischemia, cerebral ischemia, hepatic ischemia, myocardial infarction, cerebral excitotoxicity, seizures, febrile seizures, neurotoxicity, neuropathies, sleep, induction of sleep, prolongation of sleep, insomnia, and inflammatory diseases.

[0051] Neurological and psychological disorders that would benefit from inhibition of FAAH activity include, for example, pain, depression, anxiety, generalized anxiety disorder (GAD), obsessive compulsive disorders, stress, stress urinary incontinence, attention deficit hyperactivity disorders, schizophrenia, psychosis, Parkinson's disease, muscle spasticity, epilepsy, diskensia, seizure disorders, jet lag, and insomnia.

[0052] FAAH inhibitors can also be used in the treatment of a variety of metabolic syndromes, diseases, disorders and/or conditions, including but not limited to, insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, obesity, atherosclerosis and arteriosclerosis.

[0053] FAAH inhibitors are useful in the treatment of a variety of painful syndromes, diseases, disorders and/or conditions, including but not limited to those characterized by non-inflammatory pain, inflammatory pain, peripheral neuropathic pain, central pain, deafferentation pain, chronic nociceptive pain, stimulus of nociceptive receptors, phantom and transient acute pain.

[0054] Inhibition of FAAH activity can also be used in the treatment of a variety of conditions involving inflammation. These conditions include, but are not limited to arthritis (such as rheumatoid arthritis, shoulder tendonitis or bursitis, gouty arthritis, and aolymyalgia rheumatica), organ-specific inflammatory diseases (such as thyroiditis, hepatitis, inflammatory bowel diseases), asthma, other autoimmune diseases (such as multiple sclerosis), chronic obstructive pulmonary disease (COPD), allergic rhinitis, and cardiovascular diseases.

[0055] In some cases, FAAH inhibitors are useful in preventing neurodegeneration or for neuroprotection.

[0056] In addition, it has been shown that when FAAH activity is reduced or absent, one of its substrates, anandamide, acts as a substrate for COX-2, which converts anandamide to prostamides (Weber *et al. J. Lipid. Res.* 2004; 45:757). Concentrations of certain prostamides may be elevated in the presence of a FAAH inhibitor. Certain prostamides are associated with reduced intraocular pressure and ocular hypotensivity. Thus, in one embodiment, FAAH inhibitors may be useful for treating glaucoma.

[0057] In some embodiments, FAAH inhibitors can be used to treat or reduce the risk of EMDs, which include, but are not limited to, obesity, appetite disorders, overweight, cellulite, Type I and Type II diabetes, hyperglycemia, dyslipidemia, steatohepatitis, liver steatosis, non-alcoholic steatohepatitis, Syndrome X, insulin resistance, diabetic

dyslipidemia, anorexia, bulimia, anorexia nervosa, hyperlipidemia, hypertriglyceridemia, atherosclerosis, arteriosclerosis, inflammatory disorders or conditions, Alzheimer's disease, Crohn's disease, vascular inflammation, inflammatory bowel disorders, rheumatoid arthritis, asthma, thrombosis, or cachexia.

[0058] In other embodiments, FAAH inhibitors can be used to treat or reduce the risk of insulin resistance syndrome and diabetes, i.e., both primary essential diabetes such as Type I Diabetes or Type II Diabetes and secondary nonessential diabetes. Administering a composition containing a therapeutically effective amount of an *in vivo* FAAH inhibitor reduces the severity of a symptom of diabetes or the risk of developing a symptom of diabetes, such as atherosclerosis, hypertension, hyperlipidemia, liver steatosis, nephropathy, neuropathy, retinopathy, foot ulceration, or cataracts.

[0059] In another embodiment, FAAH inhibitors can be used to treat food abuse behaviors, especially those liable to cause excess weight, e.g., bulimia, appetite for sugars or fats, and non-insulin-dependent diabetes.

[0060] In some embodiments, FAAH inhibitors can be used to treat a subject suffering from an EMD and also suffers from a depressive disorder or from an anxiety disorder. Preferably, the subject is diagnosed as suffering from the depressive or psychiatric disorder prior to administration of the FAAH inhibitor composition. Thus, a dose of a FAAH inhibitor that is therapeutically effective for both the EMD and the depressive or anxiety disorder is administered to the subject. Methods for treatment of anxiety and depressive disorders by FAAH inhibition are described in, e.g., U.S. Patent Application Nos. 10/681,858 and 60/755,035.

[0061] Preferably, the subject to be treated is human. However, the methods can also be used to treat non-human mammals. Animal models of EMDs such as those described in, e.g., U.S. Patent No. 6,946,491 are particularly useful.

[0062] Symptoms, diagnostic tests, and prognostic tests for each of the above-mentioned conditions are known in the art. See, e.g., "Harrison's Principles of Internal Medicine©," 16th ed., 2004, The McGraw-Hill Companies, Inc., and the "Diagnostic and Statistical Manual of Mental Disorders©," 4th ed., 1994, American Psychiatric Association.

[0063] FAAH inhibitor compositions can also be used to decrease body-weight in individuals wishing to decrease their body weight for cosmetic, but not necessarily medical considerations.

[0064] A FAAH inhibitor composition can be administered in combination with a drug for lowering circulating cholesterol levels (e.g., statins, niacin, fibric acid derivatives, or bile acid binding resins). FAAH inhibitor compositions can also be used in combination with a weight loss drug, e.g., orlistat or an appetite suppressant such as diethylpropion, mazindole, orlistat, phendimetrazine, phentermine, or sibutramine.

[0065] The methods described herein can also include providing an exercise regimen or providing a calorie-restricted diet (e.g., a triglyceride-restricted diet) to the subject.

[0066] Esters of alkylcarbamic acids and alkylthiocarbamic acids have shown promise as selective FAAH inhibitors (Kathuria *et al.*, *Nat. Med.* 2003, 9:76-81). A series of alkylcarbamic acid aryl esters, such as, for example, cyclohexylcarbamic acid 3'-carbamoylbiphenyl-3-yl ester (also known as 5'-carbamoylbiphenyl-3-yl cyclohexyl carbamate, UCM597, URB597, and KDS-4103 (URB-597)), have been shown to be potent and selective inhibitors of FAAH activity. Alkylcarbamic acid aryl esters, such as, for example, cyclohexylcarbamic acid 3'-carbamoylbiphenyl-3-yl ester, have been shown to be potent and selective inhibitors of FAAH activity, which do not significantly interact with

selected serine hydrolases or with cannabinoid receptors (Mor *et al.* *J. Med. Chem.* 2004, 47:4998-5008; Piomelli *et al.* International Patent Publication No. WO 2004/033422; incorporated by reference).

Benefits of Therapeutic Release Agents

[0067] Alkylcarbamic acid aryl esters inhibit FAAH activity through an irreversible interaction with FAAH, possibly due to a nucleophilic attack of an active serine residue (Serine 241) of FAAH on the carbamate moiety of the alkylcarbamic acid aryl ester compounds (Kathuria *et al.* *Nature Medicine*, vol. 9, no. 1, 76-81, 2003; Deutsch *et al.* *Prostaglandins, Leukotrienes and Essential Fatty Acids* (2002) 66(2&3), 201-210; Alexander *et al.* *Chemistry & Biology*, vol. 12, 1179-1187; 2005). Metabolism of the alkylcarbamic acid aryl ester inhibitors by the FAAH enzyme results in the hydrolysis of the carbamate compounds and release of the aryloxy portion of the alkylcarbamic acid aryl ester inhibitor. Carbamate compounds disclosed herein, such as for example, compounds of Formula (I), are metabolized by amidases, such as for example, FAAH. Carbamate compounds disclosed herein, such as for example, compounds of Formula (I), are hydrolyzed by amidases, such as FAAH, and release a therapeutic agent that contains at least one aromatic ring that is functionalized with at least one hydroxy moiety. Thus, the metabolism of the carbamate compounds of Formula (I) by amidases results in the release of a second therapeutic agent.

[0068] In some embodiments are FAAH inhibitors that bind to the FAAH enzyme thereby releasing a therapeutic agent having an arylhydroxy moiety. In other embodiments, are FAAH inhibitors that bind reversibly to the FAAH enzyme thereby releasing a therapeutic agent having an arylhydroxy moiety. In a further embodiment, are partially irreversible FAAH inhibitors which partially irreversibly bind to the FAAH enzyme thereby releasing a therapeutic agent having an arylhydroxy moiety in that partial irreversible inhibition occurs under physiological conditions. In a further embodiment are FAAH inhibitors which modulate the FAAH enzyme thereby releasing a therapeutic release agent having an arylhydroxy moiety.

[0069] The use of multiple drugs may target multiple targets, multiple subpopulations, or multiple diseases simultaneously. The use of multiple drugs with different mechanisms or modes of action may also direct the effect against a single target or a disease and treat it more effectively. The possible favorable outcomes for synergism include 1) increasing the efficacy of the therapeutic effect, 2) decreasing the dosage but increasing or maintaining the same efficacy to avoid toxicity, 3) minimizing or slowing down the development of drug resistance, and 4) providing selective synergism against target (or efficacy synergism) versus host (or toxicity antagonism). For these therapeutic benefits, drug combinations have been widely used and became the leading choice for treating the most dreadful diseases, such as cancer and infectious diseases, including AIDS.

[0070] In some embodiments, the carbamate compounds described herein and the therapeutic agent that is released upon metabolism of the carbamate compound by an amidase, such as, for example, FAAH, have similar basic modes of action.

[0071] In other embodiments, the carbamate compounds described herein and the therapeutic agent that is released upon metabolism of the carbamate compound by an amidase, such as, for example, FAAH, have totally independent modes of action.

[0072] In some other embodiments, the carbamate compounds described herein and the therapeutic agent that is released upon metabolism of the carbamate compound by an amidase, such as, for example, FAAH, have an effect that is additive of the effects of the carbamate compound alone and the effects of the therapeutic agent alone.

[0073] In some other embodiments, the carbamate compounds described herein and the therapeutic agent that is released upon metabolism of the carbamate compound by an amidase, such as, for example, FAAH, have an effect that is greater than the additive effects of the effects of the carbamate compound alone and the effects of the therapeutic agent alone.

[0074] In some embodiments, the carbamate compounds described herein and the therapeutic agent that is released upon metabolism of the carbamate compound by an amidase, such as, for example, FAAH, have an effect that is greater than the effects of the carbamate compound alone (e.g., amidase inhibition alone).

[0075] In some other embodiments, the carbamate compounds described herein and the therapeutic agent that is released upon metabolism of the carbamate compound by an amidase, such as, for example, FAAH, have an effect that is greater than the effects of the therapeutic agent alone.

Synergistic Effects

[0076] Inhibition of FAAH is expected to lead to an increase in the level of anandamide and other fatty acid amides. Thus, an increase in the level of fatty acid amides due to FAAH inhibition may be used to treat diseases, disorders, or conditions involving inflammation. In one embodiment, FAAH inhibitors having an arylhydroxy therapeutic release agent may be used to treat conditions involving inflammation. While not being bound by theory, metabolism of the FAAH inhibitor by the FAAH enzyme results in the hydrolysis of the carbamate and releases the therapeutic agent having an arylhydroxy portion. Thus, in one embodiment, the FAAH inhibitor synergistically treats diseases, disorders, or conditions involving inflammation by releasing the therapeutic agent having an arylhydroxy portion that is useful for treating inflammation. In another embodiment, a FAAH inhibitor may contain a nonsteroidal anti-inflammatory drug (NSAID) as the arylhydroxy releasing agent. Such inhibitors may synergistically inhibit COX activity. By way of example only, a FAAH inhibitor containing diflunisal, a generic NSAID having an arylhydroxy portion, which acts by inhibiting the production of prostaglandin, may be used to treat inflammation in conditions such as arthritis. Or, by way of example only, a FAAH inhibitor containing magnesium salicyclate as the arylhydroxy releasing agent may be used to synergistically treat inflammation, pain, or fever. In other embodiments, the released therapeutic agent may be an arylhydroxy metabolite of compounds which treat inflammatory conditions. In other embodiments, the use of FAAH inhibitors having an arylhydroxy releasing agent may be used in a variety of painful diseases, disorders, conditions, including but not limited to those characterized by non-inflammatory pain, inflammatory pain, peripheral neuropathic pain, central pain, deafferentation pain, chronic nociceptive pain, stimulus of nociceptive receptors, phantom and transient acute pain.

Therapeutic Release Agents and FAAH inhibition side effects

[0077] Synergism of the FAAH inhibitor containing an arylhydroxy releasing therapeutic agent may be used to obtain the desired effect at doses to which side effects are minimal. By way of example only, a patient may be treated for a disease, disorder, or condition which benefits from FAAH inhibition, such as metabolic syndromes, diseases, disorders and/or conditions, including but not limited to, insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease,

obesity, atherosclerosis and arteriosclerosis, while concomitantly being treated for a side effect of the FAAH inhibition, such as nausea, through the benefit of the released arylhydroxy containing therapeutic agent. The therapeutic agent which contains the released arylhydroxy portion may be, by way of example only, an antiemetic. For example, a patient being treated for obesity via use of a FAAH inhibitor may also be treated for nausea. Such a treatment may be realized by release of the arylhydroxy containing therapeutic agent via hydrolysis of the FAAH inhibitor. For example, a FAAH inhibitor having carvacrol as the arylhydroxy portion of the alkylcarbamic acid aryl ester inhibitor may treat conditions related to obesity as well as treat nausea, a common side effect of obesity treatment. Carvacrol, a constituent of the etherial oil of *Origanum hirtum*, and which also may be synthesized, is found to be a treatment for nausea and vomiting. In some embodiments, the arylhydroxy containing therapeutic agent may treat side effects related to the treatment of Alzheimer's Disease, schizophrenia, depression, alcoholism, addiction, suicide, Parkinson's disease, Huntington's disease, stroke, emesis, miscarriage, embryo implantation, endotoxic shock, liver cirrhosis, cancer, traumatic head injury, glaucoma and bone cement implantation syndrome. In other embodiments, the arylhydroxy containing therapeutic agent may treat side effects related to the treatment of a variety of painful syndromes, diseases, disorders and/or conditions, including but not limited to those characterized by non-inflammatory pain, inflammatory pain, peripheral neuropathic pain, central pain, deafferentation pain, chronic nociceptive pain, stimulus of nociceptive receptors, phantom and transient acute pain. In other embodiments, the arylhydroxy containing therapeutic agent may treat side effects related to the treatment of inflammation, including but not limited to arthritis (such as rheumatoid arthritis, shoulder tendonitis or bursitis, gouty arthritis, and polymyalgia rheumatica), organ-specific inflammatory diseases (such as thyroiditis, hepatitis, inflammatory bowel diseases), asthma, other autoimmune diseases (such as multiple sclerosis), chronic obstructive pulmonary disease (COPD), allergic rhinitis, and cardiovascular diseases. In some embodiments, the arylhydroxy containing therapeutic agent may counteract or modulate a potentially unwarranted effect of the FAAH inhibitor.

[0078] In some embodiments, the arylhydroxy containing therapeutic agent may treat side effects such as, but not limited to, headaches, infection, nausea, diarrhea, generalized pain, asthenia, abdominal pain, dizziness, myalgia, fever, back pain, vomiting, SGPT elevation, and dyspepsia.

[0079] In some instances, the arylhydroxy containing therapeutic agent may treat side effects related to the prevention of neurodegeneration or for neuroprotection.

Therapeutic Release Agents and Localized FAAH inhibition

[0080] FAAH inhibitors, provided herein, may inhibit the FAAH enzyme in areas where FAAH is expressed or where FAAH may be found. For example, FAAH inhibitors may act in the CNS, particularly in the neocortex, hippocampus, basal ganglia, or in the pancreas, brain, kidney, skeletal muscle, placenta, and liver. Subsequently, localized delivery of the FAAH inhibitor to areas where FAAH is expressed or found may increase the efficacy and/or decrease toxicity and potentially modify biodistribution of an arylhydroxy containing therapeutic agent which is released by hydrolysis of the carbamate moiety of the FAAH inhibitor. Such FAAH inhibitor localization may enable a therapeutic concentration of the arylhydroxy containing therapeutic agent to be administered to the desired target without exposing the entire body to a similar dose.

[0081] As disclosed herein, FAAH is detected in the skeletal muscle. In some embodiments, administration of a FAAH inhibitor, provided herein, can inhibit FAAH found in the skeletal muscle while concomitantly treating diseases,

disorders, or conditions related to the skeletal muscle which may benefit from the use of a therapeutic agent released by hydrolysis of the FAAH inhibitor. By way of example only, FAAH inhibitors having an arylhydroxy therapeutic release agent may treat spasticity and/or musculoskeletal conditions including, but not limited to, fibromyalgia, tension headaches, myofascial pain syndrome and mechanical low back or neck pain. In some embodiments, the effectiveness of the released therapeutic agent may be a result of the localization of the FAAH inhibitor in skeletal muscle. In other embodiments, the effectiveness of the released therapeutic agent may be the result of a synergistic effect. In some embodiments, the benefit experienced may be the result of an additive effect of two or more released therapeutic agents. In other embodiments, the released therapeutic agent, resulting from hydrolysis of the FAAH inhibitor, may be an arylhydroxy metabolite of compounds which treat spasticity and/or musculoskeletal conditions.

[0082] As FAAH is abundantly expressed throughout the CNS, FAAH inhibitors having an arylhydroxy therapeutic release agent may treat diseases, disorders, or conditions related to the CNS. By way of example only, FAAH inhibitors having an arylhydroxy therapeutic release agent may treat CNS diseases, disorders, or conditions, such as, amblyopia, brain neoplasms, dementia, encephalitis, epilepsy, basal ganglia diseases, cerebellar diseases, hypothalamic diseases, headache disorders, neuroaxonal dystrophies, intracranial hypotension, intracranial hypertension, CNS bacterial infections, meningitis, myelitis, prion diseases, encephalomyelitis, chronic fatigue syndrome, Angelman Syndrome, palsy, hepatolenticular degeneration, dystonic disorders, choreatic disorders, multiple system atrophy, tic disorders and Parkinson's disease. Traditionally, L-dopa, or 3,4-dihydroxy-L-phenylalanine, is used as a prodrug to increase dopamine levels for the treatment of Parkinson's disease, since it is able to cross the blood-brain barrier whereas dopamine cannot. Once L-dopa has entered the CNS, it is metabolized to dopamine by aromatic-L-amino-acid decarboxylase. Thus, by way of example only, a FAAH inhibitor having an arylhydroxy therapeutic release agent such as L-dopa may be used to treat Parkinson's disease. In some embodiments, the effectiveness of the released therapeutic agent may be a result of the localization of the FAAH inhibitor in the CNS where FAAH is expressed. In other embodiments, the released therapeutic agent may be an arylhydroxy metabolite of known compounds which treats CNS diseases, disorders, or conditions.

[0083] As disclosed herein, FAAH is detected in the liver. In some embodiments, administration of a FAAH inhibitor, provided herein, can inhibit FAAH found in the liver while concomitantly treating diseases, disorders, or conditions related to the liver which may benefit from the use of a therapeutic agent released by hydrolysis of the FAAH inhibitor. By way of example only, FAAH inhibitors having an arylhydroxy therapeutic release agent may treat liver disease/conditions including, but not limited to, Alagille Syndrome, alpha-1-antitrypsin deficiency, autoimmune hepatitis, biliary atresia, chronic hepatitis, cancer of the liver, cirrhosis, liver cysts, fatty liver, galactosemia, Gilbert's Syndrome, primary biliary cirrhosis, hepatitis A, hepatitis B, hepatitis C, primary sclerosing cholangitis, Reye's Syndrome, sarcoidosis, tyrosinemia, Type I glycogen storage disease, Wilson's disease, neonatal hepatitis, non-alcoholic steatohepatitis, porphyria, and hemochromatosis. In some embodiments, the effectiveness of the released therapeutic agent may be a result of the localization of the FAAH inhibitor in the liver. In other embodiments, the released therapeutic agent, resulting from hydrolysis of the FAAH inhibitor, may be an arylhydroxy metabolite of compounds which treat liver diseases.

[0084] In other embodiments, administration of a FAAH inhibitor, provided herein, can inhibit FAAH found in the pancreas, brain, kidney, and placenta while concomitantly treating diseases, disorders, or conditions related to these areas

which may benefit from the use of a therapeutic agent released by hydrolysis of the FAAH inhibitor. In other embodiments, administration of a FAAH inhibitor, provided herein, can inhibit the FAAH enzyme in areas where FAAH is expressed or found.

COMPOUNDS OF FORMULA (I)

[0085] Certain compounds that inhibit the activity of amidases, such as fatty acid amide hydrolase (FAAH), play a role in health. In certain embodiments, amidases inhibitor compounds are useful in treating any of a variety of diseases, disorders or conditions. In certain embodiments, compounds provided herein are selective FAAH inhibitor compounds.

[0086] FAAH inhibitor compositions have been described in U.S. Patent Application Nos. 10/681,858, 60/755,035; U.S. Patent Nos. 6,462,054, 6,949,574 and 6,891,043; International Patent Publication No. WO 04020430, WO 04067498, WO 04099176, WO 05033066, WO 02087569, WO 03065989, WO 9749667, WO 9926584, WO 04033652, and WO 06044617; Cravatt *et al.* *Current Opinion in Chemical Biology*, 2003, 7:469-475.; Kathuria *et al.* *Nature Medicine*, vol. 9, no. 1, pp76-81, 2003.; Tarzia *et al.* *J. Med. Chem.* 2003, 46, 2352-2360.; and Drysdale *et al.* *Current Medicinal Chemistry*, 2003, 10, 2719-2732.

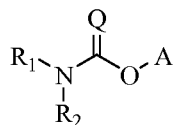
[0087] Also described herein are pharmaceutically acceptable salts, pharmaceutically active metabolites and pharmaceutically acceptable prodrugs of such compounds. Pharmaceutical compositions that include at least one such compound or a pharmaceutically acceptable salt, pharmaceutically active metabolite or pharmaceutically acceptable prodrug of such compound, are provided.

[0088] In some embodiments, compounds provided herein are ionizable and do not substantially cross the blood brain barrier. In some embodiments, provided herein are carbamate FAAH inhibitors that are ionizable at physiological pH, and therefore less likely to cross the blood brain barrier. In some embodiments, compounds provided herein have a moiety that is ionizable at physiological pH. In other embodiments, compounds provided herein have a charge at physiological pH. In some other embodiments, compounds provided herein are protonated at physiological pH. In other embodiments, compounds provided herein are deprotonated at physiological pH. Such FAAH inhibitors are particularly useful when it is desirable to minimize and/or avoid psychotropic effects caused by FAAH inhibition in the central nervous system.

[0089] Any combination of the groups described above for the various variables is contemplated herein. It is understood that substituents and substitution patterns on the compounds provided herein can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be synthesized by techniques known in the art, as well as those set forth herein.

[0090] Fatty acid amides, such as, for example, anandamide, exert their effects at many receptors in the body. For example, anandamide is a target at, but not limited to, the cannabinoid 1 receptor (CB1), cannabinoid 2 receptor (CB2), vanilloid receptor (VR1), cyclo-oxygenase receptors, as well as other receptors in the body. Anandamide is broken down (metabolized) by fatty acid amide hydrolase (FAAH), COX, NPAA, as well as other amidases and other enzymes.

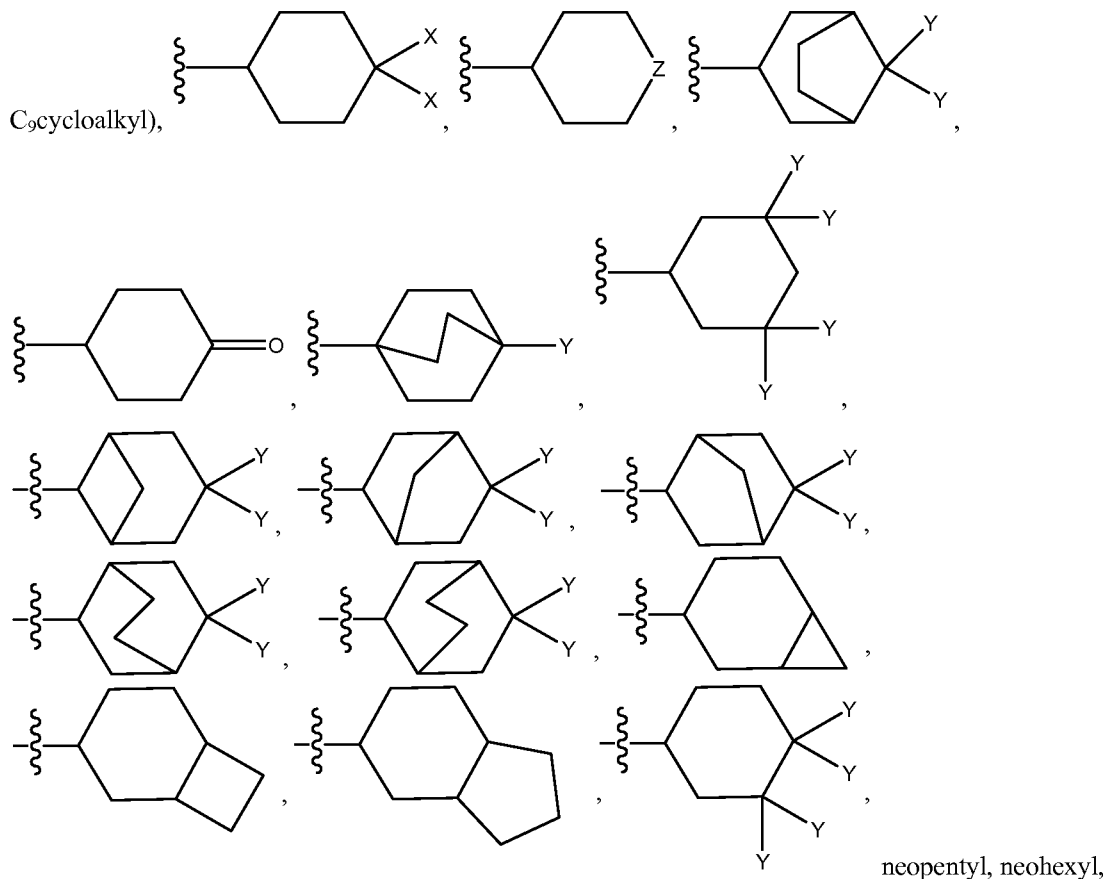
[0091] Certain compounds that inhibit the activity of amidases, such as for example, fatty acid amide hydrolase (FAAH), are described herein. In one aspect, is an inhibitor of an amidase having the structure of Formula (I):



Formula (I),

wherein

R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

O-A is the deprotonated form of a hydroxy containing therapeutic agent disclosed herein;

and pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

[0092] Therapeutic agents, which provide relief to the system they act on, include, but are not limited to: ACE-inhibitors, α -adrenergic agonists, β -adrenergic agonists, α -adrenergic blockers, β -adrenergic blockers, adrenocortical

steroids, analeptic agents, analgesics, anesthetics, angiotensin II receptor antagonists, anti-allergic agents, anti-alopecia agents, anti-amebic agents, anti-anginal agents, anti-asthmatic agents, anti-bacterial agents, anti-bacterial adjuncts, antibiotics, anti-cancer agents, anti-cholesteremic agents, anti-cholinergic agents, anti-convulsants, anti-depressants, anti-diabetic agents, anti-dyskinetic agents, anti-emetics, anti-epileptics, anti-fibrotics, anti-histaminic agents, anti-hypercholesterolemic agents, anti-hyperlipidemic agents, anti-hyperlipoproteinemic agents, anti-hyperparathyroid agents, anti-hyperphosphatemic agents, anti-hypertensives, anti-hyperthyroids, anti-hypotensives, anti-infectives, anti-inflammatory agents, anti-lipemic agents, anti-manic agents, anti-migraine agents, anti-muscarinic agents, anti-mycotic agents, anti-nauseants, anti-neoplastics, anti-obesity agents, anti-obsessional agents, anti-Parkinsonian agents, anti-peristaltic agents, anti-pheochromocytoma agents, anti-pneumocystic agents, anti-progestins, anti-prostatic hypertrophy agents, anti-pruritics, anti-psychotics, anti-peristaltics, anti-pyretics, anti-rheumatics, anti-spasmodics, anti-thrombotics, anti-tumor agents, anti-tussive agents, and anti-vertigo agents.

[0093] In the following embodiments, HOA, which is the protonated form of OA, is a therapeutic agent.

[0094] In the following embodiments (e.g. sections a. through aa), compounds of Formula (I) are further described with respect to HOA, which is the protonated form of OA. OA is released *in vivo* or *in vitro* upon inhibition of amidases by compounds of Formula (I). Upon being released *in vivo* or *in vitro*, OA may or may not be protonated. HOA is used to form compounds of Formula (I).

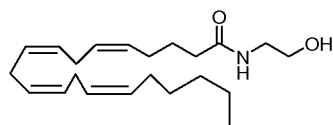
[0095] In some embodiments are FAAH inhibitors

[0096] Therapeutic agents contemplated herein include, but are not limited to: 1) therapeutic agents that contain at least one aromatic ring that is functionalized with at least one hydroxy moiety; 2) therapeutic agents that contain at least one aromatic ring, wherein the at least one aromatic ring is functionalized with at least one hydroxy moiety; and 3) hydroxy metabolites of therapeutic agents, wherein the hydroxy metabolites of therapeutic agents contain at least one aromatic ring that is functionalized with at least one hydroxy moiety.

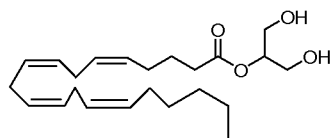
a. Compounds of Formula (I) wherein HOA is an Endocannabinoid

[0097] In one embodiment, provided herein are compounds of Formula (I), wherein OA is the deprotonated form of an endocannabinoid. In some embodiments, are compounds of Formula (I), wherein OA is the deprotonated form of an endogenous endocannabinoid. In one embodiment, carbamate compounds described herein, such as, compounds of Formula (I), are formed from: a) endocannabinoids that include at least one aromatic moiety bearing at least one hydroxy moiety; or b) hydroxy metabolites of endocannabinoids that include at least one aromatic moiety bearing at least one hydroxy moiety. Thus, carbamate compounds formed from endocannabinoids that include at least one aromatic moiety bearing at least one hydroxy moiety will inhibit FAAH and release an endocannabinoid, which will increase the endocannabinoid content.

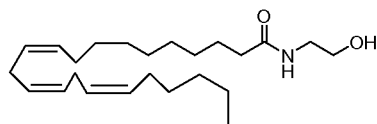
[0098] Endocannabinoids include, but are not limited to:



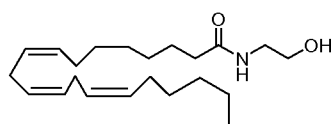
(arachidonylethanolamide; anandamide);



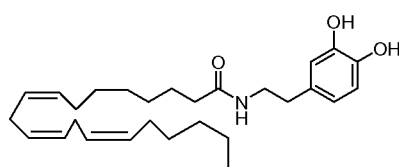
(2-arachidonoylglycerol);



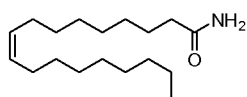
(docosatetraenylethanolamide);



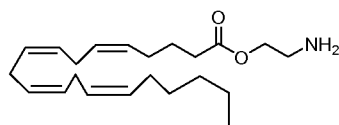
(homo-γ-linolenylethanolamide);



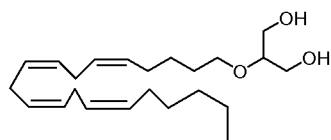
(arachidonyldopamine);



(oleamide);



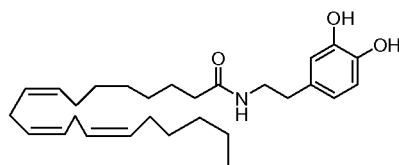
(O-arachidonylethanolamine);



(2-arachidonylglycerol ether; noladin ether).

[0099] Endogenous molecules related to endocannabinoids, include but are not limited to, palmitoylethanolamide, stearoylethanolamide, oleoylethanolamide, arachidonoylglycerine.

[00100] For example, in one embodiment, the endocannabinoid containing at least one aromatic moiety bearing at least one hydroxy moiety, which is used to form carbamates that are FAAH inhibitors, include, but are not limited to:



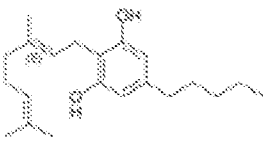
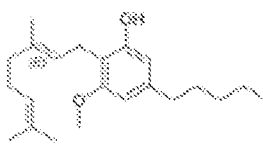
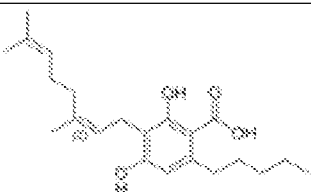
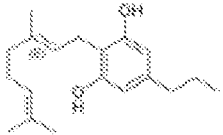
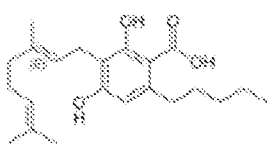
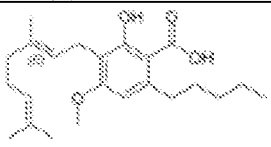
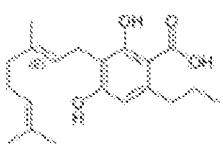
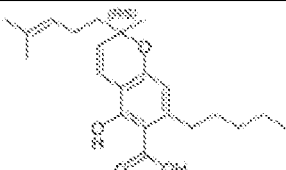
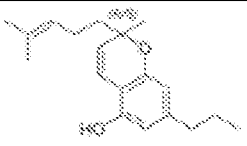
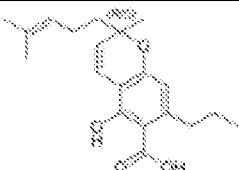
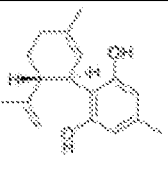
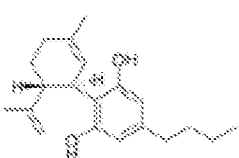
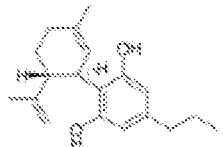
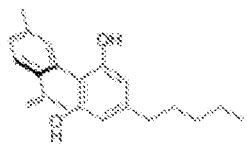
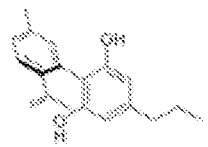
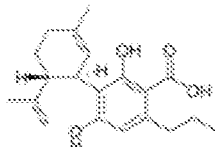
(arachidonyldopamine).

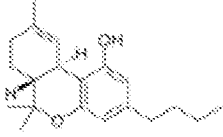
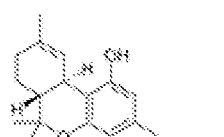
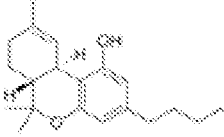
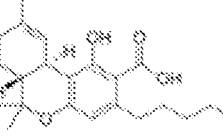
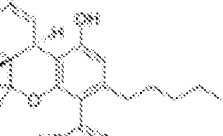
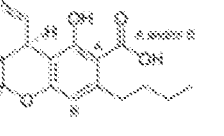
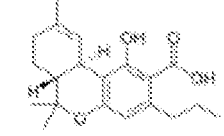
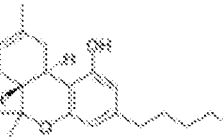
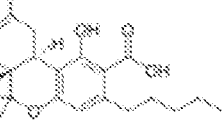
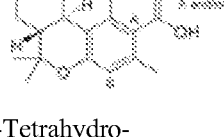
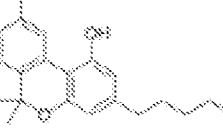
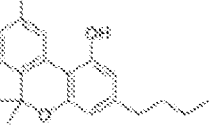
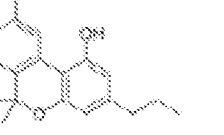
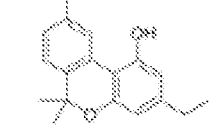
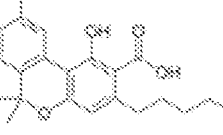
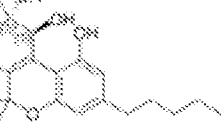
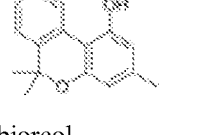
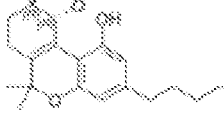
b. Compounds of Formula (I) wherein HOA is a Cannabinoid

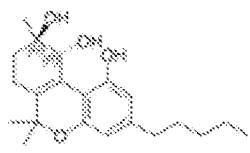
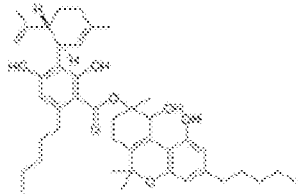
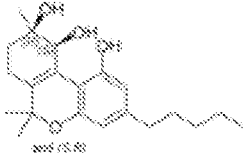
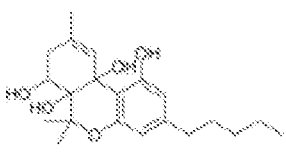
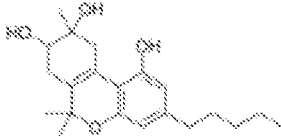
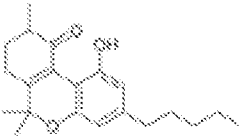
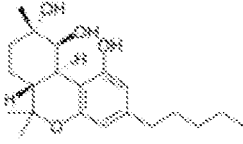
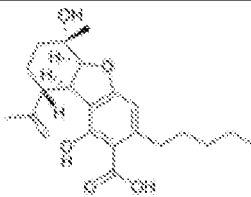
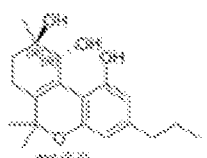
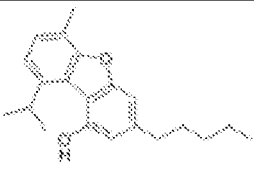
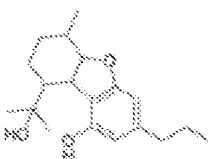
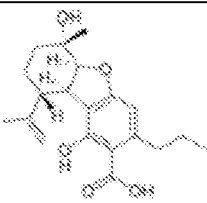
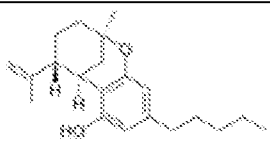
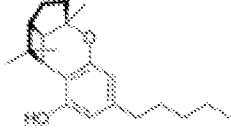
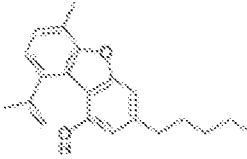
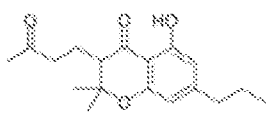
[00101] Cannabinoids interact with the CB1 and/or CB2 receptors. In one embodiment, cannabinoids that contain at least one aromatic moiety bearing at least one hydroxy moiety are used to form carbamate compounds that are inhibitors of FAAH. Thus upon metabolism of the carbamate compounds (derived from cannabinoids) by FAAH, a cannabinoid is released increasing the effects of anandamide or other endocannabinoids at the CB1 and/or CB2 receptors.

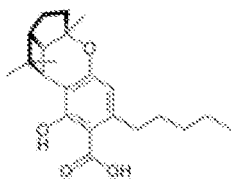
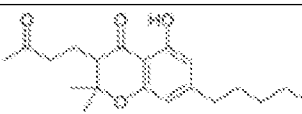
[00102] Cannabinoids contemplated herein include, but are not limited to, those depicted in Table 1.

Table 1. Exemplary Cannabinoids

			
Cannabigerol (<i>E</i>)-CBG-C ₅	Cannabigerol monomethyl ether (<i>E</i>)-CBGM-C ₅ A	Cannabinerolic acid A (<i>Z</i>)-CBGA-C ₅ A	Cannabigerovarín (<i>E</i>)-CBGV-C ₃
			
(±)-Cannabichromene CBC-C ₅	Cannabigerolic acid A (<i>E</i>)-CBGA-C ₅ A	Cannabigerolic acid A monomethyl ether (<i>E</i>)-CBGAM-C ₅ A	Cannabigerovarínic acid A (<i>E</i>)-CBGVA-C ₃ A
			
(±)-Cannabichromenic acid A CBCA-C ₅ A	(±)-Cannabivarichromene, (±)-Cannabichromevarine CBCV-C ₃	(±)-Cannabichromevarinic acid A CBCVA-C ₃ A	Cannabidiol CBD-C ₁
			
(-)-Cannabidiol CBD-C ₅	Cannabidiol monomethyl ether CBDM-C ₅	Cannabidiol-C ₄ CBD-C ₄	(-)-Cannabidivarin CBDV-C ₃
			
Cannabinodiol CBND-C ₅	Cannabinodivarin CBND-C ₃	Cannabidivarinic acid CBDVA-C ₃	Cannabidiolic acid CBDA-C ₅

 Δ^9-Tetrahydrocannabinol- C₄ Δ^9-THC-C₄	 Δ^9-Tetrahydrocannabivarin Δ^9-THCV-C₃	 Δ^9-Tetrahydrocannabiorcol Δ^9-THCO-C₁	 Δ^9-Tetrahydrocannabinol Δ^9-THC-C₅
 Δ^9-Tetrahydro- cannabinolic acid A Δ^9-THCA-C₅ A	 Δ^9-Tetrahydro- cannabinolic acid B Δ^9-THCA-C₅ B	 Δ^9-Tetrahydro- cannabinolic acid-C₄ A and/or B Δ^9-THCA-C₄ A and/or B	 Δ^9-Tetrahydro- cannabivarinic acid A Δ^9-THCVA-C₃ A
 (-)-Δ^8-<i>trans</i>-(6aR,10aR)- Δ^8-Tetrahydrocannabinol Δ^8-THC-C₅	 (-)-Δ^8-<i>trans</i>-(6aR,10aR)- Tetrahydrocannabinolic acid A Δ^8-THCA-C₅ A	 (-)-(6aS,10aR)-Δ^9- Tetrahydrocannabinol (-)-<i>cis</i>-Δ^9-THC-C₅	 Δ^9-Tetrahydro- cannabiorcolic acid A and/or B Δ^9-THCOA-C₁ A and/or B
 Cannabinol CBN-C₅	 Cannabinol-C₄ CBN-C₄	 Cannabivarin CBN-C₃	 Cannabinol-C₂ CBN-C₂
 Cannabinolic acid A CBNA-C₅ A	 (+)-(9S,10S)-Cannabitrinol (+)-<i>trans</i>-CBT-C₅	 Cannabiorcol CBN-C₁	 (-)-(9R,10R)-<i>trans</i>- 10-O-Ethyl-cannabitrinol (-)-<i>trans</i>-CBT-OEt-C₅

 (-)-(9<i>R</i>,10<i>R</i>)-<i>trans</i>-Cannabitrinol (-)-<i>trans</i>-CBT-C₅	 Cannabidiolic acid A cannabitrinol ester CBDA-C₅ 9-OH-CBT-C₅ ester	 (±)-(9<i>R</i>,10<i>S</i>/9<i>S</i>,10<i>R</i>)-Cannabitrinol (±)-<i>cis</i>-CBT-C₅	 (-)-6<i>a</i>,7,10<i>a</i>-Trihydroxy-Δ^9-tetrahydrocannabinol (-)-Cannabitetrol
 8,9-Dihydroxy-$\Delta^{6a(10a)}$-tetrahydrocannabinol 8,9-Di-OH-CBT-C₅	 10-Oxo-$\Delta^{6a(10a)}$-tetrahydrocannabinol OTHC	 (-)-(6<i>aR</i>,9<i>S</i>,10<i>S</i>,10<i>aR</i>)-9,10-Dihydroxy-hexahydrocannabinol, Cannabiripsol Cannabiripsol-C₅	 (5<i>aS</i>,6<i>S</i>,9<i>R</i>,9<i>aR</i>)-C₃-Cannabielsoin CBE-C₃
 (5<i>aS</i>,6<i>S</i>,9<i>R</i>,9<i>aR</i>)-Cannabielsoin CBE-C₅	 (5<i>aS</i>,6<i>S</i>,9<i>R</i>,9<i>aR</i>)-Cannabielsoic acid B CBEA-C₅ B	 (±)-(9<i>R</i>,10<i>R</i>/9<i>S</i>,10<i>S</i>)-Cannabitrinol-C₃ (±)-<i>trans</i>-CBT-C₃	 Cannabifuran CBF-C₅
 (5<i>aS</i>,6<i>S</i>,9<i>R</i>,9<i>aR</i>)-Cannabielsoic acid A CBEA-C₅ A	 Cannabiglendol-C₃ OH-iso-HHCV-C₃	 (5<i>aS</i>,6<i>S</i>,9<i>R</i>,9<i>aR</i>)-C₃-Cannabielsoic acid B CBEA-C₃ B	 (-)-Δ^7-<i>trans</i>-(1<i>R</i>,3<i>R</i>,6<i>R</i>)-Isotetrahydrocannabinol
 (±)-(1<i>aS</i>,3<i>aR</i>,8<i>bR</i>,8<i>cR</i>)-Cannabicyclol	 (±)-(1<i>aS</i>,3<i>aR</i>,8<i>bR</i>,8<i>cR</i>)-Cannabicyclovarin	 Dehydrocannabifuran	 Cannabichromanone-C₃ CBCN-C₃

CBL-C ₅	CBLV-C ₃	DCBF-C ₅	
 (±)-(1a<i>S</i>,3a<i>R</i>,8b<i>R</i>,8c<i>R</i>)- Cannabicyclic acid A CBLA-C₅ A	 (-)-Δ⁷-<i>trans</i>-(1<i>R</i>,3<i>R</i>,6<i>R</i>)- Isotetrahydrocannabivarin	 (±)-Δ⁷-1,2-<i>cis</i>- (1<i>R</i>,3<i>R</i>,6<i>S</i>/1<i>S</i>,3<i>S</i>,6<i>R</i>)- Isotetrahydro- cannabivarin	 Cannabichromanone CBCN-C₅

[00103] In one embodiment, carbamate compounds described herein are formed from CB1 agonist compounds that include at least one aromatic moiety bearing at least one hydroxy moiety.

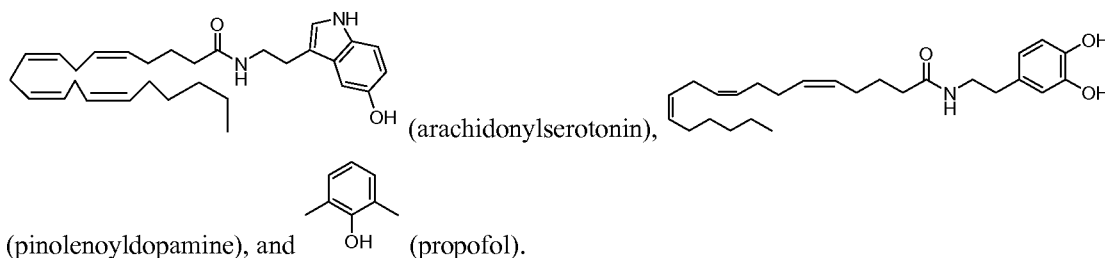
[00104] In one embodiment, carbamate compounds described herein are formed from CB1 inverse agonist compounds that include at least one aromatic moiety bearing at least one hydroxy moiety.

[00105] In one embodiment, carbamate compounds described herein are formed from CB2 agonist compounds that include at least one aromatic moiety bearing at least one hydroxy moiety.

[00106] In one embodiment, carbamate compounds described herein are formed from CB2 inverse agonist compounds that include at least one aromatic moiety bearing at least one hydroxy moiety.

c. Compounds of Formula (I) wherein HOA is a FAAH Inhibitor

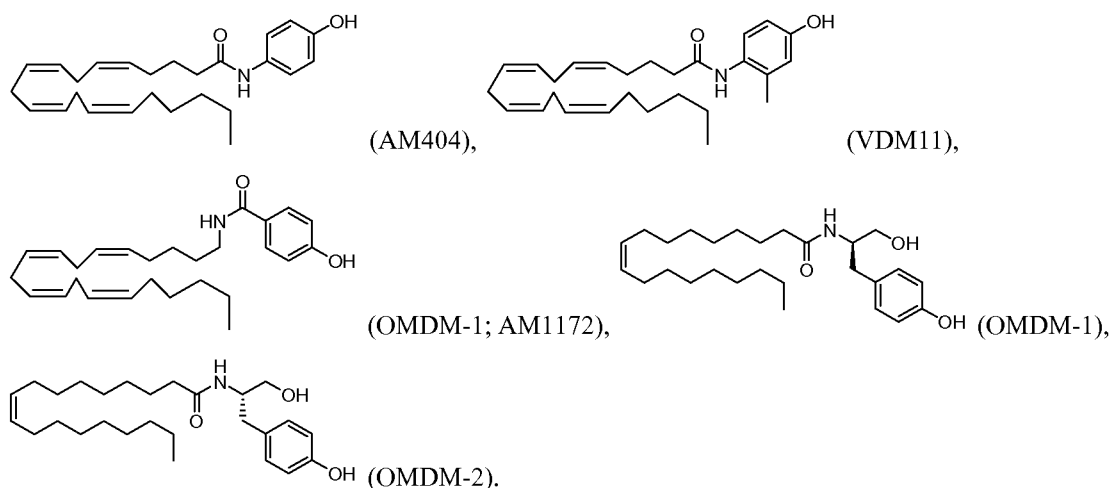
[00107] In one embodiment, carbamate compounds described herein are formed from other FAAH inhibitor compounds that contain at least one aromatic moiety bearing at least one hydroxy moiety. Thus, in one embodiment, carbamates disclosed herein inhibit FAAH and upon inhibition release a second FAAH inhibitor that reversibly or irreversibly inhibit FAAH. For example, the FAAH inhibitor that contains at least one aromatic moiety bearing at least one hydroxy moiety, which is used to form the FAAH carbamate inhibitors described herein, include but are not limited to:



[00108] Other FAAH inhibitor compounds, which contain at least one aromatic moiety bearing at least one hydroxy moiety, that are contemplated herein are disclosed in U.S. Patent Application Nos. 10/681,858, 60/755,035; U.S. Patent Nos. 6,462,054, 6,949,574 and 6,891,043; International Patent Publication No. WO 04020430, WO 04067498, WO 04099176, WO 05033066, WO 02087569, WO 03065989, WO 9749667, WO 9926584, WO 04033652, and WO 06044617; Cravatt *et al.* *Current Opinion in Chemical Biology*, 2003, 7:469-475.; Kathuria *et al.* *Nature Medicine*, vol. 9, no. 1, pp76-81, 2003.; Tarzia *et al.* *J. Med. Chem.* 2003, 46, 2352-2360.; and Drysdale *et al.* *Current Medicinal Chemistry*, 2003, 10, 2719-2732.

d. Compounds of Formula (I) wherein HOA is an Anandamide Membrane Transport Inhibitor

[00109] In another embodiment, carbamate compounds described herein are formed from inhibitors of the anandamide membrane transporter, which contain at least one aromatic moiety bearing at least one hydroxy moiety (Lopez-Rodriguez *et al. Curr Med. Chem. Cent. Nerv. Syst. Agents*, 2004; 4; 155-160; *Bioorg. Med. Chem.* 2004; 12:5161-5169; Lopez-Rodriguez *et al. J. Med. Chem.* 2003; 46:1512-1522; U.S. Patent Publication No. 2004/0209959). Anandamide membrane transporters and FAAH are two possible methods of endocannabinoid inactivation. Simultaneous inhibition of anandamide membrane transporters and FAAH have been shown to elicit neuroprotection through the CB1 receptor (Karanian *et al. The Journal of Neuroscience*, 2005, 25(34), 7813-7820). In one embodiment, carbamates disclosed herein inhibit FAAH and upon inhibition of FAAH release an inhibitor of the anandamide membrane transporter. Thus, compounds that satisfy this embodiment increase the levels of anandamide by preventing anandamide degradation and/or removal from the site of action. For example, inhibitors of the anandamide transporter that contain at least one aromatic moiety bearing at least one hydroxy moiety that are used to form carbamate compounds described herein, which are FAAH inhibitors, include but are not limited to:



e. Compounds of Formula (I) wherein HOA is a TRPV1 Vanilloid Receptor Modulator

[00110] The Vanilloid Receptor 1 (TRPV1) is an ion channel that plays a role in modulating pain and heat perception. TRPV1 Vanilloid receptors are essential for normal thermal nociception and for thermal hyperalgesia induced by inflammation (Caterina, M.J. *et al., Science*, 288, 306-313, 2000).

[00111] The receptor may be activated by heat, low pH, vanilloids, the daphnane diterpenoid resiniferatoxin (RTX), and a range of endogenous mediators encompassing products of the lipoxygenase pathway, bradykinin, and the endocannabinoid anandamide. The numerous activators, often associated with tissue injury or inflammation, appear to operate by reducing the heat threshold of the receptor.

[00112] Vanilloids, such as capsaicin, elicit a biphasic action on sensory neurons characterized by an initial excitatory phase (pain and/or inflammation) followed by desensitization.

[00113] TRPV1 is localized on sensory neurons and has been associated with disease related pain, such as, inflammatory pain, neuropathic pain, acute pain, chronic pain, post-operative pain, migraine, arthralgia, nerve injury, neurodegeneration, neuropathies, diabetic neuropathy, hyperactive urinary bladder, hypersensitive urinary bladder, urinary incontinence, interstitial cystitis, painful bladder disorders, irritable bowel syndrome, inflammatory bowel

disease, inflammatory disease, asthma, chronic obstructive pulmonary disease, digestive tract ulcer, slun irritation, eye irritation, mucous membrane irritation. In general, compounds which act as ligands for TRVP1 are known as vanilloids.

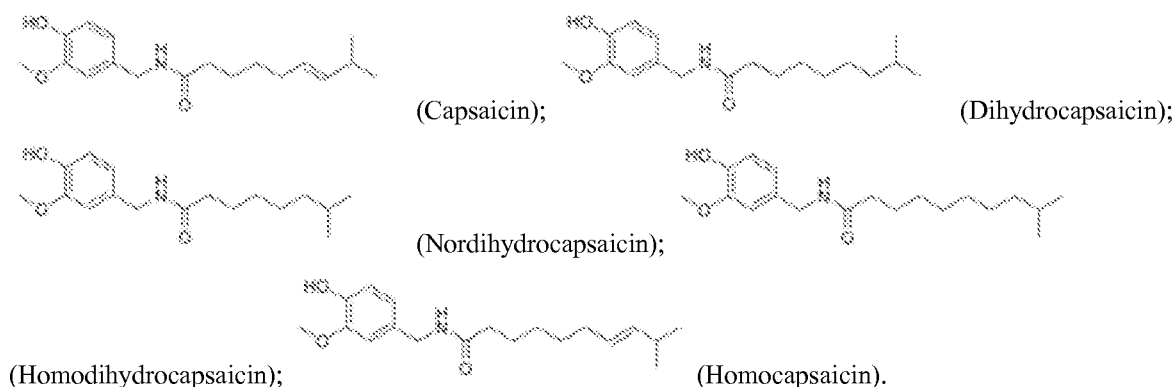
[00114] Often vanilloids are structurally related to the chili-pepper extract capsaicin, and that are thought to exert their effects by acting as a selective agonist of TRPV1.

[00115] The TRVP1 protein is a ligand-gated ion channel that can be activated by a broad range of agonists. TRVP1 agonists include capsaicin, heat, protons, and a variety of endogenous lipids including but not limited to N-arachidonoyl dopamine (NADA), anandamide, and the eicosanoid 15-(S)-HETE (Gunthorpe, et al, TIPS 2002). In particular, NADA acts on both the TRVP1 receptor and the CB1 receptor and has been shown to have analgesic and anti-inflammatory effects (Szallasi *et al.*, *Trends in Neurological Sciences* 23; 491-497 (2000) and Bisogno *et al.*, *Biochemical Journal* 351317-824 (2000)). Agonist-mediated activation of TRVP1 results in channel opening, and subsequent influx of calcium and sodium ions (PCa>PNa) into the sensory neurons expressing TRVP 1. The influx of calcium and sodium ions serves a signaling role in the activation of these neurons by TRVP1 agonists.

[00116] The TRVP1 is expressed predominantly in small sensory neurons (e.g. dorsal root ganglia (DRG), cranial ganglia), most particularly in the small myelinated C-fibers that are thought to process or transmit painful sensory stimuli. TRVP1 is also localized and expressed in small sensory neurons that serve a sensory role in visceral tissues such as bladder. Localization of TRVP1 to sensory neurons that are 'hard wired' to pain pathways sensory supports a close association between TRVP1 activation and sensation of pain.

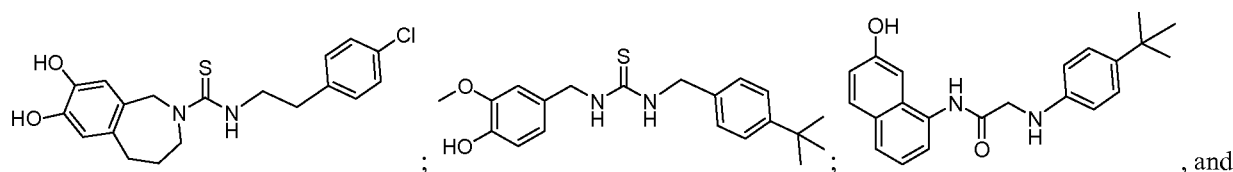
[00117] In addition to anatomical connections between TRVP1 and pain pathways, a strong correlation between activation of TRVP 1 and the sensation of pain has been noted in humans and in animal studies. The simplest example of this is the burning sensation caused by exposure of human mucosa to chili peppers, or to purified extracts of peppers, namely the selective TRVP1 agonist capsaicin. Further supporting this correlation, a TRVP1 knock-out mouse has been characterized with a phenotype that is consistent with a role of TRVP 1 in pain transmission.

[00118] Agonists of TRVP1 are irritants upon application but ultimately lead to receptor desensitization and a concomitant reduction in sensitivity to painful stimuli. Agonists of TRVP1 include, but are not limited to: Arvanil (N-[(4-Hydroxy-3-methoxyphenyl)methyl]-5Z,8Z,11Z,14Z-eicosatetraenamide); Capsaicin; Dihydrocapsaicin; Olvanil ((N-Vanillyl)-9-oleamide); Phorbol 12,13-didecanoate 20-homovanillate; Resiniferatoxin; Phorbol 12,13-dinonanoate 20-homovanillate; Scutigeral (2,3,4-Trihydroxy-6-methyl-5-[(2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyl]benzaldehyde); Tityatoin; N-Vanillylnonanamide (N-(4-Hydroxy-3-methoxybenzyl)nonanamide; Pseudocapsaicin);



[00119] *In vivo*, a number of lines of evidence support the strategy that functional inhibition of TRPV1 activity holds therapeutic promise for reduction of pain. Examples of TRPV1 blockade resulting in reduction of pain come from both pure receptor antagonists, and from agonist-induced desensitization, both in humans and in animal studies. For example, TRPV1 antagonists have been shown to be active as blockers of pain as measured in animal pain models (Walker et al, JPET 2003). Many of these inhibitors are being developed for treatment of a variety of pain conditions, utilizing the underlying strategy that blockade of TRPV1 activity results in pain relief.

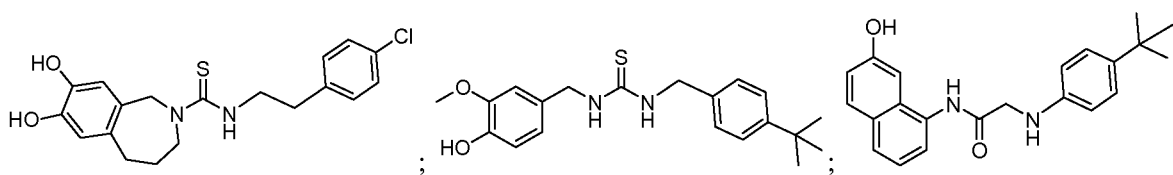
[00120] TRPV1 antagonists include, but are not limited to,



others, such as, those described in Breitenbucher *et al. Annual Reports in Medicinal Chemistry*, Vol. 40, 185-198, 2005).

[00121] In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from TRPV1 vanilloid receptor agonists that contain at least one aromatic moiety bearing at least one hydroxy moiety; hydroxy metabolites of TRPV1 vanilloid receptor agonists that contain at least one aromatic moiety bearing at least one hydroxy moiety; or a TRPV1 vanilloid receptor agonist having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment, TRPV1 vanilloid receptor agonists are selected from capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin.

[00122] In another embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from TRPV1 vanilloid receptor antagonists that contain at least one aromatic moiety bearing at least one hydroxy moiety; hydroxy metabolites of TRPV1 vanilloid receptor antagonists that contain at least one aromatic moiety bearing at least one hydroxy moiety; or a TRPV1 vanilloid receptor antagonist having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment, TRPV1 vanilloid receptor antagonists are selected from



and others, such as, those described in Breitenbucher *et al. Annual Reports in Medicinal Chemistry*, Vol. 40, 185-198, 2005).

f. Compounds of Formula (I) wherein HOA is Serotonin

[00123] As described herein, FAAH inhibitors may be useful for the treatment of weight loss, obesity, clinical depression, irritable bowel syndrome, fibromyalgia, and anxiety disorders. Low levels of serotonin have been associated with these conditions. Recent research suggests that serotonin plays an important role in liver regeneration and acts as a mitogen, i.e., it induces cell division, throughout the body. In contrast, extremely high levels of serotonin can have a toxic and potentially fatal effect, causing a condition known as serotonin syndrome. It therefore follows that in some

embodiments is a FAAH inhibitor having a serotonin or serotonin-like compound representing an arylhydroxy release agent. In another embodiment is a FAAH inhibitor having a serotonin or serotonin-like compound representing an arylhydroxy release agent for the treatment of diseases, disorders, or conditions related to serotonin. In another embodiment is a FAAH inhibitor having a serotonin or serotonin-like compound representing an arylhydroxy release agent wherein the amount of serotonin or serotonin-like compound is used for the treatment of weight loss, obesity, clinical depression, irritable bowel syndrome, fibromyalgia, anxiety, migraines, bipolar disorder and tinnitus. In another embodiment is a FAAH inhibitor having a serotonin or serotonin-like compound representing an arylhydroxy release agent wherein the amount of serotonin or serotonin-like compound delivered potentiates the amount of serotonin to treat serotonin related conditions. In another embodiment, the potentiating amount of serotonin via administration of a FAAH inhibitor having a serotonin or serotonin-like compound representing an arylhydroxy release agent is realized through synergistic means. In another embodiment, the potentiating amount of serotonin via administration of a FAAH inhibitor having a serotonin or serotonin-like compound representing an arylhydroxy release agent is realized through additive means. In another embodiment is a FAAH inhibitor wherein the arylhydroxy containing release agent is a metabolite of a serotonin-like compound.

g. Compounds of Formula (I) wherein HOA is Tyrosine

[00124] In another embodiment is a FAAH inhibitor having a tyrosine or tyrosine-like compound representing an arylhydroxy release agent. In another embodiment is a FAAH inhibitor having a tyrosine or tyrosine-like compound representing an arylhydroxy release agent for the treatment of diseases, disorders, or conditions related to tyrosine. In another embodiment is a FAAH inhibitor having a tyrosine or tyrosine-like compound representing an arylhydroxy release agent wherein the amount of tyrosine or tyrosine-like compound is used for the treatment of weight loss, obesity, clinical depression, irritable bowel syndrome, fibromyalgia, anxiety, migraines, bipolar disorder and tinnitus. In another embodiment is a FAAH inhibitor having a tyrosine or tyrosine-like compound representing an arylhydroxy release agent wherein the amount of tyrosine or tyrosine-like compound delivered potentiates the amount of tyrosine to treat tyrosine related conditions. In another embodiment, the potentiating amount of tyrosine via administration of a FAAH inhibitor having a tyrosine or tyrosine-like compound representing an arylhydroxy release agent is realized through synergistic means. In another embodiment, the potentiating amount of tyrosine via administration of a FAAH inhibitor having a tyrosine or tyrosine-like compound representing an arylhydroxy release agent is realized through additive means. In another embodiment is a FAAH inhibitor wherein the arylhydroxy containing release agent is a metabolite of a tyrosine-like compound.

h. Compounds of Formula (I) wherein HOA is Acetaminophen

[00125] Acetaminophen (*N*-acetyl-4-aminophenol; paracetamol), belongs to a class of drugs called analgesics (pain relievers) and antipyretics (fever reducers). Acetaminophen acts to relieve pain by elevating the pain threshold and reduces fever through its action on the heat-regulating center of the brain. Antipyretics interfere with those processes by which pyrogenic factors produce fever, but do not appear to lower body temperature in afebrile subjects. It has been historically accepted that the antipyretics exert their actions within the CNS, primarily at the hypothalamic thermoregulatory center but more recent evidence suggests that peripheral actions may also contribute.

[00126] Even though acetaminophen has been used clinically for more than a century, its mechanism of action is still not fully understood. It is known that acetaminophen differs from most other non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and cyclo-oxygenase (COX) inhibitors, in that it is a weak anti-inflammatory agent and displays a low incidence of COX-related adverse effects, such as platelet activity and gastrointestinal ulcerogenicity. Thus, while it is known that the analgesic, antipyretic, and anti-inflammatory effects of NSAIDs depend on their ability to inhibit COX-2, the mechanism by which acetaminophen exerts its analgesic and antipyretic effects has not been reconciled. The fact that acetaminophen is an effective antipyretic-analgesic but a weak anti-inflammatory may be due to its greater inhibition of prostaglandin biosynthesis in the CNS than in the periphery.

[00127] While acetaminophen has been extensively used to treat pain and to reduce fever, a serious drawback of acetaminophen therapy is its well characterized toxic effects on the liver and kidney, and the potential for liver necrosis as a complication in patients intoxicated with acetaminophen. Overdoses of acetaminophen can produce potentially fatal hepatic necrosis, renal tubular necrosis and hypoglycemic coma.

[00128] In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from acetaminophen or acetaminophen-like compounds.

i. Compounds of Formula (I) wherein HOA is an Opioid

[00129] Opioids work by binding to opioid receptors which are primarily found in the central nervous system and in the gastrointestinal tract. Of the more than 17 major classes of opioid receptors, the μ , κ , and δ -receptors are G-protein coupled receptors which act on GABAergic neurotransmission. The μ -opioid receptor exists either presynaptically (in the periaqueductal gray region) or postsynaptically depending on the cell type. Activation of the μ -opioid receptor by an agonist causes analgesia and sedation. κ -opioid receptors are also involved with analgesia. Further, κ -opioid agonism is neuroprotective against hypoxia/ischemia. δ -opioid receptor activation also produces analgesia, with the endogenous ligands for these receptors, being enkephalins. The four broad classes of opioids are endogenous opioid peptides (produced naturally in the body), opium alkaloids, such as morphine and codeine, semi-synthetic opioids, and opioids that are fully synthesized, such as methadone and pethidine.

[00130] Opioids include, but are not limited to, Alfentanil, Allylprodine, Alphaprodine, Anileridine, Betmeprodine, Betaprodine, Bezitramide, Buprenorphine, Butorphanol, Carfentanil, Codeine, Dextropropoxyphene, Dextromoramide, Dihydrocodeine, Dipipanone, Etorphine, Fentanyl, Diamorphine (Heroin), Hydromorphone, Hydrocodone, Levorphanol, Methadone, Metopon, Morphine, Nalbuphine, Nicomorphine, Omnopon, Opium, Oxycodone, Oxymorphone, Pantopon, Papaveretum, Paregoric, Pentazocine, Pethidine (Meperidine), Phenoperidine, Piritramide, Prodine, Proheptazine, Propiram, Propoxyphene, Racemorphan, Remifentanil, Sufentanil, Tetraon, Tilidine, Tramadol, Trimeperidine; salicylic acid, salicylic acid derivatives such as Aspirin (acetylsalicylic acid), Diflunisal, and Ethenzamide; pyrazolones such as aminophenazone, metamizole, and phenazone; anilides such as, Paracetamol (acetaminophen) and Phenacetin; tetrahydrocannabinol, Ibuprofen, Ketoprofen, mefenamic acid, Naproxen, Diclofenac, Flurbiprofen, Diflunisal, Fenoprofen, Indomethacin, Ketorolac, Meclofenamate, Meloxicam, Piroxicam, and Tolmetin.

[00131] In one embodiment, carbamate compounds described herein are formed from opioid compounds that include, at least one aromatic moiety bearing at least a hydroxy moiety; hydroxy metabolites of opioid compounds that contain at least one hydroxy moiety; or at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the

introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment the opioid compound is selected from among: Alfentanil, Anileridine, Buprenorphine, Butorphanol, Carfentanil, Codeine, Dextropropoxyphene, Dextromoramide, Dihydrocodeine, Dipipanone, Etorphine, Fentanyl, Diamorphine (Heroin), hydromorphone, hydrocodone, levorphanol, methadone, morphine, Nalbuphine, oxycodone, oxymorphone, pentazocine, pethidine (meperidine), phenoperidine, piritriamide, propoxyphene, Remifentanyl, Sufentanyl, Tramadol, aspirin, Diflunisal, ethenzamide, aminophenazone, metamizole, phenazone, paracetamol, tetrahydrocannabinol, Ibuprofen, Ketoprofen, mefenamic acid, Naproxen, Diclofenac, Flurbiprofen, Diflunisal, Fenoprofen, Indomethacin, Ketorolac, Meclofenamate, Meloxicam, Piroxicam, and Tolmetin.

i. Compounds of Formula (I) wherein HOA is an NSAID

[00132] Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of drugs commonly used to treat arthritis because of their analgesic (pain-killing), anti-inflammatory, and antipyretic (fever-reducing) properties. NSAIDs block the activity of the cyclo-oxygenase (COX) enzymes, via a mechanism distinct from that of acetaminophen, and reduce prostaglandin levels throughout the body. The mechanism of action of NSAIDs is the inhibition of the COX enzymes, which catalyzes the transformation of arachidonic acid to prostaglandins and leukotrienes. Two COX enzymes have been identified, COX-1 and COX-2, and both enzymes produce prostaglandins that promote inflammation, pain, and fever. Prostaglandins are a related family of chemicals that are produced within the cells of the body by the COX enzymes and have several important functions. Prostaglandins promote inflammation, pain, and fever, support the function of platelets that are necessary for the clotting of blood, and protect the lining of the stomach from the damaging effects of acid. However, only COX-1 produces prostaglandins that support platelets and protect the stomach.

[00133] By reducing the levels of prostaglandins, which are known to regulate inflammation, pain, and fever (antipyretic), NSAIDs can mediate inflammation, pain, and fever. As a consequence, ongoing inflammation, pain, and fever are reduced. However, treatment with NSAIDs, such as aspirin, often causes adverse gastrointestinal effects such as the formation ulcers in the stomach and an increased risk of bleeding, which is due to inhibition of COX-1, while COX-2 specific inhibitors have been shown to be associated with increased cardiovascular risks. The incidences of the unfavorable side effects increase as the dose of the NSAIDs increase, a problem that limits the therapeutic utility of this class of compounds.

[00134] NSAIDs include, but are not limited to, salicylic acids (e.g., aspirin, salicylic acid, gentisic acid, choline magnesium salicylate, choline salicylate, choline magnesium salicylate, choline salicylate, magnesium salicylate, sodium salicylate and diflunisal), propionic acids (e.g., carprofen, fenoprofen, fenoprofen calcium, flurbiprofen, ibuprofen, ketoprofen, ketorolac, ketorolac tromethamine, naproxen and oxaprozin), acetic acids (e.g. diclofenac, etodolac, indomethacin, sulindac, tolmetin), fenamates (e.g., meclofenamate, meclofenamate sodium, and mefenamic acid), oxicams (piroxicam and meloxicam), COX-2 specific inhibitors (such as, but not limited to, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337 and NS398), and others, such as nabutone. A number of chemical classes of such non-steroidal anti-inflammatory drugs have been identified, as described in CRC Handbook of Eicosanoids: Prostaglandins, and Related Lipids, Volume II, Drugs Acting via the Eicosanoids, pages 59-133, CRC Press, Boca Raton, Fla. (1989).

[00135] Certain NSAIDs contain a stereocenter center and are administered as a racemate or enantiomerically-enriched composition. In some cases one enantiomer is biologically more active than the other. Although marketed as a racemate, the (+)-enantiomer of ibuprofen possesses greater activity *in vitro* than the (-)-enantiomer. The (S)-enantiomer of naproxen is more active than the (R)-isomer.

[00136] Metabolites of NSAIDs that are not structurally different from the parent molecule would be expected to have similar pharmacological properties. Most often, NSAIDs are metabolized to hydroxy-containing molecules. In some situations, metabolites of NSAIDs also mediate inflammation, pain, and fever (Radomski *et al. Pharmacological Research Communications*, 18:1015-1030, 1986; Shen *et al., Adv. Drug. Res.* 12:90, 1977; Jeremy *et al. Prostaglandins Leukot Essent Fatty Acids*. 1990 Nov;41(3):195-9).

[00137] Thus, many of the existing analgesic, antipyretic, and anti-inflammatory drugs, such as acetaminophen and NSAIDs, are associated with serious side effects. As such, there exists a need for more effective and less toxic drugs which act to relieve pain, reduce fever, and/or prevent inflammation.

[00138] It has been shown that when FAAH activity is reduced or absent, one of its substrates, anandamide, acts as a substrate for COX-2, which converts anandamide to prostamides (Weber *et al. J. Lipid. Res.* 2004; 45:757). Concentrations of certain prostamides may be elevated in the presence of a FAAH inhibitor.

[00139] NSAIDs have been shown to inhibit FAAH activity in addition to inhibiting COX activity. NSAIDs, such as, for example, ibuprofen, suprofen, ketorolac, fenoprofen, naproxen, ketoprofen, diclofenac (Fowler *et al. J. Exp. Pharmacol. Exp. Ther.* 283:729-734, 1997), flurbiprofen (Fowler *et al. Arch. Biochem. Biophys.* 1999, 362, 191-196), and indomethacin (Fowler *et al. Br. J. Pharmacol.* 2000, 131, 498-504) have been shown to inhibit FAAH activity with potencies in the low- to high-micromolar range, depending upon the assay used. The data suggests that the use of NSAIDs, such as, for example, ibuprofen, at doses typically administered for conditions such as arthritis may lead to inhibition of FAAH activity (Fowler *et al. J. Exp. Pharmacol. Exp. Ther.* 283:729-734, 1997). However, as noted above, the use of NSAIDs at doses typically administered for conditions such as arthritis lead to undesirable side effects. It has been shown *in vitro*, that the COX enzymes can metabolize anandamide, and therefore it is reasoned that NSAIDs can also act to prevent COX removal of anandamide and thereby allow its build-up (Guindon *et al. Pain* 121, 85-93 (2006); Kozak *et al., Biochemistry*, 30:9041-9049, 2003).

[00140] The compounds of Formula (I) provided herein, wherein OA is the deprotonated form of an NSAID, and pharmaceutical compositions including the compounds, are more effective than traditional therapies (e.g. NSAIDs taken alone) in providing relief of pain, fever and inflammation and reduce the risk of adverse side effects associated with such therapies.

[00141] In certain embodiments, O-A is the deprotonated form of a hydroxy-containing NSAID selected from among salicylic acid, salicylamide, salsalate, diflunisal, gentisic acid, piroxicam, and meloxicam. In some other embodiments, O-A is the deprotonated form of a hydroxy-containing NSAID selected from among salicylic acid, salicylamide, salsalate, diflunisal, and gentisic acid.

[00142] In other embodiments, O-A is the deprotonated form of a hydroxy-containing NSAID metabolite, wherein said hydroxy-containing NSAID metabolite is a metabolite of an NSAID selected from among acetylsalicylic acid, salicylic acid, salicylamide, salsalate, diflunisal, gentisic acid, indomethacin, sulindac, tolmetin, diclofenac, etodolac,

nabumetone, ibuprofen, fenoprofen, ketoprofen, flurbiprofen, suprofen, carprofen, naproxen, ketorolac, oxaprozin, mefenamic acid, meclofenamate sodium, piroxicam, meloxicam, DuP 697, celecoxib, rofecoxib, valdecoxib, nimesulide, ns-398, parecoxib, and etoricoxib. In certain embodiments, O-A is the deprotonated form of a hydroxy-containing NSAID metabolite, wherein said hydroxy-containing NSAID metabolite is a metabolite of a single enantiomer of an NSAID, such as, for example, a hydroxy-containing metabolite of a single enantiomer of naproxen, wherein the single enantiomer is the biologically more active enantiomer. In certain embodiments, O-A is the deprotonated form of a hydroxy-containing NSAID metabolite, wherein said hydroxy-containing NSAID metabolite is a hydroxy-containing metabolite of the (S)-(+)-enantiomer of naproxen.

[00143] In some embodiments, O-A is the deprotonated form of a hydroxy-containing NSAID metabolite, wherein said hydroxy-containing NSAID metabolite is a metabolite of an NSAID selected from among indomethacin, sulindac, tolmetin, diclofenac, etodolac, nabumetone, ibuprofen, fenoprofen, ketoprofen, flurbiprofen, suprofen, carprofen, naproxen, ketorolac, oxaprozin, mefenamic acid, meclofenamate sodium, piroxicam, meloxicam, DuP 697, celecoxib, rofecoxib, valdecoxib, nimesulide, ns-398, parecoxib, and etoricoxib.

[00144] In some embodiments, O-A is the deprotonated form of a hydroxy-containing NSAID metabolite, wherein said hydroxy-containing NSAID metabolite is a metabolite of an NSAID selected from among indomethacin, nabumetone, ibuprofen, fenoprofen, ketoprofen, flurbiprofen, suprofen, carprofen, and naproxen.

[00145] In other embodiments, O-A is the deprotonated form of a hydroxy-containing NSAID metabolite, wherein said hydroxy-containing NSAID metabolite is a metabolite of an NSAID selected from among indomethacin, nabumetone, and naproxen.

[00146] In some embodiments, O-A is the deprotonated form of a hydroxy-containing NSAID metabolite, wherein said hydroxy-containing NSAID metabolite is a metabolite of an NSAID selected from among indomethacin, and naproxen.

[00147] In some embodiments, O-A is the deprotonated form of acetaminophen. In some other embodiments, O-A is the deprotonated form of propofol.

k. Compounds of Formula (I) wherein HOA is an Anesthetic Agent

[00148] The general anesthetic propofol has been characterized as a competitive inhibitor of FAAH (Patel *et al. Br. J. Pharmacol.* 2003, 139, 1005-1013). Propofol has been shown to potentiate endogenous GABAergic neurotransmission (Gamma-AminoButyric Acid) and to directly activate the GABA_A receptor (Williams *et al. J. Neurosci.*, 22, 7417-7424, 2002). Propofol is a compound that combines enhancement of GABA_A function (GABA_A agonist) and increased endocannabinoid content and that both of these pharmacological effects contribute to its sedative efficacy. Behavioral effects of GABA_A agonists, include, for example, relief of anxiety (anxiolysis), muscle relaxation, sedation, anticonvulsion, and anesthesia.

[00149] In one embodiment, carbamates disclosed herein are formed from anesthetics that contain at least one aromatic ring bearing a hydroxy moiety or at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment the anesthetic agent is selected from among, barbituates, opioids, and other anesthetic agents such as, but not limited to, droperidol, etomidate, ketamine, propanidid, and propofol. In another embodiment, the anesthetic agent is selected from among alfentanil, anileridine, fentanyl, phenoperidine, remifentanil, sufentanil, droperidol, etomidate, ketamine,

propofol, and propofol. In yet another embodiment, the anesthetic agent that is selected to form a carbamate compound disclosed herein is propofol.

I. Compounds of Formula (I) wherein HOA is a Therapeutic Agent used to treat Metabolic Disorders

[00150] In one embodiment, carbamate compounds disclosed herein are FAAH inhibitors that increase systemic levels of one or more fatty acid amides, e.g., oleoylethanolamide (OEA), palmitoylethanolamide (PEA), or anandamide (AEA) to therapeutically or cosmetically effective levels. Without being bound by theory, it is thought that certain fatty acid amides, such as OEA act through the peroxisome proliferator-activated receptor α (PPAR- α) to regulate diverse physiological processes, including, e.g., feeding and lipolysis. Consistent with this, human adipose tissue has been shown to bind and metabolize endocannabinoids such as anandamide and 2-arachidonylglycerol. See Spoto *et al.*, August 22, 2006, *Biochimie* (E-publication ahead of print); and Matias *et al.* (2006), *J. Clin. Endocrin. & Met.*, 91(8):3171-3180. Thus, inhibiting FAAH activity *in vivo* leads to reduced body fat, reduced body weight, reduced caloric intake, and reduced liver triglyceride levels. However, unlike, other anti-lipidemic agents that act through PPAR- α , e.g., fibrates, FAAH inhibitors do not cause adverse side effects such as rash, fatigue, headache, erectile dysfunction, and, more rarely, anemia, leukopenia, angioedema, and hepatitis. See, e.g., Muscari *et al.* (2002), *Cardiology*, 97:115-121. An additional therapeutic property of FAAH inhibitors, is that due to their ability to elevate anandamide levels, they effectively alleviate depression and anxiety, conditions often associated with energy metabolism disorders (EMDs) such as obesity. See Simon *et al.* (2006), *Archives of Gen. Psychiatry*, 63(7):824-830. Finally, agonism of cannabinoid receptors has also been shown to reduce the progression of atherosclerosis in animal models. See Steffens *et al.* (2005), *Nature*, 434:782-786; and Steffens *et al.* (2006), *Curr. Opin. Lipid.*, 17:519-526. Thus, increasing the level of endogenous cannabinergic fatty acid amides (e.g., anandamide) is expected to effectively treat or reduce the risk of developing atherosclerosis.

[00151] Accordingly, as described herein, FAAH inhibitors can be used to treat or reduce the risk of EMDs, which include, but are not limited to, obesity, appetite disorders, overweight, cellulite, Type I and Type II diabetes, hyperglycemia, dyslipidemia, steatohepatitis, liver steatosis, non-alcoholic steatohepatitis, Syndrome X, insulin resistance, diabetic dyslipidemia, anorexia, bulimia, anorexia nervosa, hyperlipidemia, hypertriglyceridemia, atherosclerosis, arteriosclerosis, inflammatory disorders or conditions, Alzheimers disease, vascular inflammation, or cachexia.

[00152] The methods described herein can be used to treat, e.g., insulin resistance syndrome and diabetes, i.e., both primary essential diabetes such as Type I Diabetes or Type II Diabetes and secondary nonessential diabetes. Administering a composition containing a therapeutically effective amount of an *in vivo* FAAH inhibitor reduces the severity of a symptom of diabetes or the risk of developing a symptom of diabetes, such as atherosclerosis, hypertension, hyperlipidemia, liver steatosis, nephropathy, neuropathy, retinopathy, foot ulceration, or cataracts.

[00153] In another embodiment, the methods described herein are used to treat food abuse behaviors, especially those liable to cause excess weight, e.g., bulimia, appetite for sugars or fats, and non-insulin-dependent diabetes.

[00154] In some embodiments, the subject to be treated, in addition to suffering from an EMD, also suffers from a depressive disorder or from an anxiety disorder. Preferably, the subject is diagnosed as suffering from the depressive or psychiatric disorder prior to administration of the FAAH inhibitor composition. Thus, a dose of a FAAH inhibitor that is therapeutically effective for both the EMD and the depressive or anxiety disorder is administered to the subject. Methods

for treatment of anxiety and depressive disorders by FAAH inhibition are described in, e.g., U.S. Patent Application Nos. 10/681,858 and 60/755,035.

[00155] Preferably, the subject to be treated is human. However, the methods can also be used to treat non-human mammals. Animal models of EMDs such as those described in, e.g., U.S. Patent No. 6,946,491 are particularly useful.

[00156] FAAH inhibitor compositions can also be used to decrease body-weight in individuals wishing to decrease their body weight for cosmetic, but not necessarily medical considerations.

[00157] In some embodiments, it may be beneficial to administer a FAAH inhibitor in combination with a therapeutic agent for lowering circulating cholesterol levels (e.g., statins, niacin, fibric acid derivatives, or bile acid binding resins). FAAH inhibitor compositions can also be used in combination with a weight loss drug, e.g., orlistat or an appetite suppressant such as diethylpropion, mazindole, orlistat, phendimetrazine, phentermine, or sibutramine.

[00158] The methods described herein can also include providing an exercise regimen or providing a calorie-restricted diet (e.g., a triglyceride-restricted diet) to the subject.

m. Compounds of Formula (I) wherein HOA is an Antihyperlipidemic Agent

[00159] In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from a) antihyperlipidemic agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; or b) hydroxy metabolites of antihyperlipidemic agents that contain at least one aromatic moiety bearing at least one hydroxy moiety.

[00160] Antihyperlipidemic agents include, but are not limited to, statins (e.g., Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin), peroxisome proliferator activated receptor (PPARs) modulating agents (PPARs), such as PPAR-alpha modulating agents that include fibrates (e.g., bezafibrate (e.g. Bezalip®), ciprofibrate (e.g. Modalim®), clofibrate, gemfibrozil (e.g. Lopid®), fenofibrate (e.g. TriCor®)), PPARγ (gamma) modulating agents that include thiazolidinediones (TZDs) (e.g., rosiglitazone (Avandia), pioglitazone (Actos), Troglitazone), nicotinic acid, bile acid sequestrants (resins), ezetimibe (Zetia), phytosterols. Thus, in one embodiment, are carbamate compounds formed from antihyperlipidemic agents described herein.

n. Compounds of Formula (I) wherein HOA is a Statin

[00161] In one embodiment, described herein are carbamate compounds, such as, for example, compounds of Formula (I), which upon inhibition of an amide hydrolase, is metabolized and releases a statin or a hydroxy metabolite of a statin. In another embodiment, described herein are carbamate compounds that irreversibly inhibit FAAH and release a statin or a hydroxy metabolite of a statin. In a further embodiment, described herein are carbamate compounds that reversibly inhibit FAAH and release a statin or a hydroxy metabolite of a statin.

[00162] By way of example only, FAAH inhibitors having a statin or statin-like arylhydroxy containing therapeutic release agent may be used to lower cholesterol by inhibiting HMG-CoA reductase while reducing the side effects commonly associated with the use of statins alone. In another embodiment, is a FAAH inhibitor having a statin or statin-like arylhydroxy containing therapeutic release agent wherein the FAAH inhibitor may prevent, angina, heart attacks, stroke, transient ischaemic attack or peripheral vascular disease. In another embodiment, is a FAAH inhibitor having a statin or statin-like arylhydroxy containing therapeutic release agent wherein the statin or statin-like release agent may lower or prevent a transient cholesterol raising effect of the FAAH inhibitor.

[00163] HMG-CoA reductase inhibitors (or statins) form a class of hypolipidemic agents used to lower cholesterol levels in patients with or at risk for cardiovascular disease. Statins lower cholesterol levels by competitively inhibiting the enzyme HMG-CoA reductase, an enzyme involved in the rate of cholesterol synthesis. Inhibition of the HMG-CoA reductase in the liver stimulates the LDL-receptors, resulting in an increased clearance of LDL from the bloodstream and a decrease in blood cholesterol levels.

[00164] In one embodiment, carbamate compounds described herein are FAAH inhibitors formed from: a) statins that contain at least one aromatic moiety bearing at least one hydroxy moiety; or b) hydroxy metabolites of statins that contain at least one aromatic moiety bearing at least one hydroxy moiety. Statins that contain at least one aromatic moiety include, atorvastatin, cerivastatin, fluvastatin, pitavastatin, and rosuvastatin.

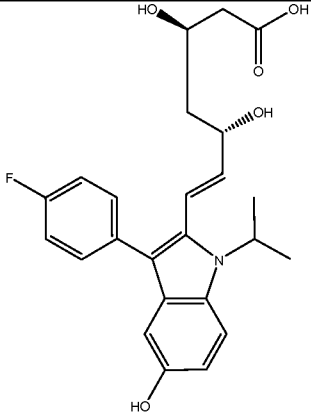
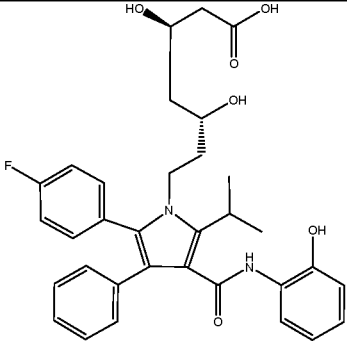
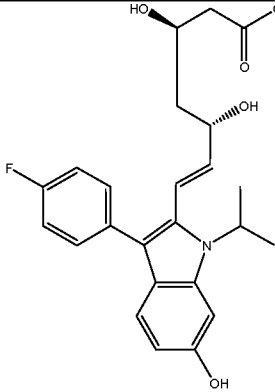
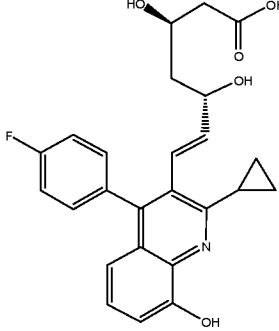
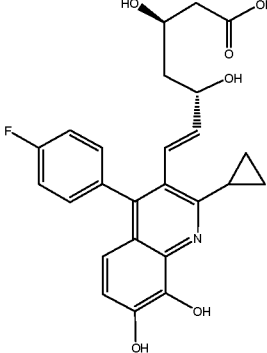
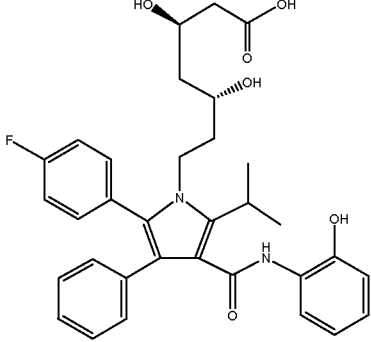
[00165] Mevastatin and related compounds are disclosed in U. S. Patent No. 3,983,140. Lovastatin (mevinolin) and related compounds are disclosed in U. S. Patent No. 4,231,938. Keto analogs of mevinolin (lovastatin) are disclosed in European Patent Application No. 0,142,146 A2, and quinoline and pyridine derivatives are disclosed in U. S. Patent No. 5,506,219 and 5,691,322. Pravastatin and related compounds are disclosed in U. S. Patent No. 4,346,227. Simvastatin and related compounds are disclosed in U. S. Patent Nos. 4,448,784 and 4,450,171. Fluvastatin and related compounds are disclosed in U. S. Patent No. 5,354,772. Cerivastatin and related compounds are disclosed in U. S. Patent Nos. 5,006,530 and 5,177,080. Atorvastatin and related compounds are disclosed in U. S. Patent Nos. 4,681,893; 5,273,995; 5,385,929 and 5,686,104. Pitavastatin (nisvastatin (NK-1 04) or itavastatin) and related compounds are disclosed in U. S. Patent No. 5,011,930. Rosuvastatin (visastatin (ZD-4522)) and related compounds are disclosed in U. S. Patent No. 5,260,440. Other possible HMG CoA reductase molecules are described in U. S. Patent Nos. 5,753,675; 4,613,610; 4,686,237; 4,647,576; and 4,499,289; and British patent no. GB 2205837.

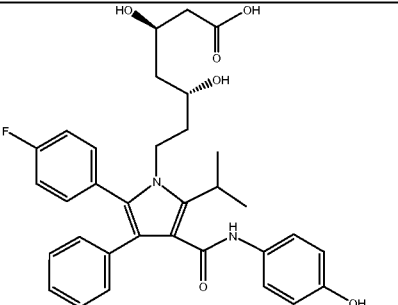
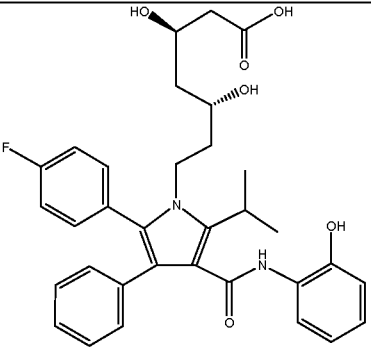
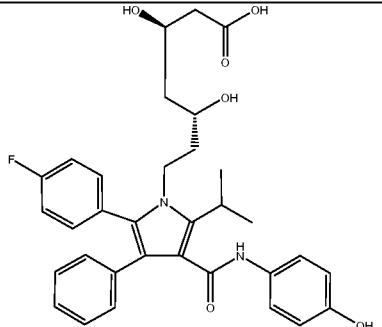
[00166] The patents cited in relation to statins or other agents identified herein describe how to make and use the statins/agents, as well as biochemically active homologs thereof, salts, pro-drugs, metabolites, and the like. Such patents are incorporated herein by reference in their entirety.

[00167] Hydroxylated metabolites of statins have been shown to possess activity. For example, the ortho- and para-hydroxylated metabolites of atorvastatin are equiactive as atorvastatin, and contribute significantly to the overall activity of atorvastatin when administered alone.

[00168] In one embodiment, carbamate compounds described herein are formed from statins that contain at least one aromatic moiety bearing at least one hydroxy moiety. In another embodiment, carbamate compounds described herein are formed from hydroxy metabolites of statins that contain at least one aromatic moiety bearing at least one hydroxy moiety. In one embodiment, carbamate compounds disclosed herein are formed from the ortho- and para-hydroxy metabolites of atorvastatin: (7-[2-(4-Fluorophenyl)-4-[N-(4-hydroxyphenyl)carbamoyl]-5-isopropyl-3-phenyl-1H-pyrrol-1-yl]-3(R),5(R)-dihydroxyheptanoic acid); (7-[2-(4-Fluorophenyl)-4-[N-(2-hydroxyphenyl)carbamoyl]-5-isopropyl-3-phenyl-1H-pyrrol-1-yl]-3(R),5(R)-dihydroxyheptanoic acid).

[00169] Other statins that contain at least one aromatic ring bearing at least one hydroxy moiety include, but are not limited to:

 (3R,6S,7E)-8-[3-(4-fluorophenyl)-5-hydroxy-1-isopropyl-1H-indol-2-yl]-3,6-dihydroxy-7-octenoic acid	 (3R,6S)-8-{2-(4-fluorophenyl)-4-[(2-hydroxyanilino)carbonyl]-5-isopropyl-3-phenyl-1H-pyrrol-1-yl}-3,6-dihydroxyoctanoic acid	 (3R,6S,7E)-8-[3-(4-fluorophenyl)-6-hydroxy-1-isopropyl-1H-indol-2-yl]-3,6-dihydroxy-7-octenoic acid
 (3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-8-hydroxy-3-quinolinyl]-3,5-dihydroxy-6-heptenoic acid	 (3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-7,8-dihydroxy-3-quinolinyl]-3,5-dihydroxy-6-heptenoic acid	 (7-[2-(4-Fluorophenyl)-4-[N-(2-hydroxyphenyl)carbamoyl]-5-isopropyl-3-phenyl-1H-pyrrol-1-yl]-3(R),5(R)-dihydroxyheptanoic acid).

 7-[2-(4-Fluorophenyl)-4-[N-(4-hydroxyphenyl)carbamoyl]-5-isopropyl-3-phenyl-1H-pyrrol-1-yl]-3(R),5(R)-dihydroxyheptanoic acid	 7-[2-(4-Fluorophenyl)-4-[N-(2-hydroxyphenyl)carbamoyl]-5-isopropyl-3-phenyl-1H-pyrrol-1-yl]-3(R),5(R)-dihydroxyheptanoic acid	 (3R,6S)-8-{2-(4-fluorophenyl)-4-[(4-hydroxyanilino)carbonyl]-5-isopropyl-3-phenyl-1H-pyrrol-1-yl}-3,6-dihydroxyoctanoic acid
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o. Compounds of Formula (I) wherein HOA is a PPAR Agonist

[00170] Peroxisome proliferator activated receptors (PPARs) play an important role in many cellular functions including lipid metabolism, cell proliferation, differentiation, adipogenesis and inflammatory signaling. PPARs are intimately connected to cellular metabolism (carbohydrate, lipid and protein) and cell differentiation. They are transcription factors.

[00171] PPARs have been found to interact with a number of endogenous lipids and drugs for the treatment of human metabolic diseases. There are three distinct PPAR subtypes which are the products of different genes and are commonly designated PPAR α , PPAR δ , and PPAR γ .

[00172] Each receptor is activated by structurally diverse compounds including endogenous long-chain fatty acids. Three types of PPARs have been identified: alpha, gamma and delta. PPAR α (PPAR-alpha) is expressed in liver, kidney, heart, muscle, adipose tissue, and others. PPAR γ (PPAR-gamma) exists in three forms: γ 1 - expressed in virtually all tissues, including heart, muscle, colon, kidney, pancreas and spleen; γ 2 - expressed mainly in adipose tissue; γ 3 - expressed in macrophages, large intestine, white adipose tissue. PPAR δ (delta) is expressed in many tissues but markedly in brain, adipose tissue and skin.

[00173] All PPARs dimerize with the retinoid X receptor (RXR) and bind to specific regions on the DNA of target genes. These DNA sequences are termed PPREs (peroxisome proliferator response elements). The DNA consensus sequence is AGGTCA $\times$ AGGTCA with $\times$ being a random nucleotide. Generally, this sequence occurs in the promoter region of a gene, and when the PPAR binds its ligand, transcription of targets genes are increased or decreased, depending on the gene. The RXR also forms a heterodimer with a number of other receptors: the vitamin D receptor and the thyroid hormone receptor.

[00174] PPAR γ is highly expressed in adipose tissue and is a key transcription factor involved in the terminal differentiation of white and brown adipose tissue. There is evidence that PPAR γ could interfere with atherogenesis, in part by exerting an anti-inflammatory activity.

[00175] The function of PPARs is modified by the exact shape of their ligand-binding domain and by a number of co-activators and co-repressors, the presence of which can stimulate or inhibit receptor function.

The ligands for the PPARs are free fatty acids and eicosanoids. PPAR γ is activated by PGJ2 (a prostaglandin). In contrast, PPAR α is activated by leukotriene B4.

[00176] Both OEA and PEA have been shown to activate peroxisome proliferator-activated receptor alpha (PPAR-alpha) (Fu J, *et al.* 2003. *Nature* 425:90-93; Guzman M, *et al.* 2004, *J Biol Chem* 279(27): 27849-54; Lo Verme J, *et al.* 2005. *Cell Mol Life Sci* 62(6): 708-16; LoVerme J, *et al.* 2005. *Life Sci* 77(14): 1685-98; Lo Verme J, *et al.* 2005. *Mol Pharmacol* 67(1): 15-9). Thus in one embodiment, carbamate compounds described herein, which are formed from PPAR agonist compounds, inhibit FAAH and thus prevent OEA and PEA degradation. Upon inhibition of FAAH by the carbamate compounds described herein, which are formed from PPAR agonist compounds, a PPAR agonist compound is released due to the metabolism of the carbamate compound. Thus, activation of the PPAR receptor(s) is achieved via a dual pathway.

p. Compounds of Formula (I) wherein HOA is a PPAR γ Agonist

[00177] PPAR γ agonists are therapeutics for Type II diabetes, insulin resistance and for a variety of metabolic and cardiovascular diseases. Type II diabetes, also referred to as adult-onset diabetes or non-insulin diabetes, is a condition where insulin is produced but the body cannot effectively use it. PPAR γ agonists are used in monotherapy or in combination therapy and have been shown to be effective in lowering blood glucose. Among the PPAR γ agonists are thiazolidinediones, including for example, rosiglitazone, pioglitazone, and troglitazone. Thus, in one aspect, is a method for treating patients suffering from a disease, disorder, or condition such as metabolic syndrome, Type II diabetes, insulin resistance, and/or heart disease by administering a therapeutically acceptable amount of a FAAH inhibitor having an arylhydroxy containing therapeutic agent which treats such conditions. In one embodiment, the arylhydroxy containing therapeutic agent is a PPAR γ agonist.

[00178] The use of a FAAH inhibitor wherein a PPAR γ agonist represents the arylhydroxy containing therapeutic agent can reduce adverse side effects that are generally induced by the use of the PPAR γ agonist alone. This approach may reduce adverse side effects like weight gain or edema. Alternatively, treatment of a FAAH inhibitor having a PPAR γ agonist which represents the arylhydroxy containing therapeutic agent potentiates the therapeutic effect of the PPAR γ agonist. As such, the patient can be administered a lower dose of a PPAR γ agonist and still achieve the same beneficial therapeutic effect normally associated with a higher dose of the same PPAR γ agonist. In one embodiment, the PPAR γ agonist is tomelukast. In some instances, the use of a FAAH inhibitor wherein a PPAR γ agonist represents the arylhydroxy containing therapeutic agent may treat patients who suffer from advanced stages of heart disease. Patients suffering from this disease are generally intolerant of conventional treatment with PPAR γ agonists. As such, the use of a FAAH inhibitor having a PPAR γ agonist representing an arylhydroxy containing therapeutic release agent, achieves a beneficial therapeutic effect as well as a reduction of adverse side effects in patients suffering from heart disease. Thus, use of a FAAH inhibitor having a PPAR γ agonist representing an arylhydroxy containing therapeutic release agent provides a method of reducing adverse side effects in a human suffering from side effects induced by a PPAR γ agonist. Thus, administering to the subject a sufficient amount of a FAAH inhibitor described herein, to potentiate an insulin

sensitizing effect of the PPAR γ agonist, will thereby reduce the amount of the PPAR γ agonist taken by the subject such that the side effects are lessened while the insulin sensitizing effect is preserved. Further, the insulin sensitizing effect of the PPAR γ agonist remains as potent at a lower dose as compared to a higher dose as a result of administering a FAAH inhibitor having a PPAR γ agonist which represents the arylhydroxy containing therapeutic agent. In some embodiments, the arylhydroxy containing therapeutic release agent is a PPAR α agonist, a PPAR δ agonist and/or PPAR agonist hybrids.

[00179] PPAR- γ is also mildly activated by certain NSAIDs (such as ibuprofen) and indoles. Known inhibitors include the experimental agent GW-9662. Additionally, thiazolidinediones (TZDs) act by binding to PPAR- γ . Compounds in this class include, rosiglitazone (Avandia), pioglitazone (Actos), and troglitazone. In one embodiment, carbamate compounds described herein are formed from TZD compounds that include, at least one aromatic moiety bearing at least a hydroxy moiety, hydroxy metabolites of opioid compounds that contain at least one hydroxy moiety, or at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment, the TZD is selected from rosiglitazone (Avandia), pioglitazone (Actos), and troglitazone. In another embodiment, the TZD is troglitazone.

q. Compounds of Formula (I) wherein HOA is a PPAR- α Agonist

[00180] PPAR- α is a nuclear transcription factor activated by structurally diverse chemicals referred to as peroxisome proliferators. Upon pharmacologic activation, PPAR- α modulates target genes encoding lipid metabolism enzymes, lipid transporters, or apolipoproteins, suggesting a role in lipid homeostasis. Transgenic mice deficient in PPAR- α lack hepatic peroxisomal proliferation and have an impaired expression and induction of several hepatic target genes. PPAR- α plays a role in regulating mitochondrial and peroxisomal fatty acid oxidation, suggesting that it is involved in the transcriptional response to fasting. For example, studies in where the response of PPAR- α -null mice subjected to a high fat diet or to fasting, were compared with those of wild-type mice. PPAR- α -null mice chronically fed a high fat diet showed a large accumulation of lipid in their livers. Also noted was a similar phenotype in PPAR- α -null mice fasting for 24 hours. Severe hypoglycemia, hypoketonemia, hypothermia, and elevated plasma-free fatty acid levels, indicated a dramatic inhibition of fatty acid uptake and oxidation. Further, to show a requirement for hepatic fatty acid oxidation, PPAR- α mRNA was induced during fasting in wild-type mice. These studies showed that PPAR- α plays a pivotal role in the management of energy stores during fasting.

[00181] PPAR- α is the main target of fibrate drugs, a class of amphipathic carboxylic acids (clofibrate, gemfibrozil, ciprofibrate, bezafibrate and fenofibrate). They are used in cholesterol disorders (generally as an adjunctive to statins) and disorders that feature high triglycerides. Fibrates include, but are not limited to bezafibrate (e.g. Bezalip®), Ciprofibrate (e.g. Modalim®), Clofibrate, Gemfibrozil (e.g. Lopid®), and Fenofibrate (e.g. TriCor®).

[00182] In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from a fibrate that contains: at least one aromatic moiety bearing at least one hydroxy moiety, or are hydroxy metabolites of fibrates that contain at least one aromatic moiety bearing at least one hydroxy moiety, or a fibrate having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In another embodiment, the fibrate compound is selected from among:

benzafibrate (e.g. Bezalip®), Ciprofibrate (e.g. Modalim®), Clofibrate, Gemfibrozil (e.g. Lopid®), and Fenofibrate (e.g. TriCor®). In a further embodiment, the fibrate compound is selected from among benzafibrate (e.g. Bezalip®), Ciprofibrate (e.g. Modalim®), Gemfibrozil (e.g. Lopid®), and Fenofibrate (e.g. TriCor®).

r. Compounds of Formula (I) wherein HOA is a Hypolipidemic Agents

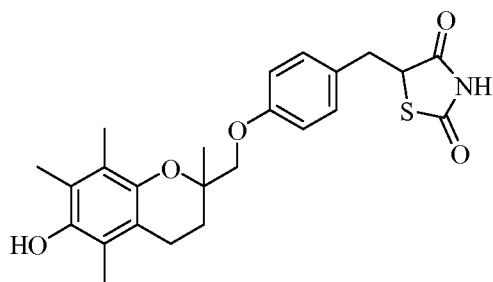
[00183] In another embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from a) hypolipidemic agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; or b) hydroxy metabolites of hypolipidemic agents that contain at least one aromatic moiety bearing at least one hydroxy moiety. Hypolipidemic agents include, but are not limited to, CETP Inhibitors (cholesteryl ester transfer protein inhibitors), and squalene synthase inhibitor.

s. Compounds of Formula (I) wherein HOA is an Anti-Diabetic Agents

[00184] Anti-diabetic drugs or oral hypoglycemic agents are used to treat diabetes mellitus. They usually work by lowering the glucose levels in the blood. There are different types of anti-diabetic drugs, and their use depends on the nature of the diabetes, age and situation of the person, as well as other factors. For example, sulfonylureas bind to an ATP-dependent K^+ channel on the cell membrane of the pancreatic β cells. This inhibits a tonic, hyperpolarizing out-flux of potassium, which causes the electric potential over the membrane to become more positive. This depolarization opens voltage-gated Ca^{2+} channels. The rise in intracellular calcium leads to increased fusion of insulin granulae with the cell membrane, and therefore increased secretion of (pro)insulin. Additionally, there is some evidence that sulfonylureas also sensitize b-cells to glucose, in that they limit glucose production in the liver, decrease lipolysis and decrease clearance of insulin by the liver.

[00185] Anti-diabetic drugs include but are not limited to sulfonylureas (e.g., but not limited to, tolbutamide (Orinase), acetohexamide (Dymelor), tolazamide (Tolinase), chlorpropamide (Diabinese), glipizide (Glucotrol), glyburide (Diabeta, Micronase, Glynase), glimepiride (Amaryl), gliclazide (Diamicon)); meglitinides (e.g., but not limited to, repaglinide (Prandin); nateglinide (Starlix)); biguanides (e.g., but not limited to, metformin (Glucophage), Phenformin (DBI)); thiazolidinediones, (e.g., but not limited to, rosiglitazone (Avandia), pioglitazone (Actos), *troglitazone* (Rezulin)); alpha glucosidase inhibitors, (e.g., but not limited to, miglitol (Glyset), acarbose (Precose/Glucobay)); DPP-4 inhibitors (e.g., but not limited to, vildagliptin, sitagliptin; PPAR α/γ ligands (e.g., muraglitazar and tesaglitazar); SGLT (sodium-dependent glucose transporter 1) inhibitors; and FBPase (fructose 1,6-bisphosphatase) inhibitors.

[00186] In another embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from a) anti-diabetic agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; b) hydroxy metabolites of anti-diabetic agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; or c) or an anti-diabetic agent having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment, the anti-diabetic agent is selected from glyburide, repaglinide, and troglitazone. In another embodiment, the anti-diabetic agent is

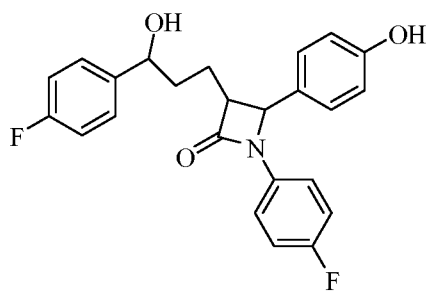


, troglitazone (5-(4-((6-hydroxy-2,5,7,8-tetramethylchroman-2-yl-methoxy)benzyl)-2,4-thiazolidinedione)).

t. Compounds of Formula (I) wherein HOA is Ezetimibe (Zetia)

[00187] Ezetimibe is used to lower cholesterol levels by decreasing cholesterol absorption in the intestine. Specifically, ezetimibe binds to the Niemann-Pick C1-Like 1 (NPC1L1) protein on the gastrointestinal tract epithelium, a critical mediator of cholesterol absorption. Decreased cholesterol absorption leads to an increase in LDL-cholesterol uptake into cells, thus decreasing levels in the blood plasma.

[00188] In another embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from



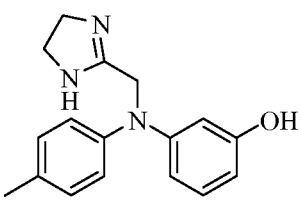
ezetimibe ((3*R*,4*S*)-1-(4-fluorophenyl)-3-((3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)-2-azetidinone).

u. Compounds of Formula (I) wherein HOA is an Anti-hypertensive

[00189] The adrenergic receptors are a class of G protein-coupled receptors that are targets of the catecholamines. Adrenergic receptors specifically bind and are activated by their endogenous ligands, the catecholamines, epinephrine and norepinephrine. There are several types of adrenergic receptors, but there are two main groups, α -adrenergic and β -adrenergic. α -adrenergic receptors bind epinephrine and norepinephrine, though norepinephrine has a higher affinity.

[00190] Hormone binding of the α_1 -adrenergic receptor activates the associated G_q protein, which is linked to phospholipase C (PLC). PLC produces IP_3 , which causes a rise in intracellular calcium levels, and diacylglycerol. Elevated calcium and diacylglycerol activate protein kinase C, which mediates the downstream, intracellular effects of the hormone. In blood vessels the principal effect is vasoconstriction. Blood vessels with α_1 receptors are present in the skin and the gastrointestinal system, and during the fight-or-flight response vasoconstriction results in the decreased blood flow to these organs. This accounts for an individual's skin appearing pale when frightened. In the GI tract, the effect is relaxation. α -adrenergic blocking agents (α -blockers) block the α_1 -adrenergic receptors in arteries and smooth muscles. These agents also treat benign prostatic hyperplasia (BPH), hypertension and symptoms of non-inflammatory chronic pelvic pain syndrome, a type of prostatitis.

[00191] α -blockers include, but are not limited to, doxazosin, phentolamine, indoramin, phenoxybenzamine, prazosin, terazosin, and tolazoline. In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from, α -blockers that contain at least one aromatic moiety bearing at least one hydroxy moiety; hydroxy metabolites of α -blockers that contain at least one aromatic moiety bearing at least one hydroxy moiety; or an α -blocker having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment, the α -blocker is selected from among: doxazosin, phentolamine, indoramin, phenoxybenzamine, prazosin, terazosin, and tolazoline. In another

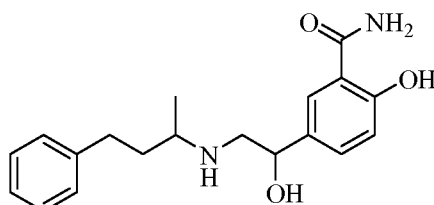
embodiment, the α -blocker is  (phentolamine; 3-[4,5-dihydro-1*H*-imidazol-2-ylmethyl]-(4-methylphenyl)-amino]phenol).

[00192] Beta-blockers (β -blockers) block the action of endogenous catecholamines, particularly epinephrine and norepinephrine, on β -adrenergic receptors. The three known types of β -receptors, β_1 , β_2 , and β_3 are located mainly in the heart; lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle; and fat cells, respectively. β -blockers act as competitive inhibitors of catecholamines, exerting their effects at both central and peripheral receptors. Blockade of β -receptors results in decreased production of intracellular cyclic adenosine monophosphate (cAMP) with a resultant blunting of multiple metabolic and cardiovascular effects of circulating catecholamines. β_1 -blockers reduce heart rate, blood pressure, myocardial contractility, and myocardial oxygen consumption. β_2 -receptor blockade inhibits relaxation of smooth muscle in blood vessels, bronchi, the gastrointestinal system, and the genitourinary tract. In addition, β -adrenergic receptor antagonism inhibits both glycogenolysis and gluconeogenesis, which may result in hypoglycemia.

[00193] β -blockers include, but are not limited to, atenolol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, and timolol. In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from, β -blockers that contain at least one aromatic moiety bearing at least one hydroxy moiety; hydroxy metabolites of β -blockers that contain at least one aromatic moiety bearing at least one hydroxy moiety; or a β -blocker having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment, the β -blocker is selected from among: atenolol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, and timolol.

[00194] Mixed α_1 and β -adrenergic blockers treat hypertension by blocking the α_1 -adrenergic receptor and β -adrenergic receptor. This decreases the sinus heart rate and peripheral vascular resistance, thereby decreasing cardiac output. Mixed α_1 and β -adrenergic blockers include, but are not limited to, bucindolol, carvedilol, and labetalol. In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from, mixed α_1 and β -adrenergic blockers that contain at least one aromatic moiety bearing at least one hydroxy moiety; hydroxy metabolites of mixed α_1 and β -adrenergic blockers that contain at least one aromatic moiety bearing at least one hydroxy moiety; or a mixed α_1 and β -

adrenergic blocker having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment, the mixed α_1 and β -adrenergic blocker is selected from among: carvedilol and labetalol. In another embodiment, the mixed α_1 and β -



adrenergic blocker is

(labetalol; 2-hydroxy-5-[1-hydroxy-2-(4-phenyl)butan-2-

ylamino)-ethyl]-benzamide).

[00195] Changes in intracellular Ca^{2+} regulate contraction through different mechanisms in cardiac and smooth muscle. For example, in cardiac muscle, Ca^{2+} binding to troponin C relieves troponin inhibition of actin-myosin interactions. Also, in smooth muscle, Ca^{2+} binding to calmodulin activates myosin light chain kinase which in turn phosphorylates the P-light chain of myosin, triggering contraction. There are a variety of ion pumps, channels, and exchangers that are directly involved in controlling intracellular Ca^{2+} .

[00196] Calcium channel blockers (CCBs) work by blocking voltage-sensitive calcium channels in the heart and in the blood vessels. This prevents calcium levels from increasing as much in the cells when stimulated, leading to less contraction. CCBs also decrease the force of contraction of the myocardium. CCBs also slow down the conduction of electrical activity within the heart, by blocking the calcium channel during the plateau phase of the action potential of the heart, causing a lowering of the heart rate. This is known as the negative chronotropic effect of CCBs. This effect makes CCBs a commonly used class of agents in individuals with atrial fibrillation in whom control of the heart rate is an issue.

[00197] CCBs include, but are not limited to, amlodipine, felodipine, isradipine, nifedipine, nimodipine, nitrendipine, diltiazem, and verapamil. In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from, CCBs that contain at least one aromatic moiety bearing at least one hydroxy moiety; hydroxy metabolites of CCBs that contain at least one aromatic moiety bearing at least one hydroxy moiety; or a CCB having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment, the CCB is selected from among amlodipine, felodipine, isradipine, nifedipine, nimodipine, nitrendipine, diltiazem, and verapamil.

[00198] Angiotensin I converting enzyme (ACE) is an exopeptidase that catalyses the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. ACE is also involved in the activation of bradykinin, a potent vasodilator. Modulation of ACE leads to the treatment of high blood pressure, heart failure, diabetic nephropathy, and type 2 diabetes mellitus. Inhibition of ACE results in decreased formation of angiotensin II and decreased inactivation of bradykinin. ACE inhibitors also lower arteriolar resistance and increase venous capacitance; and lower renovascular resistance.

[00199] ACE inhibitors include, but are not limited to, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril,trandopril, and benzapril. In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from, ACE inhibitors that contain at least one aromatic moiety bearing at least one hydroxy moiety; hydroxy metabolites of ACE inhibitors that contain at least one aromatic moiety bearing at least one hydroxy moiety; or an ACE inhibitor having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced

hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment, the ACE inhibitor is selected from among enalapril, fosinopril, lisinopril, quinapril, ramipril, trandopril, and benzapril.

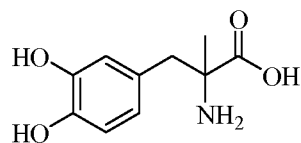
[00200] The renin-angiotensin-aldosterone system plays an important role in regulating blood volume, arterial pressure, and cardiac and vascular function. The most important site for renin release is the kidney. Sympathetic stimulation (acting via β_1 -adrenoceptors), renal artery hypotension, and decreased sodium delivery to the distal tubules stimulate the release of renin by the kidney. Renin is an enzyme that acts upon a circulating substrate, angiotensinogen, that undergoes proteolytic cleavage to form the decapeptide angiotensin I. Vascular endothelium, particularly in the lungs, has an enzyme, angiotensin converting enzyme (ACE), that cleaves off two amino acids to form the octapeptide, angiotensin II (AII). AII constricts resistance vessels (via AII receptors), thereby increasing systemic vascular resistance and arterial pressure. Also, AII acts upon the adrenal cortex to release aldosterone, stimulates the release of vasopressin from the posterior pituitary, facilitates norepinephrine release from the sympathetic nerve endings, inhibits norepinephrine re-uptake by nerve endings thereby enhancing sympathetic adrenergic function, and stimulates cardiac hypertrophy and vascular hypertrophy.

[00201] Angiotensin II receptor antagonists, modulate the renin-angiotensin-aldosterone system. As a result, angiotensin II receptor antagonists are primarily used for the treatment of hypertension, where the patient is intolerant to ACE inhibitor therapy. Angiotensin II receptor antagonists include, but are not limited to, candesartan, irbesartan, losartan, telmisartan, and valsartan. In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from, angiotensin II receptor antagonists that contain at least one aromatic moiety bearing at least one hydroxy moiety; hydroxy metabolites of angiotensin II receptor antagonists that contain at least one aromatic moiety bearing at least one hydroxy moiety; or an angiotensin II receptor antagonist having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment, the angiotensin II receptor antagonist is selected from among: candesartan, irbesartan, losartan, telmisartan, and valsartan.

[00202] Indirect-acting anti-adrenergic agents prevent the stimulation of peripheral adrenergic receptors and can be categorized into two groups, adrenergic neuron-blocking agents which decrease norepinephrine release and centrally acting adrenergic agents (α -agonists) which reduce the impulse along the sympathetic nerves.

[00203] Centrally acting adrenergic agents or central α -agonists lower blood pressure by stimulating α -receptors in the brain which open peripheral arteries easing blood flow. Centrally acting adrenergic agents include, but are not limited to, clonidine, guanabenz, and methyldopa. In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from, centrally acting adrenergic agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; hydroxy metabolites of centrally acting adrenergic agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; or a centrally acting adrenergic agent having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In one embodiment, centrally acting adrenergic agents are selected from the group consisting of:

clonidine, guanabenz, and methyl dopa. In another embodiment, the centrally acting adrenergic agent is



, methyl dopa (2-amino-3-(3,4-dihydroxyphenyl)-2-methyl-propanoic acid).

[00204] Adrenergic neuron-blocking agents include but are not limited to guanethidine and reserpine. In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from, adrenergic neuron-blocking agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; hydroxy metabolites of adrenergic neuron-blocking agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; or an adrenergic neuron-blocking agent having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein. In another embodiment the adrenergic neuron-blocking agent is reserpine.

v. Compounds of Formula (I) wherein HOA is a Decongestant Agent

[00205] Nasal congestion may be relieved through the use of a class of medications known as decongestants. Generally, decongestants work by reducing swelling of the mucous membranes in the nasal passages. The effects, however, are not limited to the nose and can cause an increase in hypertension (blood pressure). To combat the increase in hypertension, decongestants are often used in combination with antihistamines. Antihistamines themselves, however, have accompanying side effects such as sedation, dizziness, blurred vision, euphoria, uncoordination, anxiety, insomnia, nausea and vomiting. Thus, in one instance, a FAAH inhibitor having a decongestant representing an arylhydroxy containing release agent may be utilized to relieve nasal congestion. Since the decongestant is an integrated part of the FAAH inhibitor, reduction in the swelling of the mucous membrane in the nasal passage may be realized without the accompanying side effects. By way of example only, a FAAH inhibitor having a phenylephrine or phenylephrine-like moiety representing an arylhydroxy containing release agent may be utilized to treat conditions related to nasal congestion. Phenylephrine or neosynephrine, an α -adrenergic receptor agonist, acts as a vasoconstrictor wherein the lumina of blood vessels are narrowed and is advantageous over pseudoephedrine in that it does not cause the release of endogenous noradrenaline. Thus, phenylephrine is less likely to cause side-effects such as CNS stimulation, insomnia, anxiety, irritability and restlessness. In one embodiment is a FAAH inhibitor that when hydrolyzed by an amide hydrolase releases phenylephrine or a phenylephrine-like compound which is a vasoconstrictor. In another embodiment, is a FAAH inhibitor which may more effectively deliver the released phenylephrine or phenylephrine-like compound to an α -adrenergic receptor. In another embodiment, is a FAAH inhibitor having a phenylephrine or phenylephrine-like compound representing an arylhydroxy containing release agent, wherein effective treatment by the FAAH inhibitor is realized by synergistic means. In another embodiment, is a FAAH inhibitor having a phenylephrine or phenylephrine-like compound representing an arylhydroxy containing release agent, wherein effective treatment of the FAAH inhibitor is realized by additive means.

[00206] Epinephrine increases peripheral resistance via α -stimulated vasoconstriction in cardiac dysrhythmia resulting in diminished or absent cardiac output. It activates β -adrenergic receptors of the liver and muscle cells, thereby activating the adenylate cyclase signaling pathway, which in turn increases glycogenesis. Additionally, epinephrine is

used to treat anaphylaxis and sepsis and may be used as a bronchodilator for asthma. Thus, in one embodiment is a FAAH inhibitor having an epinephrine or an epinephrine-like arylhydroxy containing therapeutic agent for treatment of cardiac dysrhythmia. In another embodiment, is a FAAH inhibitor having an epinephrine or an epinephrine-like arylhydroxy containing therapeutic agent wherein effective treatment of cardiac dysrhythmia is realized by synergistic means. In another embodiment, is a FAAH inhibitor having an epinephrine or an epinephrine-like arylhydroxy containing therapeutic agent wherein effective treatment of cardiac dysrhythmia is realized by additive means. In another embodiment, is a FAAH inhibitor wherein the arylhydroxy containing therapeutic agent is a metabolite of epinephrine or epinephrine-like compound.

w. Compounds of Formula (I) wherein HOA is a Phytochemical

[00207] In another embodiment is a FAAH inhibitor having a phytochemical or phytochemical-like compound as an arylhydroxy release agent. In another embodiment, the FAAH inhibitor having a phytochemical or phytochemical-like compound as an arylhydroxy release agent treats a disease, disorder, or condition related to inflammation. In another embodiment, the FAAH inhibitor having a phytochemical or phytochemical-like compound as an arylhydroxy release agent is an antibiotic. In another embodiment, the FAAH inhibitor having a phytochemical or phytochemical-like compound as an arylhydroxy release agent promotes the function of the immune system, treats and/or prevents cancer and cardiovascular diseases.

[00208] Phytochemicals derived from the plants remain the basis for a large proportion of the commercial medications used today for the treatment of a wide range of diseases such as high blood pressure, pain, and asthma. For instance, ephedrine, a phytochemical, is used in the commercial pharmaceutical preparations for the relief of asthma symptoms and other respiratory problems.

[00209] In some embodiments, the therapeutic agent containing at least one aromatic ring bearing at least one hydroxy moiety is oleocanthal. Oleocanthal or (3*S*,4*E*)-2-(4-hydroxyphenyl)ethyl 4-formyl-3-(2-oxoethyl)-4-hexenoate is an organic compound isolated from olive oil and has been found to have anti-inflammatory and antioxidant properties. Studies have shown that similar to NSAIDs, oleocanthal is a non-selective inhibitor of cyclooxygenase 1 and 2 (COX-1 and COX-2). In one embodiment, described herein is a FAAH inhibitor wherein oleocanthal is released upon FAAH inhibition, wherein such carbamate compound is used in the treatment of diseases, disorders, or conditions related to, but not limited to, inflammation. In another embodiment described herein is a FAAH inhibitor wherein a metabolite of an oleocanthal-like compound is released upon FAAH inhibition. In another embodiment, is a FAAH inhibitor wherein the oleocanthal or oleocanthal-like release agent provides an effective treatment of diseases, disorders, or conditions related to inflammation via synergistic means. In another embodiment, is a FAAH inhibitor wherein the oleocanthal or oleocanthal-like release agent provides an effective treatment of diseases, disorder, or conditions related to inflammation via additive means.

[00210] In another embodiment is a FAAH inhibitor having a coumaric acid or coumaric acid-like compound representing an arylhydroxy release agent. In another embodiment is a FAAH inhibitor having a coumaric acid or coumaric acid-like compound representing an arylhydroxy release agent for the treatment of diseases, disorders, or conditions related to coumaric acid. In another embodiment is a FAAH inhibitor having a coumaric acid or coumaric acid-like compound representing an arylhydroxy release agent wherein the amount of coumaric acid or coumaric acid-

like compound is used for the treatment of cancer. In another embodiment is a FAAH inhibitor having a coumaric acid or coumaric acid-like compound representing an arylhydroxy release agent wherein the amount of coumaric acid or coumaric acid-like compound is used as an antioxidant. In another embodiment is a FAAH inhibitor having a coumaric acid or coumaric acid-like compound representing an arylhydroxy release agent wherein the amount of coumaric acid or coumaric acid-like compound is used to reduce the formation of carcinogenic nitrosamines. In another embodiment is a FAAH inhibitor having a coumaric acid or coumaric acid-like compound representing an arylhydroxy release agent wherein the amount of coumaric acid or coumaric acid-like compound delivered potentiates the amount of coumaric acid to treat coumaric acid related conditions. In another embodiment, the potentiating amount of coumaric acid via administration of a FAAH inhibitor having a coumaric acid or coumaric acid-like compound representing an arylhydroxy release agent is realized through synergistic means. In another embodiment, the potentiating amount of coumaric acid via administration of a FAAH inhibitor having a coumaric acid or coumaric acid-like compound representing an arylhydroxy release agent is realized through additive means. In another embodiment is a FAAH inhibitor wherein the arylhydroxy containing release agent is a metabolite of a coumaric acid-like compound.

[00211] Animal studies have provided evidence that resveratrol can provide anti-ageing, life-span extending, and/or delayed motor and cognitive age-related benefits. Other animal studies have shown that resveratrol improves mitochondrial function thereby increasing athletic performance characteristics. In another embodiment described herein is a FAAH inhibitor having a resveratrol or resveratrol-like compound as the therapeutic release agent. In another embodiment are the use of such inhibitors for the treatment of diseases, disorders, or conditions in which resveratrol has shown efficacy, including for the treatment of cancer. In another embodiment are the uses of such inhibitors as an antioxidant, antiviral, neuroprotective, anti-aging, and/or anti-inflammatory agent. In another embodiment such inhibitors are used to inhibit lipase and reduce the absorption of fat through the intestinal walls. In another embodiment, such inhibitors are used to delay motor and cognitive age-related degradation in a subject. In another embodiment, such inhibitors are used to increase athletic performance characteristics in a subject.

[00212] In another embodiment is a FAAH inhibitor having a resveratrol or resveratrol-like compound representing an arylhydroxy release agent. In another embodiment is a FAAH inhibitor having a resveratrol or resveratrol-like compound representing an arylhydroxy release agent for the treatment of diseases, disorders, or conditions related to resveratrol. In another embodiment is a FAAH inhibitor having a resveratrol or resveratrol-like compound representing an arylhydroxy release agent wherein the amount of resveratrol or resveratrol-like compound is used for the treatment of cancer. In another embodiment is a FAAH inhibitor having a resveratrol or resveratrol-like compound representing an arylhydroxy release agent wherein the amount of resveratrol or resveratrol-like compound is used as an antioxidant, antiviral, neuroprotective, anti-aging, and anti-inflammatory. In another embodiment is a FAAH inhibitor having a resveratrol or resveratrol-like compound representing an arylhydroxy release agent wherein the amount of resveratrol or resveratrol-like compound induces Fas/Fas ligand mediated apoptosis, p53 and cyclins A, B1 and cyclin-dependent kinases cdk 1 and 2. In another embodiment is a FAAH inhibitor having a resveratrol or resveratrol-like compound representing an arylhydroxy release agent wherein the amount of resveratrol or resveratrol-like compound activates SIRT1 and PGC-1 α . In another embodiment is a FAAH inhibitor having a resveratrol or resveratrol-like compound representing an arylhydroxy release agent wherein the amount of resveratrol or resveratrol-like compound inhibits lipase and reduces the

absorption of fat through the intestinal walls. In another embodiment is a FAAH inhibitor having a resveratrol or resveratrol-like compound representing an arylhydroxy release agent wherein the amount of resveratrol or resveratrol-like compound delivered potentiates the amount of resveratrol to treat resveratrol related conditions. In another embodiment, the potentiating amount of resveratrol via administration of a FAAH inhibitor having a resveratrol or resveratrol-like compound representing an arylhydroxy release agent is realized through synergistic means. In another embodiment, the potentiating amount of resveratrol via administration of a FAAH inhibitor having a resveratrol or resveratrol-like compound representing an arylhydroxy release agent is realized through additive means. In another embodiment is a FAAH inhibitor wherein the arylhydroxy containing release agent is a metabolite of a resveratrol-like compound.

[00213] Natural Products, including but not limited to phytochemicals.

[00214] Phytochemicals include, but are not limited to: Alkaloids, Anthocyanins, Carotenes, Coumestans (phytoestrogens), Flavan-3-Ols, Flavonoids such as, but are not limited to: luteolin, apigenin (see for example, *Pharmacological Review*, 2000, 52:673-751, and *The American Journal of Chemical Nutrition*, 2002; 76: 560-68, which are herein incorporated by reference in their entirety), Hydroxycinnamic Acids, Isoflavones such as but not limited to genistein and daidzein, Lignans (see for example, *JPET* #100149 "Sesamin Metabolites Induce an Endothelial Nitric Oxide-Dependent Vasorelaxation through Their Antioxidative Property-Independent Mechanisms: Possible Involvement of the Metabolites in the Antihypertensive Effect of Sesamin," which is herein incorporated by reference in its entirety), Monophenols, Monoterpenes, Organosulfides, Phenolic Acids, Phytosterols, Saponins, Triterpenoids, Xanthophylls.

[00215] Non-limiting examples of phytochemicals include:

Apiol, Carnosol, Carvacrol, Quercetin, Gingerol, Kaempferol, Resveratrol, Rutin, Hesperidin, Silybin (Silibinin; Silymarin), Baicalein, Catechin, Epigallocatechin Gallate (3,4-dihydro-5,7-dihydroxy-2R-(3,4,5-trihydroxyphenyl)-2H-1-benzopyran-3R-yl-3,4,5-trihydroxy-benzoate), Genistein, Hesperetin, Quercetin, Daidzein, Diethylstilbestrol, Estrone, Tannic Acid, Apigenin, Epicatechin, Epigallocatechin, Anthocyanidin, Aurantinidin, Cyanidin, Delphinidin, Europinidin, Luteolinidin, Pelargonidin, Malvidin, Peonidin, Petunidin, Rosinidin, Ellagic Acid, Gallic acid, Chicoric acid, Kaempferol, Naringin, Proanthocyanidins, Ferulic acid, Scopoletin, Daidzein Hydroxytyrosol, Amnacanthol, Capsaicin, Rosmarinic acid, rosmarinol; flavonoids (polyphenols), such as but not limited to, flavonols such as but not limited to: myricetin, quercetin, and kaempferol, flavanones such as but not limited to: hesperetin and naringenin, flavones, flavan-3-ols, such as but not limited to: catechin, epicatechin, and epigallocatechin, anthocyanins (flavonols), such as but not limited to: cyanidin, malvidin, and delphinidin, isoflavones (phytoestrogens), dihydroflavonols, chalcones,; salicylic acid, tannic acid, vanillin, capsaicin, curcumin, caffeic acid, chlorogenic acid, cinnamic acid, ferulic acid, lignans (phytoestrogens), silymarin, matairesinol, secoisolariciresinol, tocopherols (vitamin E), quercetin, gingerol, kaempferol, resveratrol, rutin, apigenin, tangeritin, catechins, pelargonidin, peonidin, cyanidin, delphinidin, malvidin, daidzein (formononetin), genistein (biochanin A), glycitein, coumestrol.

[00216] Anthocyanins and Anthochlors

Abyssinone VI, Apigeninidin, Aurantinidin, Aureusidin, Bracteatin, Butein, Capensinidin, Carthamone, Isosalipurpol, Cyanidin, Cyanidin 3-O-galactoside, Cyanidin 3-O-glucoside, Cyanidin 3-O-(6"-glucosyl-2"-xylosylgalactoside), Cyanidin 3-O-rutinoside, Cyanidin 3,5,3'-tri-O-glucoside, Cyanin, Delphinidin,

Delphinidin 3,3',5'-tri-O-glucoside, Gentiodelphin, Heavenly blue anthocyanin, Hirsutidin, Hispidol, 6-Hydroxycyanidin, Isobavachalcone, Isobutrin, Isoliquiritigenin, Leptosidin, Luteolinidin, Malonylawobanin, Malvidin, Malvin, Maritimetin, 4,5-Methylenedioxy-6-hydroxyaurone, Monardaein, Okanin, Pelargonidin, Pelargonin, Peonidin, Petunidin, Riccionidin A, Rosinidin, Sulphuretin, Xenognosin A

[00217] Benzofurans

Albafuran A, Albanol A, alpha-Cotonefuran, beta-Cotonefuran, Dehydrotremetone, 2,8-Dihydroxy-3,4,7-trimethoxydibenzofuran, Eriobofuran, Griseofulvin, 6-Hydroxytremetone, Lithospermic acid, 6-Methoxy-alpha-pyrufuran, 6-O-Methyleuparin, Moracin A, Mulberrofuran A, Mulberrofuran C, alpha-Pyrufuran, beta-Pyrufuran, psi-Rhodomyrtoxin, Sainfuran, Toxol, Toxyl angelate, Tremetone, (-)-Usnic acid, Vignafuran

[00218] Chromones and Chromenes

Aloesin, Aurasperone D, Biflorin, Butyrylmallotochromene, Cannabichromene, Capillarisin, Cimifugin, 5,7-Dihydroxychromone, 8-(3,3-Dimethylallyl)spatheliachromene, 2,2-Dimethyl-8-prenylchromene 6-carboxylic acid, Drummondin A, Encecalin, Eupatoriachromene, Flindersiachromene, Frutinone A, Isobutyrylmallotochromene, Khellin, Khellol glucoside, Lathodoratin, Mallotochromene, 2-(4-Methoxyphenethyl)chromone, 5-O-Methylallopteroxylin, Methylripariochromene A, 5-O-Methylvisaminol, Precocene 1, Precocene 2, Ptaerochromenol, Ptaeroglycol, Pulverochromenol, Quinquangulin, Rubrofusarin, Spathelia bischromene, Visnagin

[00219] Coumarins

Aflatoxin B1, Alloimperatorin, Ammoresinol, Angelicin, Archangelicin, Athamantin, Bergapten, Byakangelicin, Calanolide A, Calophyllolide, Chalepensisin, Chartreusin, Cichoriin, Columbianetin, Coumarine, Coumermycin A1, 7,8-Dihydroxycoumarin, Daphnoretin, Decuroside III, Decursin, Decursinol, Dicumarol, Dihydrosamidin, Disenecionyl cis-khellactone, (3'R,4'R)-3'-Epoxyangeloyloxy-4'-acetoxy-3',4'-dihydroseselin, Esculetin, Esculin, Fraxetin, Fraxin, Heliettin, Herniarin, Imperatorin, Isopimpinellin, Isosamidin, Leptodactylone, Libanorin, Luvangetin, Mammeisin, Marmesin, Micromelin, Nodakenetin, Nodakenin, Novobiocin, Osthol, Ostruthin, Oxypeucedanin, Peucedanin, Peucenidin, Pimpinellin, Psoralen, Pteryxin, Rutamarin, Rutarin, Samidin, Scoparone, Scopoletin, Scopolin, Seselin, 5,6,7-Trimethoxycoumarin, 4,8,5'-Trimethylpsoralen, Umbelliferone, Visnadin, Xanthotoxin, Xanthotoxol, Xanthyletin

[00220] Minor Flavonoids

Abyssinone I, Abyssinone V, Afzelechin, Dihydromyricetin, Dihydrokaempferol, Asebogenin, Auriculoside, Betagarin, Broussin, Broussonin C, Butin, Butrin, (+)-Catechin, Catechin 7-O-beta-D-xyloside, Davidigenin, Diffutin, 7,4'-Dihydroxyflavan, 2',6'-Dihydroxy-4'-methoxydihydrochalcone, 7,3'-Dihydroxy-4'-methoxy-8-methylflavan, 7,4'-Dihydroxy-8-methylflavan, 6,8-Diprenylnaringenin, Dracorubin, (-)-Epicatechin, ent-Epicatechin, Epigallocatechin 3-gallate, Eriocitrin, Eriodictyol, Farrerol, Fisetinidol, Fisetinidol-4beta-ol, Fustin, Garbanzol, Glabranin, Glepidotin B, Glycyphyllin, Hesperetin, Hesperidin, Homoeriodictyol, 7-Hydroxyflavan, Isochamaejasmin, 4'-Methoxy-5,7-dihydroxyflavonone, Isouvetarin, Kazinol A, Kolaflavanone, Liquiritigenin, Manniflavanone, 6-Methoxyaromadendrin 3-O-acetate, 6-Methoxytaxifolin, 2'-O-Methylodoratol, Naringenin, Naringin, Narirutin, Neoastilbin, Neoeriodictin, Neohesperidin, Odoratol,

Phellamurin, Phloretin, Phlorizin, Pinobanksin, Pinocebrin, Pinocebrin 7-rhamnosylglucoside, Piperaduncin B, Poncirin, 5'-Prenylhomoeiodictyol, 6-Prenylnaringenin, Naringenin 7-O-beta-D-glucoside, Sakuranetin, Sanggenon C, Sanggenon D, Silandrin, Silymarin, Silychristin, Sophoranone, Strobopinin, Taxifolin, Taxifolin 3-O-acetate, Tephrowatsin A, Theasinensin A, 2',4',6'-Trihydroxy-3'-formyldihydrochalcone, Uvaretin

[00221] Flavones and Flavonols

Acacetin, Acerosin, Agathisflavone, Amentoflavone, Apigenin, Apigenin 7,4'-dimethyl ether, 7-O-beta-D-Glucosyl-5,7,4'-trihydroxyflavone, Apigenin 7-(6"-malonylglucoside), 7-O-(beta-D-apiofuranosyl-1,2-beta-D-glucosyl)-5,7,4'-trihydroxyflavone, Axillarin, Azaleatin, Baicalein, Baicalein 5,6,7-trimethyl ether, Baicalin, Carlinoside, Chlorflavonin, Chrysin, Chrysin 5,7-dimethyl ether, 5,7,4'-Trihydroxy-3'-methoxyflavone, Chrysosplenin, Chrysosplenol C, Cirsilineol, Cirsiliol, Cupressuflavone, Dasytrichone, Datisctetin, 5-Deoxykaempferol, Diosmetin, Diosmin, Eupatilin, Fisetin, Fisetin 8-C-glucoside, Flavone, Galangin, Galangin 3,5,7-trimethyl ether, Genkwanin, Geraldone, Ginkgetin, Glepidotin A, 3,3',4',5,7,8-Hexahydroxyflavone, Gossypetin 8-rhamnoside, Gossypin, 8-Hydroxykaempferol, Hinokiflavone, Hispidulin, 6-Hydroxykaempferol, 6-Hydroxyluteolin, Hyperin, Hypolaetin, Isoetin, Isoorientin, Quercetin 3-O-glucoside, Isorhamnetin, Isoscaparin, Isoscutellarein, Apigenin-6-C-glucoside, Kaempferide, Kaempferol, 3-Methoxyapigenin, Kuwanone G, Kuwanone H, Lucenin-2, Luteolin, Luteolin 7-O-beta-D-glucoside, Luteolin 7-O-(6"-malonylglucoside), 6-Methoxyluteolin 7-rhamnoside, Morin, Morusin, Myricetin, Myricitrin, Neocarlinoside, Neoschaftoside, Nevadensin, Nobiletin, Norwogonin, Orientin, Oxyayanin A, Oxyayanin B, Pachypodol, Patuletin, Pedalitin, Pinoquercetin, Primetin, Quercetagenin, Quercetin, 3',4',5,7-Tetrahydroxy-3-methoxyflavone, Quercetin 3-(2G-xylosylrutinoside), Quercetin 7-O-glucoside, Quercitrin, Rhamnetin, Robinetin, Robinin, Robustaflavone, Rutin, Santin, Schaftoside, Sciadopitysin, Scullcapflavone II, Scutellarein, Sexangularetin, Sinensetin, Swertiajaponin, Tamarixetin, Tambulin, Tangeretin, Thymonin, Tricetin, Tricin, Velloquercetin, Vicenin-2, Violanthin, Vitexin, Wogonin

[00222] Isoflavonoids and Neoflavonoids

(-)-Acanthocarpin, Afrormosin, Anhydroglycinol, Betavulgarin, Biochanin A, Bowdichione, Cajanin, Cajanol, Coumestrol, Cristacarpin, Cyclokievitone, Daidzein, Daidzin, Dalbergin, (+)-Dalbergioidin, Dalpanin, Deguelin, (+)-5-Deoxykievitone, Ferreirin, Formononetin, Genistein, Genistein 8-C-glucoside, Genistein 7-O-beta-D-glucoside, Glabridin, Glyceollin, (-)-Glyceollin II, Hildecarpin, Hispaglabridin A, Homoferreirin, 4-Hydroxyhomopterocarpin, 12a-Hydroxyrotenone, Iridin, Iridone, Irisolidone, Kievitone, Licoisoflavone A, Lonchocarpin, Lotisoflavan, Luteone, (-)-Maackiain, (-)-Medicarpin, Melannin, (R)-4-Methoxydalbergione, Millettone, Mucronulatol, (-)-Nissolin, Ononin, Orobol, Osajin, Pachyrrhizone, Paniculatin, Phaseollidin, (-)-Phaseollin, (-)-Phaseollinisoflavan, Pisatin, Piscerythramine, Pomiferin, Pratensein, Prunetin, Pseudobaptigenin, Psoralidin, Puerarin, Rotenone, Rotenonone, (-)-Sativan, Sayanedin, Sojagol, Sophoraisoflavanone A, (-)-Sparticarpin, Sumatrol, Tectoridin, Tectorigenin, Tephrosin, Texasin, Toxicarol, Trifolirhizin, (-)-Variabilin, Vestitol, Vestitone, Wedelolactone, Wightone

[00223] Lignans

Acanthoside D, 1-Acetoxyypinoresinol, (-)-Arctigenin, Austrobailignan 1, Burseran, Cleistanthin A, Cubebin, Dehydrodieugenol, 5'-Demethoxydeoxypodophyllotoxin, 4'-Demethyldeoxypodophyllotoxin, 4'-Demethylpodophyllotoxin, Denudatin B, Deoxygomisin A, Deoxypodophyllotoxin, Dihydroanhydropodorhizol, Dihydrocubebin, Diphyllin, Eucommin A, (+)-Eudesmin, Eudesobovatol A, Fargesone A, Futoquinol, (+)-Galbacin, Gomisin L1 methyl ether, Grandisin, Hinokinin, cis-Hinokiresinol, Honokiol, Justicidin A, Justicidin B, Kadsurenone, Kadsurin A, Lariciresinol, Licarin A, Magnolol, Magnosalicin, Magnoshinin, Matairesinol, Megaphone, Neoisostegane, Nordihydroguaiaietic acid, Nortrachelogenin, Otobain, alpha-Peltatin, beta-Peltatin A methyl ether, Phymarolin I, Phyllanthin, Phyllanthostatin A, Picropodophyllin, Pinoresinol, Plicatic acid, Podophyllotoxin, Podophyllotoxone, Podorhizol beta-D-glucoside, Prostalidin A, Randainol, Saucernetin, Savinin, Schisantherin A, Sesamin, Sesamolol, Sesartemin, Simplexoside, Steganacin, Styraxin, Surinamensin, (+)-Syringaresinol, (+)-Syringaresinol O-beta-D-glucoside, Trachelogenin, (+)-Veraguensin, Wuweizisu C, Yangambin

[00224] Phenols and Phenolic Acids

Anacardic acid, p-Anisaldehyde, Antiarol, Arbutin, Ascosalitoxin, Bilobol, Cannabidiol, Cannabidiolic acid, 2,6-Dimethoxyphenol, Ellagic acid, Gallate, 2,5-Dihydroxybenzoate, Gentisyl alcohol, Geranylhydroquinone, Ginkgoic acid, 1-O-Galloyl-beta-D-glucose, Grevillol, Guaiacol, 5-(Heptadec-12-enyl)resorcinol, Hydroquinone, 4-Hydroxybenzaldehyde, 4-Hydroxybenzoate, 2-Hydroxymethylbenzoic acid, Leiocarposide, 4-Methylcatechol, 6-Methylsalicylate, Orcinol, 5-Pentadecylresorcinol, Phenylethyl alcohol, Phloroglucinol, Piperonal, Populin, 3,4-Dihydroxybenzoate, 2,3-Dihydroxybenzoate, 2,3-Trihydroxybenzene, Resorcinol, Salicin, Salicylate, Sesamol, Syringic acid, Dronabinol, Theogallin, Trichocarpin, 3,4,3'-Tri-O-methylellagic acid, Turgorin, Turricolol E, Urushiol III, Vanillate, 4-Hydroxy-3-methoxy-benzaldehyde, Zinniol

[00225] Phenolic Ketones

Acetophenone, Acetosyringone, 3-Acetyl-6-methoxybenzaldehyde, Agrimol C, Agrimophol, Apocynin, Aspidin, Aspidinol, Danielone, 3',4'-Dihydroxyacetophenone, 2',6'-Dihydroxy-4'-methoxyacetophenone, 2',6'-Dimethoxy-4'-hydroxyacetophenone, Filixic acid BBB, Humulone, 4'-Hydroxyacetophenone, 4'-Hydroxy-3'-prenylacetophenone, alpha-Kosin, Lupulone, Mallotophenone, Multifidol, Paeonol, Paeonolide, Paeonoside, Picein, Rottlerin, Tricyclodehydroisohumulone, Xanthoxylin

[00226] Phenylpropanoids

1'-Acetoxychavicol acetate, 1'-Acetoxyeugenol acetate, Anethole, Apiole, beta-Asarone, 3,4-Dihydroxy-trans-cinnamate, Caffeic acid 3-glucoside, 1-Caffeoyl-4-deoxyquinic acid, 1-Caffeoyl-beta-D-glucose, N-Caffeoylputrescine, 5-O-Caffeoylshikimic acid, Carpacin, Centrolobine, Chicoric acid, Chlorogenate, Cinnamaldehyde, 4'-Cinnamoylmussatioside, Coniferin, Coniferyl alcohol, Coniferyl aldehyde, 2-Coumarate, 4-Coumarate, 4-p-Coumaroylquinic acid, 4-Coumaryl alcohol, Curcumin, 3'-Demethoxyipilartine, 1,3-Dicaffeoylquinic acid, Diferulic acid, Dihydrocaffeic acid, Dihydroconiferyl alcohol, Dillapiole, Echinacoside, Elemicin, Estragole, Eugenol, Eugenol methyl ether, Fagaramide, Ferulate, Forsythiaside, Furcadin, [6]-Gingerdione, Gingerenone A, [6]-Gingerol, Grandidentatin, Hellicoside, Isochlorogenic acid b, Isoeugenol,

Isoferulic acid, Jionoside B1, Lusitanicoside, 3-(2-Hydroxyphenyl)propanoate, p-Methoxycinnamaldehyde, p-Methoxycinnamic acid ethyl ester, Methyl caffeate, Methylisoeugenol, Myricoside, Myristicin, Orobanchoside, [6]-Paradol, Phaseolic acid, Phenethyl caffeate, Plantamajoside, Prenyl caffeate, Purpureaside C, Rosmarinic acid, Salvianolic acid A, Sarisan, [6]-Shogaol, Sinapoyl aldehyde, Sinapoylcholine, Sinapyl alcohol, Sphagnum acid, Subaphyllin, Suspensaside, 1,3,4,5-Tetracaffeoylquinic acid, Verbascoside

[00227] Quinones

Acamelin, Alizarin, Alizarin 2-methyl ether, Alkannin, Alkannin beta,beta-dimethylacrylate, Aloe-emodin, Alteichin, Altersolanol A, Anthragallol, Ardisianone, Aristolindiquinone, Arnebinone, Aurantio-obtusin beta-D-glucoside, Barbaloin, Bikaverin, Cascaroside A, Cassiamin C, Cercosporin, Chimaphyllin, 7-Chloroemodin, Chrysazin, Chryso-obtusin glucoside, Chrysophanic acid 9-anthrone, Chrysophanol, Chrysophanol 8-O-beta-D-glucoside, Coleone A, Conocurvone, Cornudentanone, Cyperaquinone, Cypripedin, Deoxylapachol, Digiferrugineol, 1,4-Dihydroxy-2-methylanthraquinone, 2,6-Dimethoxybenzoquinone, Diospyrin, Dothistromin, Droserone, Dunnione, Echinone, Eleutherin, Embelin, Emodin, Emodin 8-glucoside, Frangulin A, Frangulin B, Geranylbenzoquinone, Hibiscoquinone A, 2-Hydroxymethylanthraquinone, Hypericin, Hypoxylone, Isodiospyrin, 2-Isoprenylemodin, 5-Hydroxy-1,4-naphthoquinone, Kigelinone, Knipholone, Lapachol, beta-Lapachone, Lawsone, Lucidin, Lucidin omega-methyl ether, Mansonone C, 9-Methoxy-alpha-lapachone, 5-O-Methylembelin, Morindaparvin A, Morindone, (1S,3R)-Nanaomycin A, Naphthazarin, Norobtusifolin, Obtusifolin 2-glucoside, Physcion 8-gentiobioside, Physcion 8-glucoside, Plastoquinone-9, Plastoquinone, Plumbagin, Prenylbenzoquinone, Primin, Pseudohypericin, Pseudopurpurin, Purpurin, Purpurin 1-methyl ether, Ramentaceone, Rapanone, Rhein, Rubiadin, Sennoside A, Tectoquinone, Tricozarin A, Ubiquinone-10, Ventinone A, Phylloquinone

[00228] Stilbenoids

Agrostophyllin, Astringin, Batatasin I, Batatasin IV, Blestriarene B, Canaliculatol, Chlorophorin, Coelogen, Copalliferol B, Demethylbatatasin IV, Dihydropinosylvin, Dihydroresveratrol, 4,4'-Dihydroxy-3,5-dimethoxydihydrostilbene, 4,7-Dihydroxy-2-methoxy-9,10-dihydrophenanthrene, Flavidin, Glepidotin C, Gnetin A, Hircinol, Hydrangenol, 3-Hydroxy-5-methoxy-6-prenylstilbene-2-carboxylic acid, Isobatatasin I, Isorhapontin, Loroglossol, Lunularic acid, Lunularin, Marchantin A, 3'-O-Methylbatatasin III, Orchinol, Oxyresveratrol, Phyllostulcin, 3,3',4',5'-Tetrahydroxystilbene, Piceid, Pinosylvin, Pinosylvin methyl ether, 4-Prenyldihydropinosylvin, 4'-Prenyloxyresveratrol, 4-Prenylresveratrol, Pterostilbene, 3,4',5-Trihydroxystilbene, Rhaponticin, epsilon-Viniferin

[00229] Tannins

Afzelechin-(4 α ->8)-afzelechin, Agrimoniin, Alnusiin, Casuarictin, Casuarinin, Chebulagic acid, Chebulinic acid, Cinchonain 1a, Coriariin A, Corilagin, 3,5-Di-O-galloyl-4-O-digalloylquinic acid, Epicatechin-(4 β ->8)-ent-epicatechin, [Epicatechin-(4 β ->8)]5-epicatechin, Epigallocatechin-(4 β ->8)-epicatechin-3-O-gallate ester, Eugeniin, ent-Fisetinidol-(4 β ->8)-catechin-(6->4 β)-ent-fisetinidol, Fucofuroeckol B, Gallocatechin-(4 α ->8)-epigallocatechin, Gambiriin C, Gemin A, Geraniin, Guibourtinidol-(4 α ->6)-catechin, Isoterchebin, Kandelin A-1, Mahuannin D, Mallotusinic acid, Pedunculagin, 1,2,3,4,6-Pentakis-O-galloyl-beta-D-glucose,

Proanthocyanidin A2, Procyanidin B4, Robinetinidol-(4 α ->8)-catechin-(6->4 α)-robinetinidol, Rugosin D, Tellimagrandin I, Terminalin, 1,2,3,4-Tetragalloyl- α -D-glucose

[00230] Xanthones

Athyriol, Bellidifolin, Calophyllin B, Dehydrocycloguanandin, Demethylbellidifolin, 6-Deoxyjacareubin, 3,5-Dimethoxy-1,6-dihydroxyxanthone, Euxanthone, Gambogic acid, Gartanin, Gentiacalein, Gentisein, Gentisin, Irisxanthone, Isoathyriol, Isogentisin, 1-Isomangostin, Jacareubin, Lancerin, Macluraxanthone, Mangiferin, Mangostin, Mesuaxanthone A, Mesuaxanthone B, 2-O-Methylswertianin, Morellin, Norathyriol, Norlichexanthone, Norswertianin, Norswertianolin, Psorospermin, Swerchirin, Swertianin, Swertianolin, 1,3,5-Trihydroxyxanthone, Tripteroside

[00231] Miscellaneous Phenolics

Acrovestone, Arnebinol, Aucuparin, Bergenin, Brazilin, 3-Butylidene-7-hydroxyphthalide, Cleomiscosin A, Cyperine, Daphneticin, 5,6-Dehydrokawain, Dihydromethysticin, Euglobal-Ia1, Flossonol, Garcinol, Goniotalenol, Haematoxylin, Haemocorin, Heritonin, (+)-8-Hydroxycalamenene, Hypercalin B, Karwinaphthol B, Karwinskione, Kawain, Kolanone, Lapachenole, Maclurin, 6-Methoxymellein, Methysticin, Monocerin, Nepodin, Ochrotoxin A, Ohioensin-A, Orthosporin, Paeoniflorin, Polygonolide, Purpurogallin, Rhododendrin, Robustadial A, Robustaol A, Sarothralin, Stybandrol, Tremulacin, 2,4,8-Trihydroxy-1-tetralone, Uncinatone, Vismione D, Xanthochymol, Yangonin, Zearalenone, Zinnolide.

x. Compounds of Formula (I) wherein HOA is a Phenethylamine

[00232] Substituted phenethylamines are a broad and diverse class of compounds that include neurotransmitters, hormones, stimulants, hallucinogens, entactogens, anorectics, bronchodilators, and antidepressants.

[00233] Phenethylamines that contain at least one phenolic moiety or that can be derivatized to have at least one phenolic moiety include, but are not limited to:

[00234] Tyramine (4-hydroxy-phenethylamine); Dopamine (3,4-dihydroxy-phenethylamine); Epinephrine (Adrenaline) (β ,3,4-trihydroxy-N-methyl-phenethylamine); Norepinephrine (Noradrenaline) (β ,3,4-trihydroxyphenethylamine); Salbutamol (4-(2-(tert-Butylamino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol); Amphetamine (α -methyl-phenethylamine); Methamphetamine (N-methyl-amphetamine); Levmetamfetamine (N-methyl-amphetamine); Ephedrine; pseudoephedrine (N-methyl- β -hydroxy-amphetamine); Cathine (β -hydroxy-amphetamine); Cathinone (β -keto-amphetamine); Methcathinone (N-methyl- β -keto-amphetamine); Bupropion (3-chloro-N-tert-butyl- β -keto-amphetamine); Fenfluramine (3-trifluoromethyl-N-ethyl-amphetamine); Phentermine (α , α -dimethyl-phenethylamine); Mescaline (3,4,5-trimethoxy-phenethylamine); MDA (3,4-methylenedioxy-amphetamine); MDMA (3,4-methylenedioxy-N-methyl-amphetamine); MDMC (3,4-methylenedioxy-N-methyl- β -keto-amphetamine); DOM (2,5-dimethoxy-4-methyl-amphetamine); DOB (2,5-dimethoxy-4-bromo-amphetamine); DON (2,5-dimethoxy-4-nitro-amphetamine); 2C-B (2,5-dimethoxy-4-bromo-phenethylamine); 2C-C (2,5-dimethoxy-4-chloro-phenethylamine); DOI (2,5-dimethoxy-4-iodo-amphetamine); 2C-I (2,5-dimethoxy-4-iodo-phenethylamine); 2C-D (2,5-dimethoxy-4-methyl-phenethylamine); 2C-E (2,5-dimethoxy-4-ethyl-phenethylamine); 2C-N (2,5-dimethoxy-4-Nitro-phenethylamine); 2C-T-2 (2,5-dimethoxy-4-ethylthio-phenethylamine); 2C-T-4 (2,5-dimethoxy-4-(i)-propylthio-phenethylamine); 2C-T-7 (2,5-

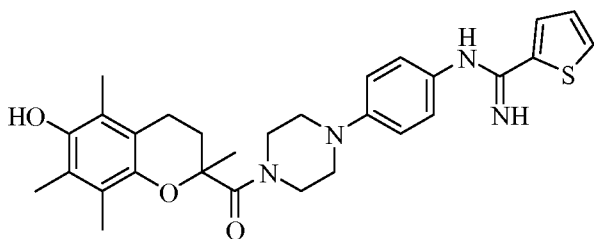
dimethoxy-4-propylthio-phenethylamine); 2C-T-8 (2,5-dimethoxy-4-cyclopropylmethylthio-phenethylamine); 2C-T-9 (2,5-dimethoxy-4-(t)-Butylthio-phenethylamine); 2C-T-21 (2,5-dimethoxy-4-(2-fluoroethylthio)-phenethylamine).

[00235] Phenethylamines that contain at least one aromatic ring bearing at least one hydroxy moiety include but are not limited to; Tyramine (4-hydroxy-phenethylamine); Dopamine (3,4-dihydroxy-phenethylamine); Epinephrine (Adrenaline) (β ,3,4-trihydroxy-N-methyl-phenethylamine); Norepinephrine (Noradrenaline) (β ,3,4-trihydroxyphenethylamine); Salbutamol (4-(2-(tert-Butylamino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol).

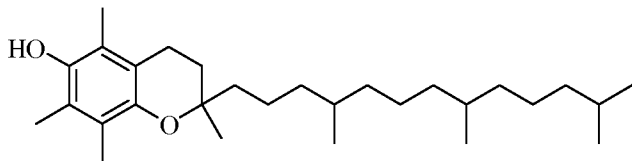
v. Compounds of Formula (I) wherein HOA is an Anti-oxidant

[00236] Anti-oxidants reduce the rate of particular oxidation reactions. They act by either reacting with intermediates and halting the oxidation reaction directly, or by reacting with the oxidizing agent and preventing the oxidation reaction from occurring. Free radicals contain unpaired electrons which make them highly reactive. Cellular macromolecules which are vulnerable to free radical damage include lipids, proteins, and nucleic acids. Free radical damage to LDL cholesterol leads to atherosclerosis, which is a factor in cardiovascular disease. Similarly, free radicals have been implicated in cancer, Alzheimer's disease, inflammatory diseases, and ischemic-reperfusion injury. Anti-oxidants neutralize free radicals by accepting or donating an electron to eliminate the unpaired condition.

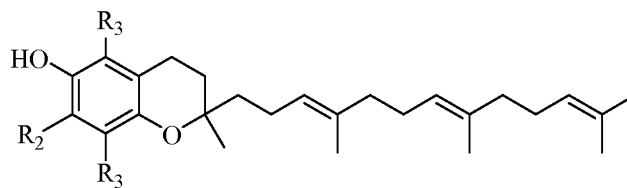
[00237] Anti-oxidants that include at least one aromatic moiety bearing at least one hydroxy moiety or at least one methoxy moiety (which can be demethylated to provide the hydroxy moiety) include but are not limited to: melatonin, vitamin E (including tocopherols and tocotrienols), and BN-80933 (N1-[4-[4-[6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-2(S)-ylcarbonyl]piperazin-1-yl]phenyl]thiophene-2-carboxamide), and other compounds possessing a 3,4-dihydro-8-methyl-2H-chromen-6-ol moiety. In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from, anti-oxidants that have at least one hydroxy moiety or at least one methoxy moiety that can be demethylated to provide the hydroxy moiety used to form the carbamate compounds described herein. In one embodiment, the anti-oxidant is selected from the group consisting of: melatonin, vitamin E (including tocopherols and tocotrienols), and BN-80933 (N1-[4-[4-[6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-2(S)-ylcarbonyl]piperazin-1-yl]phenyl]thiophene-2-carboxamide). In another embodiment, the anti-oxidant is:



BN-80933 (N1-[4-[4-[6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-2(S)-ylcarbonyl]piperazin-1-yl]phenyl]thiophene-2-carboxamide);



, tocopherols ((2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-



trimethyltridecyl]-3,4-dihydro-2H-chromen-6-ol);

, where R₁

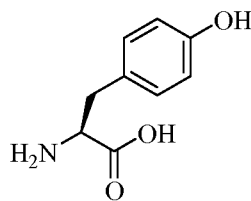
is CH₃, R₂ and R₃ is H or CH₃, tocotrienols.

z. Compounds of Formula (I) wherein HOA is a Vitamin

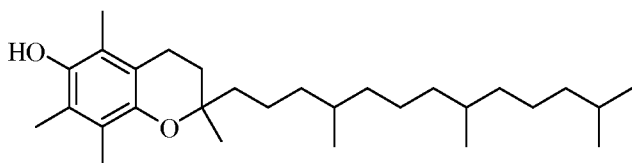
[00238] Vitamins are essential for metabolic reactions in the body. They act both as catalysts and substrates in chemical reactions. For example, vitamin K forms part of the proteases involved in blood clotting. Further, vitamins also act as co-enzymes to carry chemical groups between enzymes, for e.g. folic acid is known to transport methyl, formyl or methylene in the cell. Moreover, thiamin or vitamin B is rapidly converted to its active form, thiamin pyrophosphate (TTP) in the brain and liver by thiamin diphosphotransferase. TTP is necessary as a cofactor for the pyruvate and α -ketoglutarate dehydrogenase catalyzed reactions as well as the transketolase catalyzed reactions of the pentose phosphate pathway. A deficiency in thiamin intake leads to a severely reduced capacity of cells to generate energy as a result of its role in these reactions. Also, vitamins K₁, K₂, and K₃ function to maintain the normal levels of blood clotting proteins, factors II, VII, IX, and X, which are synthesized in the liver as inactive precursor proteins. Naturally occurring vitamin K is absorbed from the intestines only in the presence of bile salts and other lipids through interaction with chylomicrons. Therefore, fat malabsorptive diseases can result in vitamin K deficiency. The synthetic vitamin K₃ is water soluble and absorbed irrespective of the presence of intestinal lipids and bile. Since the vitamin K₂ form is synthesized by intestinal bacteria, deficiency of the vitamin in adults is rare. However, long term antibiotic treatment can lead to deficiency in adults. The intestine of newborn infants is sterile, therefore, vitamin K deficiency in infants is possible if lacking from the early diet.

[00239] Vitamins include, but are not limited to, Vitamin C, Vitamin B6 (Pyridoxine), Calcitriol, Vitamin B12, Vitamin D2 (Ergocalciferol), Calcidiol, Vitamin A, Vitamin D3 (Cholecalciferol), Vitamin B1 (Thiamine), Vitamin B2 (Riboflavin), Adenosine monophosphate, Adenine, L-Alanine, L-Arginine, L-Asparagine, L-Aspartic Acid, Adenosine triphosphate, Cysteine, Biotin, Choline, Citrulline, Creatine, L-Cystine, Icosapent, Folic Acid, L-Glutamine, L-Glutamic Acid, Glycine, Glutathione, L-Histidine, L-Isoleucine, gamma-Homolinolenic acid, L-Leucine, α -Linolenic acid, Lipoic Acid, Xanthophyll, L-Lysine, L-Methionine, N-Acetyl-D-Glucosamine, NADH, Nicotinic acid, L-Ornithine, L-Phenylalanine, Pyridoxal, Aspartame, L-Proline, Phosphatidylserine, Pyridoxal, Pyruvic acid, Retinoic acid, S-Adenosylmethionine, L-Serine, Succinic acid, Spermine, Tetrahydrofolic acid, L-Threonine, L-Tryptophan, 5-HTP, L-Tyrosine, L-Valine, Vitamin E, Vitamin K₃, Vitamin K₂, and Vitamin K₁.

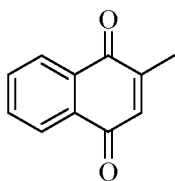
[00240] Vitamins that include at least one aromatic moiety bearing at least one hydroxy moiety include, but are not limited to, Vitamin B6 (Pyridoxine), Pyridoxal Phosphate, Pyridoxal, L-Tyrosine, Vitamin E. Vitamins that are tautomers of at least one phenolic bearing moiety include, but are not limited to, vitamins K₁, K₂, and K₃. In some embodiments are carbamate compounds having a vitamin, containing at least one aromatic moiety bearing at least one hydroxy moiety selected from among: vitamin B6 (Pyridoxine), Pyridoxal Phosphate, Pyridoxal, L-Tyrosine, and



vitamin E. In another embodiment, the vitamin is , L-tyrosine ((S)-2-Amino-3-(4-hydroxy-phenyl)-propanoic acid. In another embodiment the vitamin is



, vitamin E ((2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydro-2H-chromen-6-ol). In another embodiment are carbamate compounds having a vitamin, containing at least one aromatic moiety bearing at least one carbonyl moiety wherein the aromatic moiety bearing at least one carbonyl moiety can tautomerize to give at least one aromatic moiety bearing at least one hydroxy moiety. In one



embodiment, the vitamin is , vitamin K₃.

aa. Further Embodiments of Compounds of Formula (I)

[00241] Therapeutic agents, which provide relief to the system they act on, include, but are not limited to: ACE-inhibitors, α -adrenergic agonists, β -adrenergic agonists, α -adrenergic blockers, β -adrenergic blockers, adrenocortical steroids, analeptic agents, analgesics, anesthetics, angiotensin II receptor antagonists, anti-allergic agents, anti-alopecia agents, anti-amebic agents, anti-anginal agents, anti-asthmatic agents, anti-bacterial agents, anti-bacterial adjuncts, antibiotics, anti-cancer agents, anti-cholesteremic agents, anti-cholinergic agents, anti-convulsants, anti-depressants, anti-diabetic agents, anti-dyskinetic agents, anti-emetics, anti-epileptics, anti-fibrotics, anti-histaminic agents, anti-hypercholesterolemic agents, anti-hyperlipidemic agents, anti-hyperlipoproteinemic agents, anti-hyperparathyroid agents, anti-hyperphosphatemic agents, anti-hypertensives, anti-hyperthyroids, anti-hypotensives, anti-infectives, anti-inflammatory agents, anti-lipemic agents, anti-manic agents, anti-migraine agents, anti-muscarinic agents, anti-mycotic agents, anti-nauseants, anti-neoplastics, anti-obesity agents, anti-obsessional agents, anti-Parkinsonian agents, anti-peristaltic agents, anti-pheochromocytoma agents, anti-pneumocystic agents, anti-progestins, anti-prostatic hypertrophy agents, anti-pruritics, anti-psychotics, anti-peristaltics, anti-pyretics, anti-rheumatics, anti-spasmodics, anti-thrombotics, anti-tumor agents, anti-tussive agents, and anti-vertigo agents.

[00242] Thus, in one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from a) the list of therapeutic agents described directly above that contain at least one aromatic moiety bearing at least one hydroxy moiety; or b) hydroxy metabolites of therapeutic agents described directly above that contain at least one aromatic moiety bearing at least one hydroxy moiety.

[00243] Therapeutic agents that contain at least one aromatic ring bearing at least one hydroxy moiety or at least one methoxy moiety (which can be demethylated to provide the hydroxy moiety) include, but are not limited to:

Pentazocine, Metaraminol, Methyldopa, Phenylephrine, Oxymetazoline, Methoxamine, Midodrine, Labetalol, Albuterol, Terbutaline, Ritodrine, Arbutamine, Levallorphan, Acetaminophen, Dextromethorphan, Butorphanol, Dezocine, Nalbuphine, Hydromorphone, Meloxicam, Hydrocodone, Marinol, Propofol, Riluzole, Moexipril, Astemizole, Nabilone, Naltrexone, Salicylic Acid, Nabumetone, Piroxicam, Tenoxicam, Diflunisal, Naproxen, Vitamin B6 (Pyridoxine), Estradiol, Encainide, Glyburide, Mycophenolic acid, Hesperetin, Ezetimibe, Anisindione, Venlafaxine, Sulpiride, Edrophonium, Trimethobenzamide, Benzquinamide, Dextrothyroxine, Prazosin, Rescinnamine, Deserpidine, Alfuzosin, Fenoldopam, Phentolamine, Raloxifene, Naloxone, Diethylstilbestrol, Fulvestrant, Chlorotrianisene, Estrone, Progabide, Tolcapone, Entacapone, Apomorphine, Reserpine, Remoxipride, Levothyroxine, Isoetharine, Salmeterol, Formoterol, Isoproterenol, Dopamine, Dobutamine, Ethoxzolamide, Carbidopa, Levodopa, Metyrosine, Ranolazine, Dienestrol, Ethinyl Estradiol, Guaifenesin, Melatonin (see for example, *Pharmacological Reviews*, 2003; 55:325-95 which is herein incorporated by reference in its entirety), Allopurinol, Cisapride, Liothyronine, Repaglinide, Chlorzoxazone, Oxymorphone, Levorphanol, Buprenorphine, Tramadol, Morphine, Oxycodone, Codeine, Tubocurarine, Donepezil, Galantamine, Metaproterenol, Indomethacin, Epinephrine, Verapamil, Carvedilol, Papaverine, Diltiazem, Troglitazone.

[00244] In another embodiment, therapeutic agents that contain at least one aromatic ring bearing at least one hydroxy moiety or at least one methoxy moiety (which can be demethylated to provide the hydroxy moiety) include, but are not limited to:

Pentazocine, Metaraminol, Methyldopa, Phenylephrine, Methoxamine, Midodrine, Labetalol, Arbutamine, Acetaminophen, Butorphanol, Dezocine, Nalbuphine, Hydromorphone, Hydrocodone, Marinol, Propofol, Riluzole, Moexipril, Astemizole, Nabilone, Naltrexone, Salicylic Acid, Nabumetone, Diflunisal, Naproxen, Vitamin B6 (Pyridoxine), Estradiol, Encainide, Glyburide, Mycophenolic Acid, Hesperetin, Ezetimibe, Anisindione, Venlafaxine, Sulpiride, Edrophonium, Trimethobenzamide, Benzquinamide, Dextrothyroxine, Prazosin, Rescinnamine, Deserpidine, Bosentan, Alfuzosin, Phentolamine, Raloxifene, Naloxone, Diethylstilbestrol, Terazosin, Estrone, Gefitinib, Progabide, Tolcapone, Entacapone, Apomorphine, Reserpine, Remoxipride, Levothyroxine, Isoetharine, Salmeterol, Formoterol, Isoproterenol, Dopamine, Ethoxzolamide, Carbidopa, Levodopa, Metyrosine, Ranolazine, Dienestrol, Ethinyl Estradiol, Melatonin, Allopurinol, Cisapride, Liothyronine, Chlorzoxazone, Oxymorphone, Levorphanol, Buprenorphine, Tramadol, Morphine, Oxycodone, Codeine, Donepezil, Indomethacin, Epinephrine, Verapamil, Carvedilol, Diltiazem, Troglitazone.

[00245] Therapeutic agents that include at least one aromatic ring bearing at least one hydroxy moiety include, but are not limited to:

[00246] Antiemetics and antinauseants, such as, for example, Marinol, Nabilone.

[00247] Drugs used in diabetes, such as, Troglitazone.

[00248] Vitamins, such as, Vitamin B6 (Pyridoxine), Pyridoxal, L-Tyrosine, Vitamin E.

[00249] Antithrombotic agents, such as, Phenprocoumon, Aspirin, Warfarin.

[00250] Antihemorrhagics, such as, Epinephrine, Dicumarol.

[00251] Cardiac therapy, such as, Dopamine, Dobutamine (4-[2-[3-(4-hydroxyphenyl)-1-methyl-propyl]aminoethyl]benzene-1,2-diol), Phenylephrine, Epinephrine, Arbutamine, Fenoldopam.

- [00252] Antihypertensives, such as, Methyldopa.
- [00253] Peripheral vasodilators, such as, Phentolamine.
- [00254] Beta blocking agents, such as, Labetalol.
- [00255] Lipid modifying agents, such as, Ezetimibe, Dextrothyroxine.
- [00256] Sex hormones and modulators of the genital system, such as, Estradiol, Raloxifene, Estrone, Ethinyl Estradiol, Dienestrol, Diethylstilbestrol.
- [00257] Pituitary and hypothalamic hormones and analogs, such as, Gonadorelin.
- [00258] Thyroid therapy, such as, Levothyroxine, Liothyronine.
- [00259] Antibacterials for systemic use, such as, Oxytetracycline, Cefadroxil, Amoxicillin, Demeclocycline, Clomocycline, Minocycline, Lymecycline, Tetracycline, Doxycycline, Novobiocin, Cefpiramide.
- [00260] Antimycotics for systemic use, such as, Caspofungin, Anidulafungin.
- [00261] Antivirals for systemic use, such as, Nelfinavir.
- [00262] Antineoplastic agents, such as, Doxorubicin, Etoposide, Epirubicin, Mitoxantrone, Daunorubicin, Teniposide, Valrubicin, Topotecan, Masoprocol.
- [00263] Endocrine therapy, such as, Estradiol, Fulvestrant, Diethylstilbestrol.
- [00264] Immunosuppressive agents, such as, Mycophenolic acid.
- [00265] Antiinflammatory and antirheumatic agents, such as, Tenoxicam, Meloxicam, Piroxicam.
- [00266] Muscle relaxants, such as, Tubocurarine, Chlorzoxazone.
- [00267] Antigout agents, such as, Allopurinol.
- [00268] Anesthetics, such as, Propofol.
- [00269] Analgesics, such as, Oxymorphone, Morphine, Acetaminophen, Aspirin, Buprenorphine, Dezocine, Diflunisal, Hydromorphone, Nalbuphine, Pentazocine.
- [00270] Antiepileptics, such as, Progabide, Oxcarbazepine.
- [00271] Anti-parkinson drugs, such as, Carbidopa, Morphine, Levodopa, Entacapone, Tolcapone, Apomorphine.
- [00272] Other nervous system drugs, such as, Naltrexone, Buprenorphine.
- [00273] Drugs for obstructive airway diseases, such as, for example, Isoproterenol, Metaproterenol, Salmeterol, Epinephrine, Albuterol, Formoterol.
- [00274] Cough and cold agents, such as, Morphine.
- [00275] Various other agents include, Naloxone, Dexrazoxane, Chloroxine, Edrophonium, Hesperetin, Hydroxystilbamidine Isethionate, Isoetharine, Levallorphan, Levorphanol, Mesalamine, Methacycline, Metyrosine, Mimosine, Mycophenolate mofetil, noradrenaline, Tigecycline.
- [00276] Therapeutic agents that contain at least one aromatic ring functionalized with a hydroxy moiety include, but are not limited to:
- Pentazocine, Metaraminol, Methyldopa, Phenylephrine, Oxymetazoline, Labetalol, Albuterol, Terbutaline, Ritodrine, Arbutamine, Acetaminophen, Dezocine, Nalbuphine, Hydromorphone, Meloxicam, Marinol, Propofol, Methacycline, Lymecycline, Tetracycline, Cefpiramide, Cefadroxil, Cefprozil, Novobiocin, Vancomycin, Amoxicillin, Minocycline, Demeclocycline, Oxytetracycline, Clomocycline, Naltrexone, Nelfinavir, Salicylic acid,

Hexachlorophene, Mesalamine, Mycophenolate, mofetil, Piroxicam, Tenoxicam, Diflunisal, Vitamin B6 (Pyridoxine), Balsalazide, Tigecycline, Mycophenolic acid, Doxorubicin, Daunorubicin, Idarubicin, Hesperetin, Ezetimibe, Phenprocoumon, Edrophonium, Hydroxystilbamidine, Isethionate, Caspofungin, Micafungin, Dextrothyroxine, Fenoldopam, Phentolamine, Doxycycline, Naloxone, Diethylstilbestrol, Etoposide, Mitoxantrone, Teniposide, Epirubicin, Valrubicin, Fulvestrant, Topotecan, Estrone, Masoprocol, Apomorphine, Sulfasalazine, Chloroxine, Tolterodine, Levothyroxine, Aminosalicic Acid, Isoetharine, Salmeterol, Formoterol, Isoproterenol, Dopamine, Dobutamine, Monobenzene, Bentriomide, Levodopa, Metyrosine, Dienestrol, Ethinyl Estradiol, Allopurinol, Cisapride, Liothyronine, Chlorzoxazone, Oxymorphone, Levorphanol, Buprenorphine, Morphine, Tubocurarine, Warfarin, Metaproterenol, Dicumarol, Probenecid, Epinephrine, Troglitazone.

[00277] Metabolites which contain an arylhydroxy portion of analgesics, antianxiety drugs, antiarrhythmics, antibacterials, antibiotics, anticoagulants, anticonvulsants, antidepressants, antiemetics, antihistamines, antihypertensives, anti-inflammatories, antineoplastics, antipyretics, antivirals, barbiturates, beta-blockers, cold medicines, corticosteroids, cough suppressants, cytotoxics, decongestants, hormones, hypoglycemics, immunosuppressives, muscle relaxants, sedatives, tranquilizers, vitamins and phytochemicals may be incorporated into a FAAH inhibitor to treat the relevant condition. Thus, in some embodiments are FAAH inhibitors having as an arylhydroxy containing release agent, a metabolite selected from the group consisting of analgesics, antianxiety drugs, antiarrhythmics, antibacterials, antibiotics, anticoagulants, anticonvulsants, antidepressants, antiemetics, antihistamines, antihypertensives, anti-inflammatories, antineoplastics, antipyretics, antivirals, barbiturates, beta-blockers, cold medicines, corticosteroids, cough suppressants, cytotoxics, decongestants, hormones, hypoglycemics, immunosuppressives, muscle relaxants, sedatives, tranquilizers, vitamins and phytochemicals.

In certain instances, the aryloxy portion of the alkylcarbamic acid aryl ester inhibitor may be a therapeutic agent which treats diseases, disorders, or conditions, which benefit from the inhibition of FAAH (see above for different treatments).

[00278] Provided herein are compounds, which are esters of alkylcarbamic acids, compositions that include them, and methods of their use. In some embodiments, are therapeutic agents that contain at least one aromatic moiety bearing at least one hydroxy moiety, selected from among the agents that are shown in Figures 1-4.

[00279] ab. Compounds of Formula (I) wherein HOA is an Anti-Depressant

Anti-depressive agents include but are not limited to: venlafaxine, 5-MeO-DMT (2-5-methoxy-1H-indol-3-yl)-N,N-dimethylethanamine, escitalopram, sertraline hydrochloride, bupropion, paroxetine, citalopram, fluoxetine, fluvoxamine, dapoxetine, desvenlafaxine succinate, nefazodone, milnacipran, and radafaxine.

Venlafaxine is an antidepressant belonging to the class of serotonin-norepinephrine reuptake inhibitors (SNRI) and is prescribed for the treatment of clinical depression and anxiety disorders. SNRIs block the transporter proteins that reabsorb certain neurotransmitters thereby increasing the number of neurotransmitters active in the synapse, thereby enhancing neuronal activity and increasing responsiveness to mood.

In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from a) anti-depressive agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; b) hydroxy metabolites of anti-depressive agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; or c) an anti-depressive

agent having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein.

In one embodiment, the anti-depressive agent is venlafaxine. In another embodiment, the anti-depressive agent is desvenlafaxine succinate.

ac. Compounds of Formula (I) wherein HOA is an Anxiolytic

Anxiolytics are used for the treatment of symptoms of anxiety and anxiety disorders. By way of example only, benzodiazepines are used for the treatment of severe and disabling anxiety.

Anxiolytic agents include but are not limited to: benzodiazepines such as, alprazolam, diazepam, lorazepam, clonazepam, temazepam, oxazepam, flunitrazepam, triazolam, chlordiazepoxide, flurazepam, estazolam, nitrazepam; imidazopyridines, such as zolpidem and alpidem; and beta-receptor blockers such as oxprenolol.

In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from a) anxiolytic agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; b) hydroxy metabolites of anxiolytic agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; or c) an anxiolytic agent having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein.

ad. Compounds of Formula (I) wherein HOA is a neuroprotective agent

Neuroprotective agents that contain at least one aromatic ring include by way of example only, selegiline, rasagiline, tramadol, and trihexyphenidyl.

In one embodiment, carbamate compounds provided herein are FAAH inhibitors that are formed from a) neuroprotective agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; b) hydroxy metabolites of neuroprotective agents that contain at least one aromatic moiety bearing at least one hydroxy moiety; or c) a neuroprotective agent having at least one aromatic moiety that can be derivatized with a hydroxy moiety such that the introduced hydroxy moiety is used to form a carbamate compound disclosed herein.

Preparation of Compounds

[00280] Compounds provided herein that inhibit the activity of FAAH may be synthesized using standard synthetic techniques known to those of skill in the art or using methods known in the art in combination with methods described herein. As a further guide the following synthetic methods may also be utilized.

[00281] The reactions can be employed in a linear sequence to provide the compounds described herein or they may be used to synthesize fragments which are subsequently joined by the methods described herein and/or known in the art.

Use of Protecting Groups

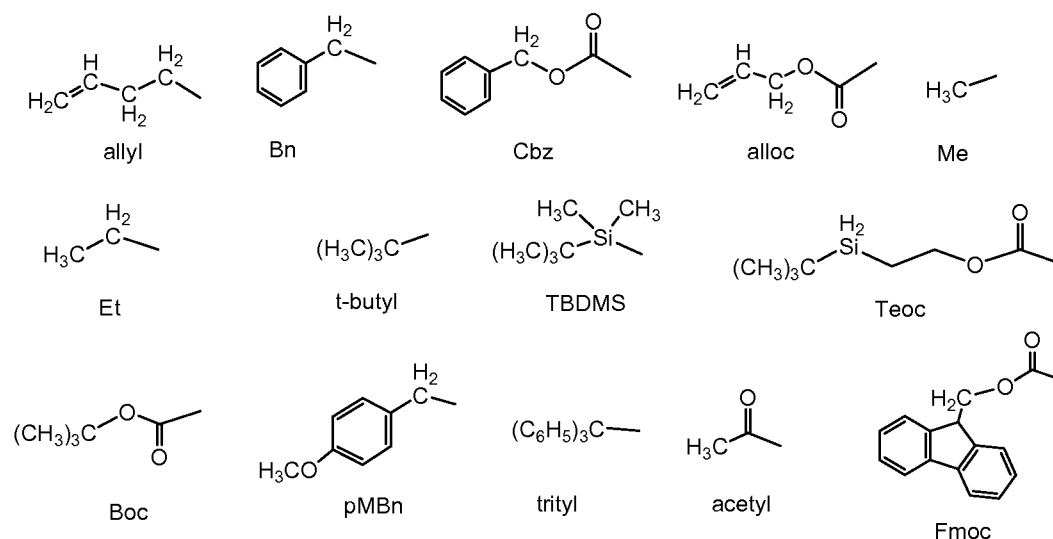
[00282] The term “protecting group” refers to chemical moieties that block some or all reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. It is preferred that each

protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal. Protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and t-butyl dimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, without limitation, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

[00283] Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be protected by conversion to simple ester derivatives as exemplified herein, or they may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates. In one embodiment, a compound containing both a carboxylic acid reactive moiety and a hydroxy reactive moiety may have one of the reactive moieties blocked while the other reactive moiety is not blocked.

[00284] Allyl blocking groups are useful in the presence of acid- and base-protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a Pd^0 -catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

[00285] Typically blocking/protecting groups may be selected from:



[00286] Other protecting groups are described in Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

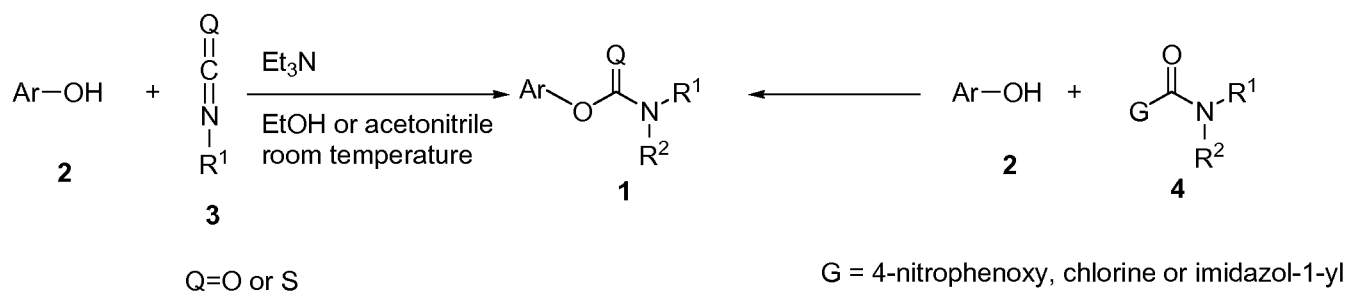
Process for the Preparation of Esters of Alkylcarbamic Acids

[00287] In certain embodiments, provided herein are methods of making and methods of using FAAH inhibitor compounds provided herein. In certain embodiments, compounds provided herein can be synthesized using the following synthetic schemes. Compounds may be synthesized using methodologies analogous to those described below by the use of appropriate alternative starting materials.

[00288] Described herein are compounds that inhibit the activity of fatty acid amide hydrolase (FAAH) and processes for their preparation. Also described herein are pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites and pharmaceutically acceptable prodrugs of such compounds. Pharmaceutical compositions that include at least one such compound or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite or pharmaceutically acceptable prodrug of such compound, are provided.

[00289] Esters of alkylcarbamic acids disclosed herein are prepared by the general process depicted in Scheme 1. Ar-OH (**2**) represents a hydroxy-containing compound selected from among substituted phenols and heteroaryls that include a hydroxyl moiety. R¹ and R₂ are as defined herein.

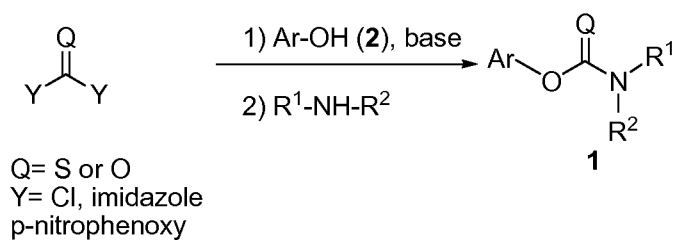
Scheme 1. Synthesis of esters of alkylcarbamic acids.



[00290] Treatment of Ar-OH (**2**) with an isocyanate or isothiocyanate (**3**) in the presence of a base, such as, for example, triethylamine, in an organic solvent, such as, for example, ethanol or acetonitrile, results in the formation of esters of alkylcarbamic acids of structure **1** (see, for example, U.S. patent. No. 5,112,859; WO 2004/033422; US 2006/0014830; *J. Med. Chem.* 2004, 47(21); 4998-5008; Tarzia *et al. J. Med. Chem.* 46:2352-2360 (2003); Kathuria *et al. Nature Medicine* 9(1): 76 (2003)). Isocyanates or isothiocyanates are commercially available. Methods for the preparation of isocyanates or isothiocyanates (**3**) are well known in the art. For example, isocyanates (**3**, Q=O) can be prepared from the corresponding carboxylic acid (i.e. R¹-COOH) or acid derivative (e.g. R¹-C(O)Cl) by treatment with an azide source such as, for example, sodium azide or diphenylphosphoryl azide followed by a Curtius-type rearrangement (see, for example, *Synth. Commun.* 1993, 23, 335; *Heterocycles* 1993, 36, 1305).

[00291] Alternatively, alkylcarbamic acid esters (**1**) can be prepared by treatment of Ar-OH (**2**) with alkylcarbamic acid derivatives of structure (**4**), where G is 4-nitrophenoxy, chlorine or imidazol-1-yl, in the presence of a base, such as, for example, triethylamine, to provide the desired compound (**1**). Compounds of structure (**4**) can be prepared using procedures well known in the art, such as, procedures described in Greene, T.W. and Wuts, P.G.M “Protective Groups in Organic Synthesis”, 3rd Edition, p.549, New York:Wiley, 1999. Briefly, alkylamines (e.g. R¹-NH₂) are treated with phosgene or a phosgene equivalent, such as, for example, trichloromethyl chloroformate or carbonyldiimidazole, to yield compounds of structure (**4**).

[00292] Esters of alkyl(thio)carbamic acids also can be synthesized by the method outlined in Scheme 2.

Scheme 2. Synthesis of esters of alkyl(thio)carbamic acids.

[00293] Esters of alkyl(thio)carbamic acids can be prepared by a two-step procedure. Thiophosgene, phosgene, or an equivalent thereof, is first treated with Ar-OH (2) in the presence of a base in a suitable organic solvent, followed by treatment with an alkylamine such as, R₁R₂NH. The order of the reaction can be reversed, i.e. thiophosgene, phosgene, or an equivalent thereof, can be treated with the alkylamine followed by Ar-OH (2). Equivalents of thiophosgene and phosgene include, but are not limited to, 1,1'-thiocarbonyldiimidazole, 1,1'-carbonyldiimidazole, and trichloromethyl chloroformate.

[00294] The requisite hydroxy-containing compounds, Ar-OH (2), can be purchased from commercial sources or prepared using procedures known in the art or outlined herein.

[00295] Using the reaction conditions described herein, esters of alkylcarbamic acids as disclosed herein are obtained in good yields and purity. The compounds prepared by the methods disclosed herein are purified by conventional means known in the art, such as, for example, filtration, recrystallization, chromatography, distillation, and combinations thereof.

[00296] Any combination of the groups described above for the various variables is contemplated herein.

Certain Chemical Terminology

[00297] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. All patents, patent applications, published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. In the event that there are a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

[00298] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

[00299] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

[00300] Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg “ADVANCED ORGANIC CHEMISTRY 4TH ED.” Vols. A (2000) and B (2001), Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art are employed. Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those known in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Standard techniques can be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Reactions and purification techniques can be performed e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification.

[00301] An “alkoxy” group refers to a (alkyl)O- group, where alkyl is as defined herein.

[00302] An “alkyl” group refers to an aliphatic hydrocarbon group. The alkyl moiety may be a “saturated alkyl” group, which means that it does not contain any alkene or alkyne moieties. The alkyl moiety may also be an “unsaturated alkyl” moiety, which means that it contains at least one alkene or alkyne moiety. An “alkene” moiety refers to a group that has at least one carbon-carbon double bond, and an “alkyne” moiety refers to a group that has at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic. Depending on the structure, an alkyl group can be a monoradical or a diradical (i.e., an alkylene group).

[00303] As used herein, C₁-C_x includes C₁-C₂, C₁-C₃ . . . C₁-C_x.

[00304] The “alkyl” moiety may have 1 to 10 carbon atoms (whenever it appears herein, a numerical range such as “1 to 10” refers to each integer in the given range; e.g., “1 to 10 carbon atoms” means that the alkyl group may have 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group of the compounds described herein may be designated as “C₁-C₄ alkyl” or similar designations. By way of example only, “C₁-C₄ alkyl” indicates that there are one to four carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from among methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Thus C₁-C₄ alkyl includes C₁-C₂ alkyl and C₁-C₃ alkyl. Alkyl groups can be substituted or unsubstituted. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

[00305] As used herein, the term “non-cyclic alkyl” refers to an alkyl that is not cyclic (i.e., a straight or branched chain containing at least one carbon atom). Non-cyclic alkyls can be fully saturated or can contain non-cyclic alkenes and/or alkynes. Non-cyclic alkyls can be optionally substituted.

[00306] The term “alkylamine” refers to the -N(alkyl)_xH_y group, where x and y are selected from among x=1, y=1 and x=2, y=0. When x=2, the alkyl groups, taken together with the N atom to which they are attached, can optionally form a cyclic ring system.

[00307] The term “alkenyl” refers to a type of alkyl group in which the first two atoms of the alkyl group form a double bond that is not part of an aromatic group. That is, an alkenyl group begins with the atoms $-C(R)=C(R)-R$, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. Non-limiting examples of an alkenyl group include $-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CHCH_3$ and $-C(CH_3)=CHCH_3$. The alkenyl moiety may be branched, straight chain, or cyclic (in which case, it would also be known as a “cycloalkenyl” group). Depending on the structure, an alkenyl group can be a monoradical or a diradical (i.e., an alkenylene group). Alkenyl groups can be optionally substituted.

[00308] The term “alkynyl” refers to a type of alkyl group in which the first two atoms of the alkyl group form a triple bond. That is, an alkynyl group begins with the atoms $-C\equiv C-R$, wherein R refers to the remaining portions of the alkynyl group, which may be the same or different. Non-limiting examples of an alkynyl group include $-C\equiv CH$, $-C\equiv CCH_3$ and $-C\equiv CCH_2CH_3$. The “R” portion of the alkynyl moiety may be branched, straight chain, or cyclic. Depending on the structure, an alkynyl group can be a monoradical or a diradical (i.e., an alkynylene group). Alkynyl groups can be optionally substituted.

[00309] An “amide” is a chemical moiety with the formula $-C(O)NHR$ or $-NHC(O)R$, where R is selected from among alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). An amide moiety may form a linkage between an amino acid or a peptide molecule and a compound described herein, thereby forming a prodrug. Any amine, or carboxyl side chain on the compounds described herein can be amidified. The procedures and specific groups to make such amides are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

[00310] The term “aromatic” refers to a planar ring having a delocalized π -electron system containing $4n+2$ π electrons, where n is an integer. Aromatic rings can be formed by five, six, seven, eight, nine, or more than nine atoms. Aromatics can be optionally substituted. The term “aromatic” includes both carbocyclic aryl (e.g., phenyl) and heterocyclic aryl (or “heteroaryl” or “heteroaromatic”) groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups.

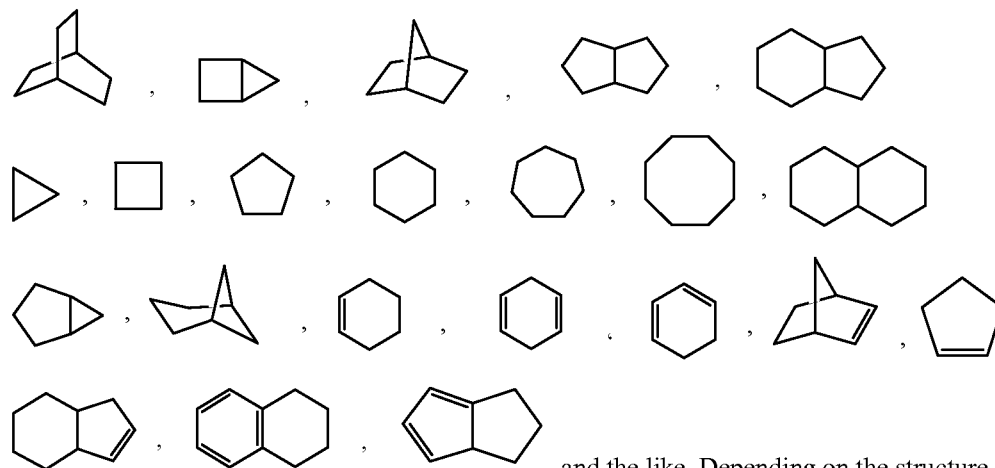
[00311] As used herein, the term “aryl” refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings can be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, naphthalenyl, phenanthrenyl, anthracenyl, fluorenyl, and indenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group).

[00312] An “aryloxy” group refers to an (aryl)O- group, where aryl is as defined herein.

[00313] The term “bond” or “single bond” refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure.

[00314] The term “carbocyclic” refers to a compound which contains one or more covalently closed ring structures, and that the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings in which the ring backbone contains at least one atom which is different from carbon.

[00315] The term “cycloalkyl” refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and may be saturated, partially unsaturated, or fully unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms. Illustrative examples of cycloalkyl groups include the following moieties:



a monoradical or a diradical (e.g., an cycloalkylene group).

[00316] As used herein, the term “carbocycle” refers to a ring, wherein each of the atoms forming the ring is a carbon atom. Carbocyclic rings can be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Carbocycles can be optionally substituted.

[00317] The term “ester” refers to a chemical moiety with formula -COOR, where R is selected from among alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). Any hydroxy, or carboxyl side chain on the compounds described herein can be esterified. The procedures and specific groups to make such esters are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

[00318] The term “halo” or, alternatively, “halogen” or “halide” means fluoro, chloro, bromo or iodo.

[00319] The terms “haloalkyl,” “haloalkenyl,” “haloalkynyl” and “haloalkoxy” include alkyl, alkenyl, alkynyl and alkoxy structures in which at least one hydrogen is replaced with a halogen atom. In certain embodiments in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are all the same as one another. In other embodiments in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are not all the same as one another. The terms “fluoroalkyl” and “fluoroalkoxy” include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine. In certain embodiments, haloalkyls are optionally substituted.

[00320] As used herein, the terms “heteroalkyl” “heteroalkenyl” and “heteroalkynyl” include optionally substituted alkyl, alkenyl and alkynyl radicals in which one or more skeletal chain atoms are selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, silicon, phosphorus or combinations thereof.

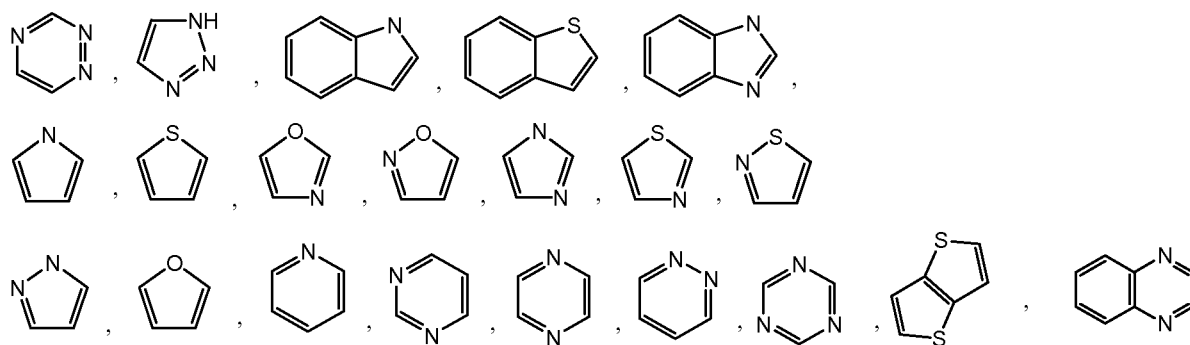
[00321] The term “heteroatom” refers to an atom other than carbon or hydrogen. Heteroatoms are typically independently selected from among oxygen, sulfur, nitrogen, silicon and phosphorus, but are not limited to these atoms.

In embodiments in which two or more heteroatoms are present, the two or more heteroatoms can all be the same as one another, or some or all of the two or more heteroatoms can each be different from the others.

[00322] As used herein, the term “ring” refers to any covalently closed structure. Rings include, for example, carbocycles (e.g., aryls and cycloalkyls), heterocycles (e.g., heteroaryls and non-aromatic heterocycles), aromatics (e.g., aryls and heteroaryls), and non-aromatics (e.g., cycloalkyls and non-aromatic heterocycles). Rings can be optionally substituted. Rings can form part of a ring system.

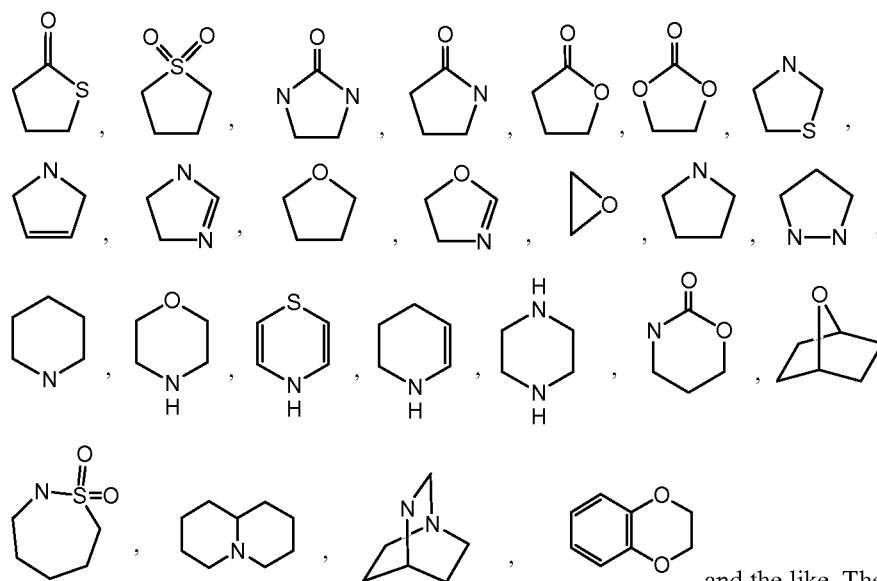
[00323] As used herein, the term “ring system” refers to two or more rings, wherein two or more of the rings are fused. The term “fused” refers to structures in which two or more rings share one or more bonds.

[00324] The terms “heteroaryl” or, alternatively, “heteroaromatic” refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. An *N*-containing “heteroaromatic” or “heteroaryl” moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. The polycyclic heteroaryl group may be fused or non-fused. Illustrative examples of heteroaryl groups include the following moieties:



and the like. Depending on the structure, a heteroaryl group can be a monoradical or a diradical (i.e., a heteroarylene group).

[00325] As used herein, the term “non-aromatic heterocycle”, “heterocycloalkyl” or “heteroalicyclic” refers to a non-aromatic ring wherein one or more atoms forming the ring is a heteroatom. A “non-aromatic heterocycle” or “heterocycloalkyl” group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. The radicals may be fused with an aryl or heteroaryl. Heterocycloalkyl rings can be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Heterocycloalkyl rings can be optionally substituted. In certain embodiments, non-aromatic heterocycles contain one or more carbonyl or thiocarbonyl groups such as, for example, oxo- and thio-containing groups. Examples of heterocycloalkyls include, but are not limited to, lactams, lactones, cyclic imides, cyclic thioimides, cyclic carbamates, tetrahydrothiopyran, 4H-pyran, tetrahydropyran, piperidine, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, morpholine, trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, pyrrolidone, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, and 1,3-oxathiolane. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:



and the like. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides.

[00326] The term "heterocycle" refers to heteroaromatic and heteroalicyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of the group does not contain two adjacent O or S atoms. Herein, whenever the number of carbon atoms in a heterocycle is indicated (e.g., C₁-C₆ heterocycle), at least one other atom (the heteroatom) must be present in the ring. Designations such as "C₁-C₆ heterocycle" refer only to the number of carbon atoms in the ring and do not refer to the total number of atoms in the ring. It is understood that the heterocyclic ring can have additional heteroatoms in the ring. Designations such as "4-6 membered heterocycle" refer to the total number of atoms that are contained in the ring (i.e., a four, five, or six membered ring, in which at least one atom is a carbon atom, at least one atom is a heteroatom and the remaining two to four atoms are either carbon atoms or heteroatoms). In heterocycles that have two or more heteroatoms, those two or more heteroatoms can be the same or different from one another. Heterocycles can be optionally substituted. Binding to a heterocycle can be at a heteroatom or via a carbon atom. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 4-membered heterocyclic group is azetidiny (derived from azetidine). An example of a 5-membered heterocyclic group is thiazolyl. An example of a 6-membered heterocyclic group is pyridyl, and an example of a 10-membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepiny, diazepiny, thiazepiny, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinoliziny. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl,

tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the groups listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl or imidazol-3-yl (both N-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or two oxo (=O) moieties such as pyrrolidin-2-one. Depending on the structure, a heterocycle group can be a monoradical or a diradical (i.e., a heterocyclene group).

[00327] The term “membered ring” can embrace any cyclic structure. The term “membered” is meant to denote the number of skeletal atoms that constitute the ring. Thus, for example, cyclohexyl, pyridine, pyran and thiopyran are 6-membered rings and cyclopentyl, pyrrole, furan, and thiophene are 5-membered rings.

[00328] An “isocyanato” group refers to a -NCO group.

[00329] An “isothiocyanato” group refers to a -NCS group.

[00330] The term “moiety” refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00331] The term “polycycloalkyl” refers to an alkyl group that comprises a bicyclic or tricyclic ring hydrocarbon ring structure, including bridged cycloalkyl rings, spiro cycloalkyl rings, or fused cycloalkyl rings. Examples include a norbornyl group, an adamantyl group, a bicyclo[x.y.z]alkyl group (where each of x, y, and z is independently 1, 2, 3, or 4), or a tricyclic alkyl group.

[00332] “Sulfinyl” refers to a -S(=O)- moiety.

[00333] “Sulfonyl” refers to a -S(=O)₂- moiety.

[00334] “Thioalkoxy” group refers to a -S-alkyl group.

[00335] As used herein, the term “O-carboxy” refers to a group of formula RC(=O)O-.

[00336] As used herein, the term “C-carboxy” refers to a group of formula -C(=O)OR.

[00337] As used herein, the term “acetyl” refers to a group of formula -C(=O)CH₃.

[00338] As used herein, the term “trihalomethanesulfonyl” refers to a group of formula X₃CS(=O)₂- where X is a halogen.

[00339] As used herein, the term “cyano” refers to a group of formula -CN.

[00340] As used herein, the term “S-sulfonamido” refers to a group of formula -S(=O)₂NR₂.

[00341] As used herein, the term “N-sulfonamido” refers to a group of formula RS(=O)₂NH-.

[00342] As used herein, the term “O-carbamyl” refers to a group of formula -OC(=O)NR₂.

[00343] As used herein, the term “N-carbamyl” refers to a group of formula ROC(=O)NH-.

[00344] As used herein, the term “O thiocarbamyl” refers to a group of formula -OC(=S)NR₂.

[00345] As used herein, the term “N thiocarbamyl” refers to a group of formula ROC(=S)NH-.

[00346] As used herein, the term “C-amido” refers to a group of formula -C(=O)NR₂.

[00347] As used herein, the term “N-amido” refers to a group of formula $RC(=O)NH-$.

[00348] As used herein, the substituent “R” appearing by itself and without a number designation refers to a substituent selected from among alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and non-aromatic heterocycle (bonded through a ring carbon).

[00349] The term “optionally substituted” or “substituted” means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, cyano, halo, carbonyl, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, perhaloalkyl, perfluoroalkyl, silyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. By way of example an optional substituents may be L_sR_s , wherein each L_s is independently selected from a bond, $-O-$, $-C(=O)-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-NH-$, $-NHC(O)-$, $-C(O)NH-$, $S(=O)_2NH-$, $-NHS(=O)_2-$, $-OC(O)NH-$, $-NHC(O)O-$, $-(\text{substituted or unsubstituted } C_1-C_6 \text{ alkyl})$, or $-(\text{substituted or unsubstituted } C_2-C_6 \text{ alkenyl})$; and each R_s is independently selected from H, (substituted or unsubstituted lower alkyl), (substituted or unsubstituted lower cycloalkyl), heteroaryl, or heteroalkyl. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references such as Greene and Wuts, above.

[00350] The compounds presented herein may possess one or more stereocenters and each center may exist in the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers may be obtained, if desired, by methods known in the art as, for example, the separation of stereoisomers by chiral chromatographic columns.

[00351] The methods and formulations described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds described herein, as well as active metabolites of these compounds having the same type of activity. In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00352] Throughout the specification, groups and substituents thereof can be chosen by one skilled in the field to provide stable moieties and compounds.

Pharmaceutical Composition/Formulation

[00353] Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art. A summary of pharmaceutical compositions described herein may be found, for example, in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

[00354] Provided herein are pharmaceutical compositions that include a compound described herein and a pharmaceutically acceptable diluent(s), excipient(s), or carrier(s). In addition, the compounds described herein can be administered as pharmaceutical compositions in which compounds described herein are mixed with other active ingredients, as in combination therapy. In some embodiments, the pharmaceutical compositions may include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In addition, the pharmaceutical compositions can also contain other therapeutically valuable substances.

[00355] In certain embodiments, compositions may also include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[00356] In other embodiments, compositions may also include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[00357] The term “pharmaceutical combination” as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, e.g. a compound described herein and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, e.g. a compound described herein and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[00358] A pharmaceutical composition, as used herein, refers to a mixture of a compound described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. In practicing the methods of treatment or use provided herein, therapeutically effective amounts of compounds described herein are administered in a pharmaceutical composition to a mammal having a disease, disorder, or condition to be treated. Preferably, the mammal is a human. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures.

[00359] The pharmaceutical formulations described herein can be administered to a subject by multiple administration routes, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations,

tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00360] Pharmaceutical compositions including a compound described herein may be manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00361] The pharmaceutical compositions will include at least one compound described herein as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein. Additionally, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

Certain Pharmaceutical Terminology

[00362] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

[00363] The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00364] As used herein, the term “selective inhibitor compound” refers to a compound that selectively inhibits a specific function/activity of one or more target proteins.

[00365] As used herein, the term “selectively inhibits” refers to the ability of a selective inhibitor compound to inhibit a specific function/activity of a target protein, such as, for example, the fatty acid amide hydrolytic activity of fatty acid amide hydrolase, with greater potency than the activity of a non-target protein. In certain embodiments, selectively inhibiting refers to inhibiting a target protein activity with a selective inhibitor that has a IC_{50} that is at least 10, 50, 100, 250, 500, 1000 or more times lower than for that of a non-target protein activity.

[00366] As used herein, amelioration of the symptoms of a particular disease, disorder or condition by administration of a particular compound or pharmaceutical composition refers to any lessening of severity, delay in onset, slowing of progression, or shortening of duration, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the compound or composition.

[00367] The term “modulate,” as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00368] As used herein, the term “modulator” refers to a compound that alters an activity of a molecule. For example, a modulator can cause an increase or decrease in the magnitude of a certain activity of a molecule compared to the

magnitude of the activity in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of one or more activities of a molecule. In certain embodiments, an inhibitor completely prevents one or more activities of a molecule. In certain embodiments, a modulator is an activator, which increases the magnitude of at least one activity of a molecule. In certain embodiments the presence of a modulator results in an activity that does not occur in the absence of the modulator.

[00369] As used herein, the term “selective modulator” refers to a compound that selectively modulates a target activity.

[00370] As used herein, the term “selective FAAH modulator” refers to a compound that selectively modulates at least one activity associated with FAAH.

[00371] As used herein, the term “selectively modulates” refers to the ability of a selective modulator to modulate a target activity to a greater extent than it modulates a non-target activity. In certain embodiments the target activity is selectively modulated by, for example about 2 fold up to more than about 500 fold, in some embodiments, about 2, 5, 10, 50, 100, 150, 200, 250, 300, 350, 400, 450 or more than 500 fold.

[00372] As used herein, the term “target activity” refers to a biological activity capable of being modulated by a selective modulator. Certain exemplary target activities include, but are not limited to, binding affinity, signal transduction, enzymatic activity, tumor growth, inflammation or inflammation-related processes, and amelioration of one or more symptoms associated with a disease or condition.

[00373] As used herein, the IC_{50} refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as inhibition of FAAH, in an assay that measures such response.

[00374] As used herein, EC_{50} refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

[00375] The term “carrier,” as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells or tissues.

[00376] The terms “co-administration” or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00377] The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition including a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms without undue adverse side effects. An appropriate “effective amount” in any individual case may be determined using techniques, such as a dose escalation study. The term “therapeutically effective amount” includes, for example, a prophylactically effective amount. An “effective amount” of a compound disclosed herein is an amount effective to achieve a desired pharmacologic effect or therapeutic improvement without undue adverse side effects. It is understood that “an effect amount” or “a therapeutically effective amount” can vary from subject to subject,

due to variation in metabolism of the compound administered, age, weight, general condition of the subject, the condition being treated, the severity of the condition being treated, and the judgment of the prescribing physician.

[00378] The terms “enhance” or “enhancing,” as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term “enhancing” refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An “enhancing-effective amount,” as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00379] The terms “kit” and “article of manufacture” are used as synonyms.

[00380] A “metabolite” of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term “active metabolite” refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term “metabolized,” as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes, such as, oxidation reactions) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyl transferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulfhydryl groups. Further information on metabolism may be obtained from *The Pharmacological Basis of Therapeutics*, 9th Edition, McGraw-Hill (1996). Metabolites of the compounds disclosed herein can be identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells *in vitro* and analysis of the resulting compounds. Both methods are well known in the art. In some embodiments, metabolites of a compound are formed by oxidative processes and correspond to the corresponding hydroxy-containing compound. In some embodiments, a compound is metabolized to pharmacologically active metabolites.

[00381] A “prodrug” refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound described herein, which is administered as an ester (the “prodrug”) to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically more active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, a pharmaceutically active compound is modified such that the active compound will be regenerated upon *in vivo* administration. The prodrug can be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, those of skill in this art, once a

pharmaceutically active compound is known, can design prodrugs of the compound. (see, for example, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392; Silverman (1992), *The Organic Chemistry of Drug Design and Drug Action*, Academic Press, Inc., San Diego, pages 352-401). Compounds provided herein may also be derivatized into suitable prodrugs. Upon *in vivo* administration, prodrugs of the esters of alkylcarbamic acids provided herein, such as, for example, prodrugs of compounds of Formula (I), will be metabolized to provide the parent ester of alkylcarbamic acid compound, i.e. compounds of Formula (I) will be formed upon *in vivo* metabolism of the prodrugs provided herein.

[00382] Compounds provided herein are inhibitors of FAAH. In some embodiments, prodrugs of compounds provided herein, such as, for example, prodrugs of compounds of Formula (I), are metabolized *in vivo* to the parent compound, i.e. compounds of Formula (I).

[00383] By “pharmaceutically acceptable,” as used herein, refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00384] The term “pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutically acceptable salts may be obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutically acceptable salts also may be obtained by reacting a compound described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods known in the art.

[00385] “Antifoaming agents” reduce foaming during processing which can result in coagulation of aqueous dispersions, bubbles in the finished film, or generally impair processing. Exemplary anti-foaming agents include silicon emulsions or sorbitan sesquoleate.

[00386] “Antioxidants” include, for example, butylated hydroxytoluene (BHT), sodium ascorbate, ascorbic acid, sodium metabisulfite and tocopherol. In certain embodiments, antioxidants enhance chemical stability where required.

[00387] In certain embodiments, compositions provided herein may also include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

[00388] Formulations described herein may benefit from antioxidants, metal chelating agents, thiol containing compounds and other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003%

to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

[00389] “Binders” impart cohesive qualities and include, e.g., alginic acid and salts thereof; cellulose derivatives such as carboxymethylcellulose, methylcellulose (e.g., Methocel[®]), hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel[®]), ethylcellulose (e.g., Ethocel[®]), and microcrystalline cellulose (e.g., Avicel[®]); microcrystalline dextrose; amylose; magnesium aluminum silicate; polysaccharide acids; bentonites; gelatin; polyvinylpyrrolidone/vinyl acetate copolymer; crosspovidone; povidone; starch; pregelatinized starch; tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac[®]), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab[®]), and lactose; a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, polyvinylpyrrolidone (e.g., Polyvidone[®] CL, Kollidon[®] CL, Polyplasdone[®] XL-10), larch arabogalactan, Veegum[®], polyethylene glycol, waxes, sodium alginate, and the like.

[00390] “Bioavailability” refers to the percentage of the weight of compounds disclosed herein dosed that is delivered into the general circulation of the animal or human being studied. The total exposure ($AUC_{(0-\infty)}$) of a drug when administered intravenously is usually defined as 100% bioavailable (F%). “Oral bioavailability” refers to the extent to which compounds disclosed herein are absorbed into the general circulation when the pharmaceutical composition is taken orally as compared to intravenous injection.

[00391] “Blood plasma concentration” refers to the concentration of compounds provided herein in the plasma component of blood of a subject. It is understood that the plasma concentration of compounds provided herein may vary significantly between subjects, due to variability with respect to metabolism and/or possible interactions with other therapeutic agents. In accordance with one embodiment disclosed herein, the blood plasma concentration of the compounds provided herein may vary from subject to subject. Likewise, values such as maximum plasma concentration (C_{max}) or time to reach maximum plasma concentration (T_{max}), or total area under the plasma concentration time curve ($AUC_{(0-\infty)}$) may vary from subject to subject. Due to this variability, the amount necessary to constitute “a therapeutically effective amount” of a compound provided herein may vary from subject to subject.

[00392] “Carrier materials” include any commonly used excipients in pharmaceuticals and should be selected on the basis of compatibility with compounds disclosed herein and the release profile properties of the desired dosage form. Exemplary carrier materials include, e.g., binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, and the like. “Pharmaceutically compatible carrier materials” may include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, polyvinylpyrrolidone (PVP), cholesterol, cholesterol esters, sodium caseinate, soy lecithin, taurocholic acid, phosphatidylcholine, sodium chloride, tricalcium phosphate, dipotassium phosphate, cellulose and cellulose conjugates, sugars sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, and the like. See, e.g., *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker,

New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed. (Lippincott Williams & Wilkins 1999).

[00393] “Dispersing agents,” and/or “viscosity modulating agents” include materials that control the diffusion and homogeneity of a drug through liquid media or a granulation method or blend method. In some embodiments, these agents also facilitate the effectiveness of a coating or eroding matrix. Exemplary diffusion facilitators/dispersing agents include, e.g., hydrophilic polymers, electrolytes, Tween[®] 60 or 80, PEG, polyvinylpyrrolidone (PVP; commercially known as Plasdone[®]), and the carbohydrate-based dispersing agents such as, for example, hydroxypropyl celluloses (e.g., HPC, HPC-SL, and HPC-L), hydroxypropyl methylcelluloses (e.g., HPMC K100, HPMC K4M, HPMC K15M, and HPMC K100M), carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate stearate (HPMCAS), noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), vinyl pyrrolidone/vinyl acetate copolymer (S630), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol), poloxamers (e.g., Pluronic F68[®], F88[®], and F108[®], which are block copolymers of ethylene oxide and propylene oxide); and poloxamines (e.g., Tetronic 908[®], also known as Poloxamine 908[®], which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Corporation, Parsippany, N.J.)), polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, polyvinylpyrrolidone/vinyl acetate copolymer (S-630), polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, sodium carboxymethylcellulose, methylcellulose, polysorbate-80, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulosics, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone, carbomers, polyvinyl alcohol (PVA), alginates, chitosans and combinations thereof. Plasticizers such as cellulose or triethyl cellulose can also be used as dispersing agents. Dispersing agents particularly useful in liposomal dispersions and self-emulsifying dispersions are dimyristoyl phosphatidyl choline, natural phosphatidyl choline from eggs, natural phosphatidyl glycerol from eggs, cholesterol and isopropyl myristate.

[00394] Combinations of one or more erosion facilitator with one or more diffusion facilitator can also be used in the present compositions.

[00395] The term “diluent” refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents can also be used to stabilize compounds because they can provide a more stable environment. Salts dissolved in buffered solutions (which also can provide pH control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution. In certain embodiments, diluents increase bulk of the composition to facilitate compression or create sufficient bulk for homogenous blend for capsule filling. Such compounds include e.g., lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose such as Avicel[®]; dibasic calcium phosphate, dicalcium phosphate dihydrate; tricalcium phosphate, calcium phosphate; anhydrous lactose, spray-dried lactose; pregelatinized starch, compressible sugar, such as Di-Pac[®] (Amstar); mannitol, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose-based diluents, confectioner’s

sugar; monobasic calcium sulfate monohydrate, calcium sulfate dihydrate; calcium lactate trihydrate, dextrates; hydrolyzed cereal solids, amylose; powdered cellulose, calcium carbonate; glycine, kaolin; mannitol, sodium chloride; inositol, bentonite, and the like.

[00396] The term "disintegrate" includes both the dissolution and dispersion of the dosage form when contacted with gastrointestinal fluid. "Disintegration agents or disintegrants" facilitate the breakup or disintegration of a substance. Examples of disintegration agents include a starch, e.g., a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel[®], or sodium starch glycolate such as Promogel[®] or Explotab[®], a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel[®], Avicel[®] PH101, Avicel[®] PH102, Avicel[®] PH105, Elcema[®] P100, Emcocel[®], Vivacel[®], Ming Tia[®], and Solka-Floc[®], methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol[®]), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crosspovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum[®] HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like.

[00397] "Drug absorption" or "absorption" typically refers to the process of movement of drug from site of administration of a drug across a barrier into a blood vessel or the site of action, e.g., a drug moving from the gastrointestinal tract into the portal vein or lymphatic system.

[00398] An "enteric coating" is a substance that remains substantially intact in the stomach but dissolves and releases the drug in the small intestine or colon. Generally, the enteric coating comprises a polymeric material that prevents release in the low pH environment of the stomach but that ionizes at a higher pH, typically a pH of 6 to 7, and thus dissolves sufficiently in the small intestine or colon to release the active agent therein.

[00399] "Erosion facilitators" include materials that control the erosion of a particular material in gastrointestinal fluid. Erosion facilitators are generally known to those of ordinary skill in the art. Exemplary erosion facilitators include, e.g., hydrophilic polymers, electrolytes, proteins, peptides, and amino acids.

[00400] "Filling agents" include compounds such as lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

[00401] "Flavoring agents" and/or "sweeteners" useful in the formulations described herein, include, e.g., acacia syrup, acesulfame K, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, bubble gum, citrus, citrus punch, citrus cream, cotton candy, cocoa, cola, cool cherry, cool citrus, cyclamate, cyclamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, monoammonium glycyrrhizinate (MagnaSweet[®]), maltol, mannitol, maple, marshmallow, menthol, mint cream, mixed berry, neohesperidine DC, neotame, orange, pear, peach, peppermint, peppermint cream, Prosweet[®] Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose,

sucrose, sodium saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, xylitol, sucralose, sorbitol, Swiss cream, tagatose, tangerine, thaumatin, tutti frutti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, or any combination of these flavoring ingredients, e.g., anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, and mixtures thereof.

[00402] “Lubricants” and “glidants” are compounds that prevent, reduce or inhibit adhesion or friction of materials. Exemplary lubricants include, e.g., stearic acid, calcium hydroxide, talc, sodium stearyl fumarate, a hydrocarbon such as mineral oil, or hydrogenated vegetable oil such as hydrogenated soybean oil (Sterotex[®]), higher fatty acids and their alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, glycerol, talc, waxes, Stearowet[®], boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol (e.g., PEG-4000) or a methoxypolyethylene glycol such as Carbowax[™], sodium oleate, sodium benzoate, glyceryl behenate, polyethylene glycol, magnesium or sodium lauryl sulfate, colloidal silica such as Syloid[™], Cab-O-Sil[®], a starch such as corn starch, silicone oil, a surfactant, and the like.

[00403] A “measurable serum concentration” or “measurable plasma concentration” describes the blood serum or blood plasma concentration, typically measured in mg, µg, or ng of therapeutic agent per ml, dl, or l of blood serum, absorbed into the bloodstream after administration. As used herein, measurable plasma concentrations are typically measured in ng/ml or µg/ml.

[00404] “Pharmacodynamics” refers to the factors which determine the biologic response observed relative to the concentration of drug at a site of action.

[00405] “Pharmacokinetics” refers to the factors which determine the attainment and maintenance of the appropriate concentration of drug at a site of action.

[00406] “Plasticizers” are compounds used to soften the microencapsulation material or film coatings to make them less brittle. Suitable plasticizers include, e.g., polyethylene glycols such as PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, triethyl cellulose and triacetin. In some embodiments, plasticizers can also function as dispersing agents or wetting agents.

[00407] “Solubilizers” include compounds such as triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, sodium lauryl sulfate, sodium docusate, vitamin E TPGS, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cyclodextrins, ethanol, n-butanol, isopropyl alcohol, cholesterol, bile salts, polyethylene glycol 200-600, glycofurol, transcitol, propylene glycol, and dimethyl isosorbide and the like.

[00408] “Stabilizers” include compounds such as any antioxidation agents, buffers, acids, preservatives and the like.

[00409] “Steady state,” as used herein, is when the amount of drug administered is equal to the amount of drug eliminated within one dosing interval resulting in a plateau or constant plasma drug exposure.

[00410] “Suspending agents” include compounds such as polyvinylpyrrolidone, e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, vinyl pyrrolidone/vinyl acetate copolymer (S630), polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, sodium carboxymethylcellulose, methylcellulose,

hydroxypropylmethylcellulose, hydroxymethylcellulose acetate stearate, polysorbate-80, hydroxyethylcellulose, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulose, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone and the like.

[00411] "Surfactants" include compounds such as sodium lauryl sulfate, sodium docusate, Tween 60 or 80, triacetin, vitamin E TPGS, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g., Pluronic® (BASF), and the like. Some other surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40. In some embodiments, surfactants may be included to enhance physical stability or for other purposes.

[00412] "Synergism," "synergy" or "synergistic means or effects" refers to two or more discrete influences, portions, or agents acting together to create an effect greater than that predicted by knowing only the separate effects of the individual discrete influences, portions or agents.

[00413] "Viscosity enhancing agents" include, e.g., methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose acetate stearate, hydroxypropylmethyl cellulose phthalate, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof.

[00414] "Wetting agents" include compounds such as oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium docusate, sodium oleate, sodium lauryl sulfate, sodium docusate, triacetin, Tween 80, vitamin E TPGS, ammonium salts and the like.

Dosage Forms

[00415] The compositions described herein can be formulated for administration to a subject via any conventional means including, but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, or intramuscular), buccal, intranasal, rectal or transdermal administration routes. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

[00416] Moreover, the pharmaceutical compositions described herein, which include a compound provided herein, can be formulated into any suitable dosage form, including but not limited to, aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by a patient to be treated, solid oral dosage forms, aerosols, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations.

[00417] Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for

example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents may be added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00418] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00419] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[00420] In some embodiments, the solid dosage forms disclosed herein may be in the form of a tablet, (including a suspension tablet, a fast-melt tablet, a bite-disintegration tablet, a rapid-disintegration tablet, an effervescent tablet, or a caplet), a pill, a powder (including a sterile packaged powder, a dispensable powder, or an effervescent powder) a capsule (including both soft or hard capsules, e.g., capsules made from animal-derived gelatin or plant-derived HPMC, or "sprinkle capsules"), solid dispersion, solid solution, bioerodible dosage form, controlled release formulations, pulsatile release dosage forms, multiparticulate dosage forms, pellets, granules, or an aerosol. In other embodiments, the pharmaceutical formulation is in the form of a powder. In still other embodiments, the pharmaceutical formulation is in the form of a tablet, including but not limited to, a fast-melt tablet. Additionally, pharmaceutical formulations of the present invention may be administered as a single capsule or in multiple capsule dosage form. In some embodiments, the pharmaceutical formulation is administered in two, or three, or four, capsules or tablets.

[00421] In some embodiments, solid dosage forms, e.g., tablets, effervescent tablets, and capsules, are prepared by mixing particles of a compound provided herein, with one or more pharmaceutical excipients to form a bulk blend composition. When referring to these bulk blend compositions as homogeneous, it is meant that the particles of the compound provided herein, are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms, such as tablets, pills, and capsules. The individual unit dosages may also include film coatings, which disintegrate upon oral ingestion or upon contact with diluent. These formulations can be manufactured by conventional pharmacological techniques.

[00422] Conventional pharmacological techniques include, e.g., one or a combination of methods: (1) dry mixing, (2) direct compression, (3) milling, (4) dry or non-aqueous granulation, (5) wet granulation, or (6) fusion. See, e.g., Lachman et al., *The Theory and Practice of Industrial Pharmacy* (1986). Other methods include, e.g., spray drying, pan coating, melt granulation, granulation, fluidized bed spray drying or coating (e.g., wurster coating), tangential coating, top spraying, tableting, extruding and the like.

[00423] The pharmaceutical solid dosage forms described herein can include a compound provided herein and one or more pharmaceutically acceptable additives such as a compatible carrier, binder, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof. In still other aspects, using standard coating procedures, such as those described in *Remington's Pharmaceutical Sciences*, 20th Edition (2000), a film coating is provided around the formulation of the compound provided herein. In one embodiment, some or all of the particles of the compound provided herein are coated. In another embodiment, some or all of the particles of the compound provided herein are microencapsulated. In still another embodiment, the particles of the compound provided herein are not microencapsulated and are uncoated.

[00424] Suitable carriers for use in the solid dosage forms described herein include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose, microcrystalline cellulose, lactose, mannitol and the like.

[00425] Suitable filling agents for use in the solid dosage forms described herein include, but are not limited to, lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrans, dextran, starches, pregelatinized starch, hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate stearate (HPMCAS), sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

[00426] In order to release the compound disclosed herein from a solid dosage form matrix as efficiently as possible, disintegrants are often used in the formulation, especially when the dosage forms are compressed with binder. Disintegrants help rupturing the dosage form matrix by swelling or capillary action when moisture is absorbed into the dosage form. Suitable disintegrants for use in the solid dosage forms described herein include, but are not limited to, natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel[®], or sodium starch glycolate such as Promogel[®] or Explotab[®], a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel[®], Avicel[®] PH101, Avicel[®] PH102, Avicel[®] PH105, Elcema[®] P100, Emcocel[®], Vivacel[®], Ming Tia[®], and Solka-Floc[®], methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol[®]), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crospovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum[®] HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like.

[00427] Binders impart cohesiveness to solid oral dosage form formulations: for powder filled capsule formulation, they aid in plug formation that can be filled into soft or hard shell capsules and for tablet formulation, they ensure the tablet remaining intact after compression and help assure blend uniformity prior to a compression or fill step. Materials suitable

for use as binders in the solid dosage forms described herein include, but are not limited to, carboxymethylcellulose, methylcellulose (e.g., Methocel[®]), hydroxypropylmethylcellulose (e.g. Hypromellose USP Pharmacoat-603, hydroxypropylmethylcellulose acetate stearate (Aqoate HS-LF and HS), hydroxyethylcellulose, hydroxypropylcellulose (e.g., KluCEL[®]), ethylcellulose (e.g., Ethocel[®]), and microcrystalline cellulose (e.g., Avicel[®]), microcrystalline dextrose, amylose, magnesium aluminum silicate, polysaccharide acids, bentonites, gelatin, polyvinylpyrrolidone/vinyl acetate copolymer, crospovidone, povidone, starch, pregelatinized starch, tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac[®]), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab[®]), lactose, a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, starch, polyvinylpyrrolidone (e.g., Povidone[®] CL, Kollidon[®] CL, Polyplasdone[®] XL-10, and Povidone[®] K-12), larch arabogalactan, Veegum[®], polyethylene glycol, waxes, sodium alginate, and the like.

[00428] In general, binder levels of 20-70% are used in powder-filled gelatin capsule formulations. Binder usage level in tablet formulations varies whether direct compression, wet granulation, roller compaction, or usage of other excipients such as fillers which itself can act as moderate binder. Formulators skilled in art can determine the binder level for the formulations, but binder usage level of up to 70% in tablet formulations is common.

[00429] Suitable lubricants or glidants for use in the solid dosage forms described herein include, but are not limited to, stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumarate, alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, magnesium stearate, zinc stearate, waxes, Stearowet[®], boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol or a methoxypolyethylene glycol such as Carbowax[™], PEG 4000, PEG 5000, PEG 6000, propylene glycol, sodium oleate, glyceryl behenate, glyceryl palmitostearate, glyceryl benzoate, magnesium or sodium lauryl sulfate, and the like.

[00430] Suitable diluents for use in the solid dosage forms described herein include, but are not limited to, sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrans and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), cyclodextrins and the like.

[00431] The term "non water-soluble diluent" represents compounds typically used in the formulation of pharmaceuticals, such as calcium phosphate, calcium sulfate, starches, modified starches and microcrystalline cellulose, and microcellulose (e.g., having a density of about 0.45 g/cm³, e.g. Avicel, powdered cellulose), and talc.

[00432] Suitable wetting agents for use in the solid dosage forms described herein include, for example, oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, quaternary ammonium compounds (e.g., Polyquat 10[®]), sodium oleate, sodium lauryl sulfate, magnesium stearate, sodium docusate, triacetin, vitamin E TPGS and the like.

[00433] Suitable surfactants for use in the solid dosage forms described herein include, for example, sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g., Pluronic[®] (BASF), and the like.

[00434] Suitable suspending agents for use in the solid dosage forms described here include, but are not limited to, polyvinylpyrrolidone, e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, vinyl pyrrolidone/vinyl acetate copolymer

(S630), sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, polysorbate-80, hydroxyethylcellulose, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulosics, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone and the like.

[00435] Suitable antioxidants for use in the solid dosage forms described herein include, for example, e.g., butylated hydroxytoluene (BHT), sodium ascorbate, and tocopherol.

[00436] It should be appreciated that there is considerable overlap between additives used in the solid dosage forms described herein. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in solid dosage forms of the present invention. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

[00437] In other embodiments, one or more layers of the pharmaceutical formulation are plasticized. Illustratively, a plasticizer is generally a high boiling point solid or liquid. Suitable plasticizers can be added from about 0.01% to about 50% by weight (w/w) of the coating composition. Plasticizers include, but are not limited to, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, triacetin, polypropylene glycol, polyethylene glycol, triethyl citrate, dibutyl sebacate, stearic acid, stearyl, stearate, and castor oil.

[00438] Compressed tablets are solid dosage forms prepared by compacting the bulk blend of the formulations described above. In various embodiments, compressed tablets which are designed to dissolve in the mouth will include one or more flavoring agents. In other embodiments, the compressed tablets will include a film surrounding the final compressed tablet. In some embodiments, the film coating can provide a delayed release of the compound disclosed herein from the formulation. In other embodiments, the film coating aids in patient compliance (e.g., Opadry® coatings or sugar coating). Film coatings including Opadry® typically range from about 1% to about 3% of the tablet weight. In other embodiments, the compressed tablets include one or more excipients.

[00439] A capsule may be prepared, for example, by placing the bulk blend of the formulation of the compound described above, inside of a capsule. In some embodiments, the formulations (non-aqueous suspensions and solutions) are placed in a soft gelatin capsule. In other embodiments, the formulations are placed in standard gelatin capsules or non-gelatin capsules such as capsules comprising HPMC. In other embodiments, the formulation is placed in a sprinkle capsule, wherein the capsule may be swallowed whole or the capsule may be opened and the contents sprinkled on food prior to eating. In some embodiments, the therapeutic dose is split into multiple (e.g., two, three, or four) capsules. In some embodiments, the entire dose of the formulation is delivered in a capsule form.

[00440] In various embodiments, the particles of the compound disclosed herein and one or more excipients are dry blended and compressed into a mass, such as a tablet, having a hardness sufficient to provide a pharmaceutical composition that substantially disintegrates within less than about 30 minutes, less than about 35 minutes, less than about 40 minutes, less than about 45 minutes, less than about 50 minutes, less than about 55 minutes, or less than about 60 minutes, after oral administration, thereby releasing the formulation into the gastrointestinal fluid.

[00441] In another aspect, dosage forms may include microencapsulated formulations. In some embodiments, one or more other compatible materials are present in the microencapsulation material. Exemplary materials include, but are not

limited to, pH modifiers, erosion facilitators, anti-foaming agents, antioxidants, flavoring agents, and carrier materials such as binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, and diluents.

[00442] Materials useful for the microencapsulation described herein include materials compatible with compounds disclosed herein, which sufficiently isolate the compound disclosed herein from other non-compatible excipients. Materials compatible with compounds disclosed herein are those that delay the release of the compounds disclosed herein *in vivo*.

[00443] Exemplary microencapsulation materials useful for delaying the release of the formulations including compounds disclosed herein, include, but are not limited to, hydroxypropyl cellulose ethers (HPC) such as Klucel[®] or Nisso HPC, low-substituted hydroxypropyl cellulose ethers (L-HPC), hydroxypropyl methyl cellulose ethers (HPMC) such as Seppifilm-LC, Pharmacoat[®], Metolose SR, Methocel[®]-E, Opadry YS, PrimaFlo, Benecel MP824, and Benecel MP843, methylcellulose polymers such as Methocel[®]-A, hydroxypropylmethylcellulose acetate stearate Aqoat (HF-LS, HF-LG, HF-MS) and Metolose[®], Ethylcelluloses (EC) and mixtures thereof such as E461, Ethocel[®], Aqualon[®]-EC, Surelease[®], Polyvinyl alcohol (PVA) such as Opadry AMB, hydroxyethylcelluloses such as Natrosol[®], carboxymethylcelluloses and salts of carboxymethylcelluloses (CMC) such as Aqualon[®]-CMC, polyvinyl alcohol and polyethylene glycol co-polymers such as Kollicoat IR[®], monoglycerides (Myverol), triglycerides (KLX), polyethylene glycols, modified food starch, acrylic polymers and mixtures of acrylic polymers with cellulose ethers such as Eudragit[®] EPO, Eudragit[®] L30D-55, Eudragit[®] FS 30D, Eudragit[®] L100-55, Eudragit[®] L100, Eudragit[®] S100, Eudragit[®] RD100, Eudragit[®] E100, Eudragit[®] L12.5, Eudragit[®] S12.5, Eudragit[®] NE30D, and Eudragit[®] NE 40D, cellulose acetate phthalate, sepiifilms such as mixtures of HPMC and stearic acid, cyclodextrins, and mixtures of these materials.

[00444] In still other embodiments, plasticizers such as polyethylene glycols, e.g., PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, and triacetin are incorporated into the microencapsulation material. In other embodiments, the microencapsulating material useful for delaying the release of the pharmaceutical compositions is from the USP or the National Formulary (NF). In yet other embodiments, the microencapsulation material is Klucel. In still other embodiments, the microencapsulation material is methocel.

[00445] Microencapsulated compounds disclosed herein may be formulated by methods known by one of ordinary skill in the art. Such known methods include, e.g., spray drying processes, spinning disk-solvent processes, hot melt processes, spray chilling methods, fluidized bed, electrostatic deposition, centrifugal extrusion, rotational suspension separation, polymerization at liquid-gas or solid-gas interface, pressure extrusion, or spraying solvent extraction bath. In addition to these, several chemical techniques, e.g., complex coacervation, solvent evaporation, polymer-polymer incompatibility, interfacial polymerization in liquid media, in situ polymerization, in-liquid drying, and desolvation in liquid media could also be used. Furthermore, other methods such as roller compaction, extrusion/spheronization, coacervation, or nanoparticle coating may also be used.

[00446] In one embodiment, the particles of compounds disclosed herein are microencapsulated prior to being formulated into one of the above forms. In still another embodiment, some or most of the particles are coated prior to being further formulated by using standard coating procedures, such as those described in *Remington's Pharmaceutical Sciences*, 20th Edition (2000).

[00447] In other embodiments, the solid dosage formulations of the compounds disclosed herein are plasticized (coated) with one or more layers. Illustratively, a plasticizer is generally a high boiling point solid or liquid. Suitable plasticizers can be added from about 0.01% to about 50% by weight (w/w) of the coating composition. Plasticizers include, but are not limited to, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, triacetin, polypropylene glycol, polyethylene glycol, triethyl citrate, dibutyl sebacate, stearic acid, stearyl, stearate, and castor oil.

[00448] In other embodiments, a powder including the formulations with a compound disclosed herein may be formulated to include one or more pharmaceutical excipients and flavors. Such a powder may be prepared, for example, by mixing the formulation and optional pharmaceutical excipients to form a bulk blend composition. Additional embodiments also include a suspending agent and/or a wetting agent. This bulk blend is uniformly subdivided into unit dosage packaging or multi-dosage packaging units.

[00449] In still other embodiments, effervescent powders are also prepared in accordance with the present disclosure. Effervescent salts have been used to disperse medicines in water for oral administration. Effervescent salts are granules or coarse powders containing a medicinal agent in a dry mixture, usually composed of sodium bicarbonate, citric acid and/or tartaric acid. When salts of the present invention are added to water, the acids and the base react to liberate carbon dioxide gas, thereby causing "effervescence." Examples of effervescent salts include, e.g., the following ingredients: sodium bicarbonate or a mixture of sodium bicarbonate and sodium carbonate, citric acid and/or tartaric acid. Any acid-base combination that results in the liberation of carbon dioxide can be used in place of the combination of sodium bicarbonate and citric and tartaric acids, as long as the ingredients were suitable for pharmaceutical use and result in a pH of about 6.0 or higher.

[00450] In other embodiments, the formulations described herein, which include a compound disclosed herein, are solid dispersions. Methods of producing such solid dispersions are known in the art and include, but are not limited to, for example, U.S. Pat. Nos. 4,343,789, 5,340,591, 5,456,923, 5,700,485, 5,723,269, and U.S. Pub. Appl 2004/0013734, each of which is specifically incorporated by reference. In still other embodiments, the formulations described herein are solid solutions. Solid solutions incorporate a substance together with the active agent and other excipients such that heating the mixture results in dissolution of the drug and the resulting composition is then cooled to provide a solid blend which can be further formulated or directly added to a capsule or compressed into a tablet. Methods of producing such solid solutions are known in the art and include, but are not limited to, for example, U.S. Pat. Nos. 4,151,273, 5,281,420, and 6,083,518, each of which is specifically incorporated by reference.

[00451] The pharmaceutical solid oral dosage forms including formulations described herein, which include a compound disclosed herein, can be further formulated to provide a controlled release of the compound disclosed herein. Controlled release refers to the release of the compound disclosed herein from a dosage form in which it is incorporated according to a desired profile over an extended period of time. Controlled release profiles include, for example, sustained release, prolonged release, pulsatile release, and delayed release profiles. In contrast to immediate release compositions, controlled release compositions allow delivery of an agent to a subject over an extended period of time according to a predetermined profile. Such release rates can provide therapeutically effective levels of agent for an extended period of time and thereby provide a longer period of pharmacologic response while minimizing side effects as compared to

conventional rapid release dosage forms. Such longer periods of response provide for many inherent benefits that are not achieved with the corresponding short acting, immediate release preparations.

[00452] In some embodiments, the solid dosage forms described herein can be formulated as enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical composition as described herein which utilizes an enteric coating to affect release in the small intestine of the gastrointestinal tract. The enteric coated dosage form may be a compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, powder, pellets, beads or particles of the active ingredient and/or other composition components, which are themselves coated or uncoated. The enteric coated oral dosage form may also be a capsule (coated or uncoated) containing pellets, beads or granules of the solid carrier or the composition, which are themselves coated or uncoated.

[00453] The term "delayed release" as used herein refers to the delivery so that the release can be accomplished at some generally predictable location in the intestinal tract more distal to that which would have been accomplished if there had been no delayed release alterations. In some embodiments the method for delay of release is coating. Any coatings should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention to achieve delivery to the lower gastrointestinal tract. In some embodiments the polymers for use in the present invention are anionic carboxylic polymers. In other embodiments, the polymers and compatible mixtures thereof, and some of their properties, include, but are not limited to:

[00454] Shellac, also called purified lac, a refined product obtained from the resinous secretion of an insect. This coating dissolves in media of pH > about 7;

[00455] Acrylic polymers. The performance of acrylic polymers (primarily their solubility in biological fluids) can vary based on the degree and type of substitution. Examples of suitable acrylic polymers include methacrylic acid copolymers and ammonium methacrylate copolymers. The Eudragit series E, L, S, RL, RS and NE (Rohm Pharma) are available as solubilized in organic solvent, aqueous dispersion, or dry powders. The Eudragit series RL, NE, and RS are insoluble in the gastrointestinal tract but are permeable and are used primarily for colonic targeting. The Eudragit series E dissolve in the stomach. The Eudragit series L, L-30D and S are insoluble in stomach and dissolve in the intestine;

[00456] Cellulose Derivatives. Examples of suitable cellulose derivatives are: ethyl cellulose; reaction mixtures of partial acetate esters of cellulose with phthalic anhydride. The performance can vary based on the degree and type of substitution. Cellulose acetate phthalate (CAP) dissolves in pH >6. Aquateric (FMC) is an aqueous based system and is a spray dried CAP pseudolatex with particles <1 μm . Other components in Aquateric can include pluronics, Tweens, and acetylated monoglycerides. Other suitable cellulose derivatives include: cellulose acetate trimellitate (Eastman); methylcellulose (Pharmacoat, Methocel); hydroxypropylmethyl cellulose phthalate (HPMCP); hydroxypropylmethyl cellulose succinate (HPMCS); and hydroxypropylmethylcellulose acetate succinate (e.g., AQOAT (Shin Etsu)). The performance can vary based on the degree and type of substitution. For example, HPMCP such as, HP-50, HP-55, HP-55S, HP-55F grades are suitable. The performance can vary based on the degree and type of substitution. For example, suitable grades of hydroxypropylmethylcellulose acetate succinate include, but are not limited to, AS-LG (LF), which

dissolves at pH 5, AS-MG (MF), which dissolves at pH 5.5, and AS-HG (HF), which dissolves at higher pH. These polymers are offered as granules, or as fine powders for aqueous dispersions;

[00457] Poly Vinyl Acetate Phthalate (PVAP). PVAP dissolves in pH >5, and it is much less permeable to water vapor and gastric fluids.

[00458] In some embodiments, the coating can, and usually does, contain a plasticizer and possibly other coating excipients such as colorants, talc, and/or magnesium stearate, which are well known in the art. Suitable plasticizers include triethyl citrate (Citroflex 2), triacetin (glyceryl triacetate), acetyl triethyl citrate (Citroflex A2), Carbowax 400 (polyethylene glycol 400), diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol, and dibutyl phthalate. In particular, anionic carboxylic acrylic polymers usually will contain 10-25% by weight of a plasticizer, especially dibutyl phthalate, polyethylene glycol, triethyl citrate and triacetin. Conventional coating techniques such as spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the intestinal tract is reached.

[00459] Colorants, detackifiers, surfactants, antifoaming agents, lubricants (e.g., carnuba wax or PEG) may be added to the coatings besides plasticizers to solubilize or disperse the coating material, and to improve coating performance and the coated product.

[00460] In other embodiments, the formulations described herein, which include a compound disclosed herein, are delivered using a pulsatile dosage form. A pulsatile dosage form is capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites. Pulsatile dosage forms including the formulations described herein, which include a compound disclosed herein, may be administered using a variety of pulsatile formulations known in the art. For example, such formulations include, but are not limited to, those described in U.S. Pat. Nos. 5,011,692, 5,017,381, 5,229,135, and 5,840,329, each of which is specifically incorporated by reference. Other pulsatile release dosage forms suitable for use with the present formulations include, but are not limited to, for example, U.S. Pat. Nos. 4,871,549, 5,260,068, 5,260,069, 5,508,040, 5,567,441 and 5,837,284, all of which are specifically incorporated by reference. In one embodiment, the controlled release dosage form is pulsatile release solid oral dosage form including at least two groups of particles, (*i.e.* multiparticulate) each containing the formulation described herein. The first group of particles provides a substantially immediate dose of the compound disclosed herein upon ingestion by a mammal. The first group of particles can be either uncoated or include a coating and/or sealant. The second group of particles includes coated particles, which includes from about 2% to about 75%, preferably from about 2.5% to about 70%, and more preferably from about 40% to about 70%, by weight of the total dose of the compound disclosed herein in the formulation, in admixture with one or more binders. The coating includes a pharmaceutically acceptable ingredient in an amount sufficient to provide a delay of from about 2 hours to about 7 hours following ingestion before release of the second dose. Suitable coatings include one or more differentially degradable coatings such as, by way of example only, pH sensitive coatings (enteric coatings) such as acrylic resins (e.g., Eudragit® EPO, Eudragit® L30D-55, Eudragit® FS 30D Eudragit® L100-55, Eudragit® L100, Eudragit® S100, Eudragit® RD100, Eudragit® E100, Eudragit® L12.5, Eudragit® S12.5, and Eudragit® NE30D, Eudragit® NE 40D®) either alone or blended

with cellulose derivatives, e.g., ethylcellulose, or non-enteric coatings having variable thickness to provide differential release of the formulation that includes a compound disclosed herein.

[00461] Many other types of controlled release systems known to those of ordinary skill in the art and are suitable for use with the formulations described herein. Examples of such delivery systems include, e.g., polymer-based systems, such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; porous matrices, nonpolymer-based systems that are lipids, including sterols, such as cholesterol, cholesterol esters and fatty acids, or neutral fats, such as mono-, di- and triglycerides; hydrogel release systems; silastic systems; peptide-based systems; wax coatings, bioerodible dosage forms, compressed tablets using conventional binders and the like. See, e.g., Liberman et al., *Pharmaceutical Dosage Forms*, 2 Ed., Vol. 1, pp. 209-214 (1990); Singh et al., *Encyclopedia of Pharmaceutical Technology*, 2nd Ed., pp. 751-753 (2002); U.S. Pat. Nos. 4,327,725, 4,624,848, 4,968,509, 5,461,140, 5,456,923, 5,516,527, 5,622,721, 5,686,105, 5,700,410, 5,977,175, 6,465,014 and 6,932,983, each of which is specifically incorporated by reference.

[00462] In some embodiments, pharmaceutical formulations are provided that include particles of the compounds disclosed herein and at least one dispersing agent or suspending agent for oral administration to a subject. The formulations may be a powder and/or granules for suspension, and upon admixture with water, a substantially uniform suspension is obtained.

[00463] Liquid formulation dosage forms for oral administration can be aqueous suspensions selected from the group including, but not limited to, pharmaceutically acceptable aqueous oral dispersions, emulsions, solutions, elixirs, gels, and syrups. See, e.g., Singh et al., *Encyclopedia of Pharmaceutical Technology*, 2nd Ed., pp. 754-757 (2002). In addition to the particles of compound disclosed herein, the liquid dosage forms may include additives, such as: (a) disintegrating agents; (b) dispersing agents; (c) wetting agents; (d) at least one preservative, (e) viscosity enhancing agents, (f) at least one sweetening agent, and (g) at least one flavoring agent. In some embodiments, the aqueous dispersions can further include a crystalline inhibitor.

[00464] The aqueous suspensions and dispersions described herein can remain in a homogenous state, as defined in The USP Pharmacists' Pharmacopeia (2005 edition, chapter 905), for at least 4 hours. The homogeneity should be determined by a sampling method consistent with regard to determining homogeneity of the entire composition. In one embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 1 minute. In another embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 45 seconds. In yet another embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 30 seconds. In still another embodiment, no agitation is necessary to maintain a homogeneous aqueous dispersion.

[00465] Examples of disintegrating agents for use in the aqueous suspensions and dispersions include, but are not limited to, a starch, e.g., a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel[®], or sodium starch glycolate such as Promogel[®] or Explotab[®]; a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel[®], Avicel[®] PH101, Avicel[®] PH102, Avicel[®] PH105, Elcema[®] P100, Emcocel[®], Vivacel[®], Ming Tia[®], and Solka-Floc[®], methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol[®]), cross-linked carboxymethylcellulose, or cross-linked croscarmellose; a

cross-linked starch such as sodium starch glycolate; a cross-linked polymer such as crospovidone; a cross-linked polyvinylpyrrolidone; alginate such as alginic acid or a salt of alginic acid such as sodium alginate; a clay such as Veegum[®] HV (magnesium aluminum silicate); a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth; sodium starch glycolate; bentonite; a natural sponge; a surfactant; a resin such as a cation-exchange resin; citrus pulp; sodium lauryl sulfate; sodium lauryl sulfate in combination starch; and the like.

[00466] In some embodiments, the dispersing agents suitable for the aqueous suspensions and dispersions described herein are known in the art and include, for example, hydrophilic polymers, electrolytes, Tween[®] 60 or 80, PEG, polyvinylpyrrolidone (PVP; commercially known as Plasdene[®]), and the carbohydrate-based dispersing agents such as, for example, hydroxypropylcellulose and hydroxypropyl cellulose ethers (e.g., HPC, HPC-SL, and HPC-L), hydroxypropyl methylcellulose and hydroxypropyl methylcellulose ethers (e.g. HPMC K100, HPMC K4M, HPMC K15M, and HPMC K100M), carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, hydroxypropylmethyl-cellulose acetate stearate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), polyvinylpyrrolidone/vinyl acetate copolymer (Plasdene[®], e.g., S-630), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol), poloxamers (e.g., Pluronic F68[®], F88[®], and F108[®], which are block copolymers of ethylene oxide and propylene oxide); and poloxamines (e.g., Tetronic 908[®], also known as Poloxamine 908[®], which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Corporation, Parsippany, N.J.)). In other embodiments, the dispersing agent is selected from a group not comprising one of the following agents: hydrophilic polymers; electrolytes; Tween[®] 60 or 80; PEG; polyvinylpyrrolidone (PVP); hydroxypropylcellulose and hydroxypropyl cellulose ethers (e.g., HPC, HPC-SL, and HPC-L); hydroxypropyl methylcellulose and hydroxypropyl methylcellulose ethers (e.g. HPMC K100, HPMC K4M, HPMC K15M, HPMC K100M, and Pharmacoat[®] USP 2910 (Shin-Etsu)); carboxymethylcellulose sodium; methylcellulose; hydroxyethylcellulose; hydroxypropylmethyl-cellulose phthalate; hydroxypropylmethyl-cellulose acetate stearate; non-crystalline cellulose; magnesium aluminum silicate; triethanolamine; polyvinyl alcohol (PVA); 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde; poloxamers (e.g., Pluronic F68[®], F88[®], and F108[®], which are block copolymers of ethylene oxide and propylene oxide); or poloxamines (e.g., Tetronic 908[®], also known as Poloxamine 908[®]).

[00467] Wetting agents suitable for the aqueous suspensions and dispersions described herein are known in the art and include, but are not limited to, cetyl alcohol, glycerol monostearate, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens[®] such as e.g., Tween 20[®] and Tween 80[®] (ICI Specialty Chemicals)), and polyethylene glycols (e.g., Carbowax 3350[®] and 1450[®], and Carbopol 934[®] (Union Carbide)), oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium oleate, sodium lauryl sulfate, sodium docusate, triacetin, vitamin E TPGS, sodium taurocholate, simethicone, phosphatidylcholine and the like.

[00468] Suitable preservatives for the aqueous suspensions or dispersions described herein include, for example, potassium sorbate, parabens (e.g., methylparaben and propylparaben), benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl alcohol or benzyl alcohol, phenolic compounds

such as phenol, or quaternary compounds such as benzalkonium chloride. Preservatives, as used herein, are incorporated into the dosage form at a concentration sufficient to inhibit microbial growth.

[00469] Suitable viscosity enhancing agents for the aqueous suspensions or dispersions described herein include, but are not limited to, methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, Plasdon[®] S-630, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof. The concentration of the viscosity enhancing agent will depend upon the agent selected and the viscosity desired.

[00470] Examples of sweetening agents suitable for the aqueous suspensions or dispersions described herein include, for example, acacia syrup, acesulfame K, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, bubble gum, citrus, citrus punch, citrus cream, cotton candy, cocoa, cola, cool cherry, cool citrus, cyclamate, cyclamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, monoammonium glycyrrhizinate (MagnaSweet[®]), maltol, mannitol, maple, marshmallow, menthol, mint cream, mixed berry, neohesperidine DC, neotame, orange, pear, peach, peppermint, peppermint cream, Prosweet[®] Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose, sucrose, sodium saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, sucralose, sorbitol, swiss cream, tagatose, tangerine, thaumatin, tutti frutti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, or any combination of these flavoring ingredients, e.g., anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, and mixtures thereof. In one embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.001% to about 1.0% the volume of the aqueous dispersion. In another embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.005% to about 0.5% the volume of the aqueous dispersion. In yet another embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.01% to about 1.0% the volume of the aqueous dispersion.

[00471] In addition to the additives listed above, the liquid formulations can also include inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, sodium lauryl sulfate, sodium doccusate, cholesterol, cholesterol esters, taurocholic acid, phosphatidylcholine, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

[00472] In some embodiments, the pharmaceutical formulations described herein can be self-emulsifying drug delivery systems (SEDDS). Emulsions are dispersions of one immiscible phase in another, usually in the form of droplets. Generally, emulsions are created by vigorous mechanical dispersion. SEDDS, as opposed to emulsions or microemulsions, spontaneously form emulsions when added to an excess of water without any external mechanical dispersion or agitation. An advantage of SEDDS is that only gentle mixing is required to distribute the droplets throughout the solution. Additionally, water or the aqueous phase can be added just prior to administration, which

ensures stability of an unstable or hydrophobic active ingredient. Thus, the SEDDS provides an effective delivery system for oral and parenteral delivery of hydrophobic active ingredients. SEDDS may provide improvements in the bioavailability of hydrophobic active ingredients. Methods of producing self-emulsifying dosage forms are known in the art and include, but are not limited to, for example, U.S. Pat. Nos. 5,858,401, 6,667,048, and 6,960,563, each of which is specifically incorporated by reference.

[00473] It is to be appreciated that there is overlap between the above-listed additives used in the aqueous dispersions or suspensions described herein, since a given additive is often classified differently by different practitioners in the field, or is commonly used for any of several different functions. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in formulations described herein. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

Intranasal Formulations

[00474] Intranasal formulations are known in the art and are described in, for example, U.S. Pat. Nos. 4,476,116, 5,116,817 and 6,391,452, each of which is specifically incorporated by reference. Formulations that include a compound provided herein, which are prepared according to these and other techniques well-known in the art are prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, for example, Ansel, H. C. et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Sixth Ed. (1995). Preferably these compositions and formulations are prepared with suitable nontoxic pharmaceutically acceptable ingredients. These ingredients are known to those skilled in the preparation of nasal dosage forms and some of these can be found in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 21st edition, 2005, a standard reference in the field. The choice of suitable carriers is highly dependent upon the exact nature of the nasal dosage form desired, e.g., solutions, suspensions, ointments, or gels. Nasal dosage forms generally contain large amounts of water in addition to the active ingredient. Minor amounts of other ingredients such as pH adjusters, emulsifiers or dispersing agents, preservatives, surfactants, gelling agents, or buffering and other stabilizing and solubilizing agents may also be present. Preferably, the nasal dosage form should be isotonic with nasal secretions.

[00475] For administration by inhalation, the compounds disclosed herein may be in a form as an aerosol, a mist or a powder. Pharmaceutical compositions described herein are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound described herein and a suitable powder base such as lactose or starch.

Buccal Formulations

[00476] Buccal formulations that include compounds disclosed herein may be administered using a variety of formulations known in the art. For example, such formulations include, but are not limited to, U.S. Pat. Nos. 4,229,447, 4,596,795, 4,755,386, and 5,739,136, each of which is specifically incorporated by reference. In addition, the buccal dosage forms described herein can further include a bioerodible (hydrolysable) polymeric carrier that also serves to adhere the dosage form to the buccal mucosa. The buccal dosage form is fabricated so as to erode gradually over a

predetermined time period, wherein the delivery of the compound disclosed herein is provided essentially throughout. Buccal drug delivery, as will be appreciated by those skilled in the art, avoids the disadvantages encountered with oral drug administration, e.g., slow absorption, degradation of the active agent by fluids present in the gastrointestinal tract and/or first-pass inactivation in the liver. With regard to the bioerodible (hydrolysable) polymeric carrier, it will be appreciated that virtually any such carrier can be used, so long as the desired drug release profile is not compromised, and the carrier is compatible with the compound disclosed herein, and any other components that may be present in the buccal dosage unit. Generally, the polymeric carrier comprises hydrophilic (water-soluble and water-swellaable) polymers that adhere to the wet surface of the buccal mucosa. Examples of polymeric carriers useful herein include acrylic acid polymers and co, e.g., those known as "carbomers" (Carbopol[®], which may be obtained from B.F. Goodrich, is one such polymer). Other components may also be incorporated into the buccal dosage forms described herein include, but are not limited to, disintegrants, diluents, binders, lubricants, flavoring, colorants, preservatives, and the like. For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in a conventional manner.

Transdermal Formulations

[00477] Transdermal formulations described herein may be administered using a variety of devices which have been described in the art. For example, such devices include, but are not limited to, U.S. Pat. Nos. 3,598,122, 3,598,123, 3,710,795, 3,731,683, 3,742,951, 3,814,097, 3,921,636, 3,972,995, 3,993,072, 3,993,073, 3,996,934, 4,031,894, 4,060,084, 4,069,307, 4,077,407, 4,201,211, 4,230,105, 4,292,299, 4,292,303, 5,336,168, 5,665,378, 5,837,280, 5,869,090, 6,923,983, 6,929,801 and 6,946,144, each of which is specifically incorporated by reference in its entirety.

[00478] The transdermal dosage forms described herein may incorporate certain pharmaceutically acceptable excipients which are conventional in the art. In one embodiments, the transdermal formulations described herein include at least three components: (1) a formulation of a compound disclosed herein; (2) a penetration enhancer; and (3) an aqueous adjuvant. In addition, transdermal formulations can include additional components such as, but not limited to, gelling agents, creams and ointment bases, and the like. In some embodiments, the transdermal formulation can further include a woven or non-woven backing material to enhance absorption and prevent the removal of the transdermal formulation from the skin. In other embodiments, the transdermal formulations described herein can maintain a saturated or supersaturated state to promote diffusion into the skin.

[00479] Formulations suitable for transdermal administration of compounds described herein may employ transdermal delivery devices and transdermal delivery patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. Still further, transdermal delivery of the compounds described herein can be accomplished by means of iontophoretic patches and the like. Additionally, transdermal patches can provide controlled delivery of the compounds disclosed herein. The rate of absorption can be slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. Conversely, absorption enhancers can be used to increase absorption. An absorption enhancer or carrier can include absorbable pharmaceutically acceptable solvents to assist passage through the skin. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the

compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Injectable Formulations

[00480] Formulations that include a compound disclosed herein, suitable for intramuscular, subcutaneous, or intravenous injection may include physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, cremophor and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Formulations suitable for subcutaneous injection may also contain additives such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[00481] For intravenous injections, compounds described herein may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For other parenteral injections, appropriate formulations may include aqueous or nonaqueous solutions, preferably with physiologically compatible buffers or excipients. Such excipients are generally known in the art.

[00482] Parenteral injections may involve bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The pharmaceutical composition described herein may be in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

Other Formulations

[00483] In certain embodiments, delivery systems for pharmaceutical compounds may be employed, such as, for example, liposomes and emulsions. In certain embodiments, compositions provided herein can also include an

mucoadhesive polymer, selected from among, for example, carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[00484] In some embodiments, the compounds described herein may be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compounds can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[00485] The compounds described herein may also be formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

Methods of Dosing and Treatment Regimens

[00486] The compounds described herein can be used in the preparation of medicaments for the inhibition of fatty acid amide hydrolase, or for the treatment of diseases or conditions that would benefit, at least in part, from inhibition of fatty acid amide hydrolase. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions containing at least one compound disclosed herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to the subject.

[00487] The compositions containing the compound(s) described herein can be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. Amounts effective for this use will depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. It is considered well within the skill of the art for one to determine such therapeutically effective amounts by routine experimentation (including, but not limited to, a dose escalation clinical trial).

[00488] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. It is considered well within the skill of the art for one to determine such prophylactically effective amounts by routine experimentation (*e.g.*, a dose escalation clinical trial). When used in a patient, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

[00489] In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds may be administered chronically, that is, for an extended period of time, including throughout the

duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00490] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the compounds may be given continuously; alternatively, the dose of drug being administered may be temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). The length of the drug holiday can vary between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday may be from 10%-100%, including, by way of example only, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.

[00491] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00492] The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease or condition and its severity, the identity (*e.g.*, weight) of the subject or host in need of treatment, but can nevertheless be routinely determined in a manner known in the art according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. In general, however, doses employed for adult human treatment will typically be in the range of about 0.02 to about 5000 mg per day, preferably about 1 to about 1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00493] The pharmaceutical composition described herein may be in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. The unit dosage may be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers can be used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection may be presented in unit dosage form, which include, but are not limited to ampoules, or in multi-dose containers, with an added preservative.

[00494] The daily dosages appropriate for the compounds described herein are from about 0.01 to about 2.5 mg/kg per body weight. An indicated daily dosage in the larger mammal, including, but not limited to, humans, is in the range from about 0.5 mg to about 100 mg, conveniently administered in divided doses, including, but not limited to, up to four times a day or in extended release form. Suitable unit dosage forms for oral administration include from about 1 to about 50 mg active ingredient. The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon. Such dosages may be altered depending on a number of variables, not limited to the activity of the

compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00495] Toxicity and therapeutic efficacy of such therapeutic regimens can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Compounds exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

Combination Treatments

[00496] The compositions and methods described herein may also be used in conjunction with other well known therapeutic reagents that are selected for their particular usefulness against the condition that is being treated. In general, the compositions described herein and, in embodiments where combinational therapy is employed, other agents do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

[00497] In certain instances, it may be appropriate to administer at least one compound described herein in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is nausea, then it may be appropriate to administer an anti-nausea agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant may have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[00498] The particular choice of compounds used will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol. The compounds may be administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the disease, disorder, or condition, the condition of the patient, and the actual choice of compounds used. The determination of the order of administration, and the number of repetitions of administration of

each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient.

[00499] It is known to those of skill in the art that therapeutically-effective dosages can vary when the drugs are used in treatment combinations. Methods for experimentally determining therapeutically-effective dosages of drugs and other agents for use in combination treatment regimens are described in the literature. For example, the use of metronomic dosing, i.e., providing more frequent, lower doses in order to minimize toxic side effects, has been described extensively in the literature. Combination treatment further includes periodic treatments that start and stop at various times to assist with the clinical management of the patient.

[00500] For combination therapies described herein, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In addition, when co-administered with one or more biologically active agents, the compound provided herein may be administered either simultaneously with the biologically active agent(s), or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein in combination with the biologically active agent(s).

[00501] In any case, the multiple therapeutic agents (one of which is a compound disclosed herein) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may vary from more than zero weeks to less than four weeks. In addition, the combination methods, compositions and formulations are not to be limited to the use of only two agents; the use of multiple therapeutic combinations are also envisioned.

[00502] It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, can be modified in accordance with a variety of factors. These factors include the disorder from which the subject suffers, as well as the age, weight, sex, diet, and medical condition of the subject. Thus, the dosage regimen actually employed can vary widely and therefore can deviate from the dosage regimens set forth herein.

[00503] The pharmaceutical agents which make up the combination therapy disclosed herein may be a combined dosage form or in separate dosage forms intended for substantially simultaneous administration. The pharmaceutical agents that make up the combination therapy may also be administered sequentially, with either therapeutic compound being administered by a regimen calling for two-step administration. The two-step administration regimen may call for sequential administration of the active agents or spaced-apart administration of the separate active agents. The time period between the multiple administration steps may range from, a few minutes to several hours, depending upon the properties of each pharmaceutical agent, such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the pharmaceutical agent. Circadian variation of the target molecule concentration may also determine the optimal dose interval.

[00504] In addition, the compounds described herein also may be used in combination with procedures that may provide additional or synergistic benefit to the patient. By way of example only, patients are expected to find therapeutic and/or prophylactic benefit in the methods described herein, wherein pharmaceutical composition of a compound disclosed

herein and /or combinations with other therapeutics are combined with genetic testing to determine whether that individual is a carrier of a mutant gene that is known to be correlated with certain diseases or conditions.

[00505] The compounds described herein and combination therapies can be administered before, during or after the occurrence of a disease or condition, and the timing of administering the composition containing a compound can vary. Thus, for example, the compounds can be used as a prophylactic and can be administered continuously to subjects with a propensity to develop conditions or diseases in order to prevent the occurrence of the disease or condition. The compounds and compositions can be administered to a subject during or as soon as possible after the onset of the symptoms. The administration of the compounds can be initiated within the first 48 hours of the onset of the symptoms, preferably within the first 48 hours of the onset of the symptoms, more preferably within the first 6 hours of the onset of the symptoms, and most preferably within 3 hours of the onset of the symptoms. The initial administration can be via any route practical, such as, for example, an intravenous injection, a bolus injection, infusion over 5 minutes to about 5 hours, a pill, a capsule, transdermal patch, buccal delivery, and the like, or combination thereof. A compound is preferably administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease, such as, for example, from about 1 month to about 3 months. The length of treatment can vary for each subject, and the length can be determined using the known criteria. For example, the compound or a formulation containing the compound can be administered for at least 2 weeks, preferably about 1 month to about 5 years, and more preferably from about 1 month to about 3 years.

Kits/Articles of Manufacture

[00506] For use in the therapeutic applications described herein, kits and articles of manufacture are also described herein. Such kits can include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) including one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

[00507] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, e.g., U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any disease, disorder, or condition that would benefit by inhibition of fatty acid amide hydrolase (FAAH), or in which FAAH is a mediator or contributor to the symptoms or cause.

[00508] For example, the container(s) can include one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container can be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods described herein.

[00509] A kit will typically may include one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[00510] A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

[00511] In certain embodiments, the pharmaceutical compositions can be presented in a pack or dispenser device which can contain one or more unit dosage forms containing a compound provided herein. The pack can for example contain metal or plastic foil, such as a blister pack. The pack or dispenser device can be accompanied by instructions for administration. The pack or dispenser can also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, can be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier can also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Treatments and/or Uses of FAAH Inhibitor Compounds

[00512] The enzyme FAAH catalyzes the hydrolysis of endogenous amide and ester derivatives of various fatty acids such as, but not limited to, N-arachidonylethanolamine (anandamide), N-palmitoylethanolamine, N-oleoylethanolamine, oleamide and 2-arachidonoylglycerol. These derivatives exert different pharmacological activities by interacting, inter alia, with the cannabinoid and vanilloid receptors. Compounds provided herein block this degradation pathway and increase the tissue content of these endogenous substances. They may be used in this respect in the prevention and treatment of pathologies in which the endogenous cannabinoids, and/or any other substrates metabolized by the enzyme FAAH, are involved.

[00513] In some embodiments, compounds provided herein can be used to treat and/or prevent emesis, dizziness, vomiting, and nausea, especially after chemotherapy.

[00514] In some embodiments, compounds provided herein may be administered to alleviate pain in a subject. The treatment may be prophylactic or therapeutic. The treatment may be administered to a human subject. The treatment may or may not be administered in a combination therapy with another pain reliever or anti-inflammatory agent.

[00515] In some embodiments, compounds provided herein can be used in treatment of all varieties of pain including pain associated with a cough condition, pain associated with cancer, preoperative pain, arthritic pain and other forms of chronic pain such as post-operative pain, lumbosacral pain, musculo-skeletal pain, headache, migraine, muscle ache, lower back and neck pain, toothache and the like. In some embodiments, the compounds provided herein are useful for the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting

pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. The symptoms of neuropathic pain are heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

[00516] In some embodiments, compounds provided herein are useful in the prevention and/or treatment of pain, in particular acute or chronic neurogenic pain, migraine, neuropathic pains including the forms associated with herpes virus and diabetes, acute or chronic pain associated with the inflammatory diseases: arthritis, rheumatoid arthritis, osteoarthritis, spondylitis, gout, vascularitis, Crohn's disease, irritable bowel syndrome and acute/sharp or chronic pains at the periphery.

[00517] In some embodiments, compounds and compositions provided herein, may be used to treat non-inflammatory pain and/or inflammatory pain. The compounds are administered as therapeutics for various types of non-inflammatory pain including, without limitation:

- peripheral neuropathic pain, which is pain caused by a lesion or dysfunction in the peripheral nervous system, for example, painful neuropathies where pain persists long after the tissue damage has healed;
- central pain, which is pain caused by a lesion or dysfunction of the central nervous system, for example, thalamic lesions accompanied by severe pain in an unaffected part of the body;
- deafferentation pain, which is pain due to loss of sensory input into the central nervous system, for example, pain resulting from an injury where dorsal roots are torn away from the spinal cord;
- chronic nociceptive pain, for example, certain types of cancer pain;
- noxious stimulus of nociceptive receptors, such as, for example, pain felt in response to tissue damage or impending tissue damage;
- phantom pain, which is pain felt in a part of the body that no longer exists;
- pain felt by psychiatric patients, which is pain where no physical cause may exist;
- wandering pain, wherein the pain repeatedly changes location in the body.

[00518] Compounds provided herein may be used to treat both non-inflammatory pain and inflammatory pain.

[00519] In another embodiment, compositions provided herein include a compound provided herein and at least one art-recognized analgesic or anti-inflammatory substance that is compatible with the compounds provided herein and preferably effective in oral dosage form. Examples of art-recognized analgesics and anti-inflammatory compounds include, but are not limited to: aspirin, carbaspirin, choline salicylate, diflunisal, magnesium salicylate, salicylamide, salicylic acid, salsalate, sodium thiosalicylate, acetaminophen, phenacetin, aminopyrine, mefenamic acid,

methotrimeprazine, oxyphenbutazone, phenylbutazone, indomethacin, ibuprofen, sulindac, piroxicam, meclofenamate, zomepirac, codeine, morphine, meperidine, pethidine, alphaprodine, fentanyl, levorphanol, methadone, phenazocine, butorphanol, ethoheptazine, nalbuphine, pentazocine, propoxyphene, fenoprofen, naproxen, tolmeton and the like. In a preferred embodiment, a compound provided herein is co-administered with such an art-recognized analgesic and/or anti-inflammatory compound resulting in a synergistic anti-inflammatory and/or analgesic effect.

[00520] In another embodiment, compounds and compositions provided herein may be used for reducing neuropathic pain.

[00521] As used herein, the term “neuropathic pain” means pain resulting from injury to a nerve. Neuropathic pain is distinguished from nociceptive pain, which is the pain caused by acute tissue injury involving small cutaneous nerves or small nerves in muscle or connective tissue. Pain involving a nociceptive mechanism usually is limited in duration to the period of tissue repair and generally is alleviated by available analgesic agents or opioids (Myers, *Regional Anesthesia* 20:173-184 (1995), which is incorporated herein by reference).

Neuropathic pain typically is long-lasting or chronic and often develops days or months following an initial acute tissue injury. Neuropathic pain can involve persistent, spontaneous pain as well as allodynia, which is a painful response to a stimulus that normally is not painful. Neuropathic pain also can be characterized by hyperalgesia, in which there is an accentuated response to a painful stimulus that usually is trivial, such as a pin prick. Compounds provided herein may be used in alleviating neuropathic pain regardless of the etiology of the pain. In certain embodiments, compounds and compositions provided herein can be used to alleviate neuropathic pain resulting from a peripheral nerve disorder such as neuroma; nerve compression; nerve crush, nerve stretch or incomplete nerve transection; mononeuropathy or polyneuropathy.

[00522] A neuroma can develop readily after traumatic injury to nerve, especially when a whole nerve is severely crushed or transected. In a neuroma, the neurite outgrowth that normally regenerates a peripheral nerve is aberrant or misguided due, for-example, to a physical obstruction such as scar tissue. Thus, a regenerating nerve fiber is entangled in an environment in which mechanical and physical factors precipitate abnormal electrophysiologic activity and pain (Myers, *supra*, 1995). An amputation neuroma, for example, can cause phantom pain or can cause pain triggered by the use of a limb prosthesis. As disclosed herein, such neuropathic pain can be alleviated by administration of a FAAH inhibitor, such as, for example, a compound provided herein.

[00523] Nerve compression also results in neuropathic pain. Nerve compression can be abrupt, as in the case of traumatic nerve crush, or can be prolonged and moderate, secondary to tumor growth or scar formation in the proximity of a major nerve bundle. Compression neuropathy can occur as a result of changes in blood flow to a nerve, causing severe ischemia and consequent nerve injury (Myers, *supra*, 1995).

[00524] In other embodiments, compounds and compositions provided herein can be used to alleviate neuropathic pain resulting from a disorder such as dorsal root ganglion compression; inflammation of the spinal cord; contusion, tumor or hemisection of the spinal cord; tumors of the brainstem, thalamus or cortex; or trauma to the brainstem, thalamus or cortex.

[00525] In some embodiments, administration of a compound provided herein can alleviate neuropathic pain resulting from a mononeuropathy or polyneuropathy. As used herein, a neuropathy is a functional disturbance or pathological

change in the peripheral nervous system and is characterized clinically by sensory or motor neuron abnormalities. The term mononeuropathy indicates that a single peripheral nerve is affected, while the term polyneuropathy indicates that several peripheral nerves are affected. The etiology of a neuropathy can be known or unknown (see, for example, Myers, supra, 1995; Galer, *Neurology* 45(suppl 9):S17-S25 (1995); Stevens and Lowe, *Pathology*, Times Mirror International Publishers Limited, London (1995)). Known etiologies include complications of a disease or toxic state; for example, diabetes is the most common metabolic disorder causing neuropathy. In some embodiments, a compound provided herein alleviates the neuropathic pain of a mononeuropathy resulting, for example, from diabetes, irradiation, ischemia or vasculitis. In other embodiments, a compound provided herein alleviates the neuropathic pain of a polyneuropathy resulting, for example, from post-polio syndrome, diabetes, alcohol, amyloid, toxins, HIV, hypothyroidism, uremia, vitamin deficiencies, chemotherapy, ddC or Fabry's disease. In some other embodiments, compounds provided herein also can alleviate neuropathic pain of unknown etiology.

[00526] In some embodiments, compounds provided herein may be used to treat inflammatory disorders, such as, for example, auto-immune disorders.

[00527] The term "inflammatory disorders" refers to those diseases or conditions that are characterized by one or more of the signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and loss of function (functio laesa, which may be partial or complete, temporary or permanent). Inflammation takes many forms and includes, but is not limited to, inflammation that is one or more of the following: acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative. Inflammatory disorders further include, without being limited to those affecting the blood vessels (polyarteritis, temporal arteritis); joints (arthritis: crystalline, osteo-, psoriatic, reactive, rheumatoid, Reiter's); gastrointestinal tract (chron's disease, ulcerative colitis); skin (dermatitis); or multiple organs and tissues (systemic lupus erythematosus) [Harrison's Principles of Internal Medicine, 16th Edition, Kasper DL, et al, Editors; McGraw-Hill, publishers].

[00528] Immune disorders, such as auto-immune disorders, which can be treated with a compound provided herein or compositions that include a compound provided herein include: arthritis (including rheumatoid arthritis, spondyloarthropathies, gouty arthritis, degenerative joint diseases (i.e. osteoarthritis), systemic lupus erythematosus, Sjogren's syndrome, ankylosing spondylitis, undifferentiated spondylitis, Behcet's disease, haemolytic autoimmune anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amylosis, acute painful shoulder, psoriatic, and juvenile arthritis), asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis, bursitis, skin inflammation disorders (i.e. psoriasis, eczema, burns, dermatitis), enuresis, eosinophilic disease, gastrointestinal disorders (including inflammatory bowel disease, peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, Crohn's disease, gastritis, diarrhoea, irritable bowel syndrome and ulcerative colitis), and disorders ameliorated by a gastroprokinetic agent (i.e. ileus, for example postoperative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym

GERD); eosinophilic esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP)).

[00529] Compositions that include a compound provided herein can also be used to treat, for example, inflammation associated with: vascular diseases, migraine headaches, tension headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, multiple sclerosis, and ischemia (e.g., myocardial ischemia), and the like. The compounds may be useful for treating neuroinflammation associated with brain disorders (e.g., Parkinson's disease and Alzheimer's disease) and chronic inflammation associated with cranial radiation injury. The compounds may be useful for treating acute inflammatory conditions (such as those resulting from infection) and chronic inflammatory conditions (such as those resulting from asthma, arthritis and inflammatory bowel disease). The compounds may also be useful in treating inflammation associated with trauma and non-inflammatory myalgia. The compounds can also be administered to those prior to surgery or taking anticoagulants. The compounds provided herein may reduce the risk of a thrombotic cardiovascular event which is defined as any sudden event of a type known to be caused by platelet aggregation, thrombosis, and subsequent ischemic clinical events, including thrombotic or thromboembolic stroke, myocardial ischemia, myocardial infarction, angina pectoris, transient ischemic attack (TIA; amaurosis fugax), reversible ischemic neurologic deficits, and any similar thrombotic event in any vascular bed (splanchnic, renal, aortic, peripheral, etc.).

[00530] The compounds provided herein can be used in the treatment of symptoms associated with influenza or other viral infections, common cold, sprains and strains, myositis, neuralgia, synovitis, injuries such as sports injuries and those following surgical and dental procedures, coagulation disorders, kidney disease (e.g., impaired renal function), ophthalmic disorders (including glaucoma, retinitis, retinopathies, uveitis, wet macular degeneration, and acute injury to the eye tissue), liver diseases (i.e., inflammatory liver disease including chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury, primary biliary cirrhosis, autoimmune hepatitis, nonalcoholic steatohepatitis and liver transplant rejection), and pulmonary inflammatory diseases (e.g., including asthma, allergic rhinitis, respiratory distress syndrome chronic bronchitis, and emphysema).

[00531] The compounds provided herein may be used to inhibit uterus contraction caused by hormones and prostanoid-induced smooth muscle contraction. The compounds provided herein may be useful in treating premature labor, menstrual cramps, menstrual irregularity, and dysmenorrhea.

[00532] In some embodiments, the compounds provided herein may inhibit cellular neoplastic transformations and metastatic tumor growth. The compounds may be associated with reducing the number of adenomatous colorectal polyps. Thus, compounds provided herein may be useful in reducing the risk of certain cancers, e.g., solid tumor cancers such as colon or colorectal cancer. In certain embodiments, compounds provided herein may be used in the treatment or prevention of cancer, such as, but not limited to, cancers of the bladder, cancers associated with overexpression of HER-2/neu cervix, skin, esophagus, head and neck, lung including non small-cell lung cancers, kidney, pancreas, prostate, gall bladder and bile duct and endometrial cancers, gastric cancers, gliomas, hepatocellular carcinomas, colonic adenomas, mammary cancers, ovarian cancers and salivary cancers. In addition, the compounds provided herein may be used in treating large intestine cancer and prostate cancer. The compounds may also be used in cases where the patient is at risk

for cancer including oral premalignant lesions, cervical intraepithelial neoplasia, chronic hepatitis, bile duct hyperplasia, atypical adenomatous hyperplasia of lung, prostatic, intraepithelial neoplasia, bladder dysplasia, actinic keratoses of skin, colorectal adenomas, gastric metaplasia, and Barrett's esophagus.

[00533] In certain embodiments, compounds provided herein may be used to treat cancers, such as, but not limited to, benign tumors of the skin, papillomas and cerebral tumors, prostate tumors, cerebral tumors, glioblastomas, medullary epitheliomas, medullary blastomas, neuroblastomas, tumors of embryonic origin, astrocytomas, astroblastomas, ependymomas, oligodendrogliomas, plexus tumor, neuroepithelioma, epiphysis tumor, ependyblastomas, malignant meningiomas, sarcomatosis, malignant melanomas, and schwennomas.

In some embodiments, compounds provided herein may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumor angiogenesis. In some embodiments, compounds provided herein may be used to inhibit angiogenesis, such as occurs in wet macular degeneration.

[00534] FAAH inhibitors, such as, for example, compounds provided herein, are useful for the treatment of cognitive disorders such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease (and precursors thereof), Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease), and vascular dementia (including multiinfarct dementia), as well as dementia associated with intracranial space occupying lesions, trauma, infections and related conditions (including HIV infection), metabolism, toxins, anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

[00535] FAAH inhibitors, such as, for example, compounds provided herein, may prevent neuronal injury by inhibiting the generation of neuronal free radicals (and hence oxidative stress) and therefore are of use in the treatment of stroke; epilepsy; and epileptic seizures (including grand mal, petit mal, myoclonic epilepsy and partial seizures). FAAH inhibitors, such as, compounds provided herein, may be useful to control or suppress seizures (including those that are chemically induced).

[00536] In some embodiments, FAAH inhibitor compounds, such as, for example, compounds provided herein, may be used in acute and chronic neurodegenerative diseases, such as, for example, Parkinson's disease, Alzheimer's disease, senile dementia, Huntington's chorea, lesions associated with cerebral ischaemia and cranial and medullary trauma.

[00537] In some embodiments, FAAH inhibitory compounds, such as, for example, compounds provided herein, and compositions that include them, may be useful in treating depression and depressive disorders or conditions. The compounds and compositions may be useful, for example in treating major depressive disorders (unipolar depression), dysthymic disorders (chronic, mild depression), and bipolar disorders (manic-depression). The depression may be clinical or subclinical depression.

[00538] FAAH inhibitory compounds, such as, for example, compounds provided herein, and compositions that include the compounds, may be used in treating anxiety and anxiety disorders or conditions. These compounds and compositions are useful, for example in treating anxiety, clinical anxiety, panic disorder, agoraphobia, generalized anxiety disorder, specific phobia, social phobia, obsessive-compulsive disorder, acute stress disorder, and post-traumatic stress disorder; and adjustment disorders with anxious features, anxiety disorders due to general medical conditions, substance-induced anxiety disorders, and the residual category of anxiety disorder not otherwise specified. The treatment may be

prophylactic or therapeutic. The compounds may be used for treating anxiety and anxiety disorders or conditions alone and/or also may be useful for concurrently treating another disorder or condition, such as, for example, pain, obesity, depression, or other disorder.

[00539] In some embodiments, a compound that inhibits the activity of FAAH, such as for example, compounds provided herein, and compositions that include the compounds, are useful in treating epilepsy and convulsive disorders or seizures. The compounds and compositions of the invention may be administered solely for the purposes of reducing the severity or frequency of convulsions or seizures.

[00540] In some embodiments, inhibition of FAAH induces sleep (U.S. Pat. No. 6,096,784; 6,096,784; 6,271,015; WO 98/24396). In one embodiment, the compounds provided herein can be administered to a mammal and the subsequent time (e.g., onset, duration) spent sleeping (e.g., eyes closed, motor quiescence) can be increased.

[00541] In some embodiments, a FAAH inhibitor compound may be useful in treating schizophrenia and dopamine related disorders. In some embodiments, the compounds and compositions provided herein are useful in treating schizophrenia, paranoia, paranoid ideation, flat affect or other related disorders, or other disorders of dopamine transmission.

[00542] In some embodiments, the compounds provided herein and compositions that include the compounds provided herein may be administered to induce or promote sleep in a mammal. The treatment may be prophylactic or therapeutic and may be administered to a healthy human patient solely for the purposes of reducing the severity or frequency or extent of sleeplessness. In other embodiments, compounds and compositions provided herein may be used to treat sleeping disorders, such as, but not limited to, insomnia and sleep apnoea.

[00543] In some embodiments, compounds that inhibit the activity of FAAH, such as, for example, compounds provided herein, and compositions that include the compounds, may be used to reduce appetite(s), reduce body fat and for treating or preventing obesity or overweight in a mammal and for preventing or treating the diseases associated with these health conditions. In one embodiment, administration of a FAAH inhibitor, such as, for example, a compound provided herein, may be used in reducing appetite, body fat or body weight, or for treating or preventing obesity or overweight, or for reducing food intake, or treating an appetency disorder in a mammal.

[00544] In one embodiment, compounds and compositions provided herein may be used for reducing appetite, body fat or body weight, or for treating or preventing obesity or overweight, or for reducing food intake, or treating an appetency disorder in a human patient, including alteration of body mass composition such as percent fat or alteration in lean muscle mass.

[00545] In a further embodiment, the FAAH inhibitor, such as, for example, compound provided herein, is administered in a combination therapy with oleoylethanolamide (OEA) or another fatty acid alkanolamide compound, homologue or analog, which a) reduces appetite, reduces food consumption, reduces body fat or reduces body weight and b) is subject to hydrolysis by FAAH.

[00546] In some embodiments, a FAAH inhibitor, such as, for example, compound provided herein, is administered to a subject in amounts sufficient to reduce body fat, body weight, or prevent body fat or body weight gain or to reduce appetite(s). In another embodiment, compositions provided herein include a FAAH inhibitor, such as, for example, a compound provided herein, and oleoylethanolamide, or a fatty acid amide compound, homologue or analog thereof.

[00547] In certain embodiments, FAAH inhibitors, such as, compounds provided herein, can be used to treat various metabolic disorders such as insulin resistance, diabetes, steatohepatitis, hyperlipidemia, fatty liver disease, non-alcoholic steatohepatitis, atherosclerosis and arteriosclerosis. Methods for measuring the affect of the compounds provided herein on such disorders are disclosed in US patent no. 6,946,491, which is incorporated herein by reference.

[00548] In one embodiment, compounds provided herein and pharmaceutical compositions that include the compounds provided herein, may be used to treat a condition selected from among insulin resistance syndrome and diabetes (both primary essential diabetes such as Type I Diabetes or Type II Diabetes and secondary nonessential diabetes).

Administration of a compound or composition provided herein can reduce a symptom of diabetes or the chance of developing a symptom of diabetes, such as atherosclerosis, hypertension, hyperlipidemia, fatty liver disease, nephropathy, neuropathy, retinopathy, foot ulceration and cataracts, each such symptom being associated with diabetes.

[00549] In one embodiment, compounds provided herein, and pharmaceutical compositions that include the compounds provided herein, can be used to treat hyperlipidemia. Administration of a compound or composition provided herein can reduce serum triglycerides and free fatty acids in hyperlipidemic subjects. In one embodiment, compounds and pharmaceutical compositions provided herein can be used to treat fatty liver disease. In another embodiment, compounds and pharmaceutical compositions provided herein can be used to treat atherosclerosis or arteriosclerosis.

[00550] In other embodiments, compounds and compositions provided herein may be used to treat and/or prevent food behavioral problems/feeding disorders (i.e. eating disorders, in particular anorexias and cachexias of various natures, weight loss associated with cancer and other wasting conditions).

[00551] In some embodiments, FAAH inhibitors, such as compounds provided herein, may be administered to treat or prevent glaucoma or to reduce intraocular eye pressure. In some embodiments, the compounds may be given systemically. In other embodiments, the FAAH inhibitors are direct applied to the surface of the eye (e.g., via eye drops). Ocular carrier formulations for such ocular application are taught in Remington's Pharmaceutical Sciences, Gennaro A R ed. 20th edition, 2000: Williams & Wilkins Pa., USA.

[00552] In some embodiments, compounds provided herein, and compositions that include the compounds can be administered to treat or prevent glaucoma or to reduce intraocular eye pressure. In some embodiments, the compounds may be given systemically. In other embodiments, the compounds are direct applied to the surface of the eye (e.g., via eye drops).

[00553] Other diseases, disorders, and/or conditions that can be treated and/or prevented with a compound provided herein, include: lung diseases (i.e. diseases of the respiratory tracts, bronchospasms, cough, asthma, chronic bronchitis, chronic obstruction of the respiratory tracts, emphysema); urinary incontinence, inflammation of the bladder, urinary incontinence, vesical inflammation, movement disorders, psychomotor disorders, hypertension; cardiovascular diseases, in particular hypertension, cardiac arrhythmia, arteriosclerosis, heart attack, cardiac ischaemia, renal ischaemia; neurological pathologies, psychiatric tremors, dyskinesias, dystonia, spasticity, obsessive compulsive behavior, Tourette's syndrome, mood disturbances, psychoses.

[00554] Any combination of the disorders, diseases and/or conditions listed herein may be treated with the compounds provided herein.

EXAMPLES

[00555] The person skilled in the art may further appreciate various aspects and advantages of the present disclosure upon review of the following illustrative and non-limiting examples:

Example 1. General Procedure for the Preparation of Inhibitors of FAAH

[00556] To a stirred solution of 4-Dimethylcyclohexylamine (1mmol, 127 mgs) in THF (10mL) at room temperature was added 4-nitrophenol carbonate (1mmol, 304 mgs). After 30 minutes, 60% sodium hydride in mineral oil (1mmol, 40 mgs) was added in one portion followed by 5'-hydroxybiphenyl-3-carboxamide (1mmol, 213 mgs). The reaction mixture was stirred for 5 minutes and 60% sodium hydride in mineral oil (1mmol, 40 mgs) was added in one portion. The reaction mixture was stirred for 3 more hours and was quenched with water. The crude product was extracted with ethyl acetate and the organic layer was evaporated. The residual solid was purified by reverse phase HPLC to yield the product as a white powder. MS (ESI) MH^+ :367.

Example 2. Methods of Screening Compounds for Metabolic Stability

[00557] Generally, a FAAH inhibitor was incubated in human liver S9 fractions. Incubations were conducted at 37 °C in a potassium phosphate buffer (pH 7.2). NADPH and a regenerating system consisting of NADP, glucose 6-phosphate dehydrogenase were provided to the incubates. Incubations were terminated by the addition of methanol and freezing at -80 °C. *See, e.g.,* Singh, R. et al. Rapid Commun. Mass Spectrom., 10: 1019-26 (1996).

Example 3. Methods of Screening Compound for FAAH inhibitory activity

[00558] Generally, a FAAH inhibitor used in the methods described herein is identified as an inhibitor of FAAH *in vitro*. Preferred *in vitro* assays detect an increase in the level of an unaltered FAAH substrate (e.g., anandamide, OEA) or a decrease in the release of a reaction product (e.g., fatty acid amide or ethanolamine) by FAAH-mediated hydrolysis of a substrate such as AEA or OEA. The substrate may be labeled to facilitate detection of the released reaction products. High throughput assays for the presence, absence, or quantification of particular reaction products are well known to those of ordinary skill in the art. In addition, high throughput screening systems are commercially available (*see, e.g.,* Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments, Inc. Fullerton, CA; Precision Systems, Inc., Natick, MA, etc.). These systems typically automate entire procedures including all sample and reagent pipetting, liquid dispensing, timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. Automated systems thereby allow the identification of a large number of *in vitro* FAAH inhibitors without undue effort.

[00559] Candidate *in vivo* FAAH inhibitors can be identified by their ability to increase systemic levels of one or more FAAs. Suitable FAAs include fatty acid ethanolamides with a fatty acid moiety containing 14 to 28 carbons, with 0 to 6 double bonds, such as, for example, OEA, PEA, AEA, and stearoylethanolamide (SEA). Other suitable FAAs include primary fatty acid amides with a fatty acid moiety containing 14 to 28 carbons, with 0 to 6 double bonds, such as oleamide. Biological samples from which FAA levels can be assayed include, but are not limited to, plasma, serum, blood, cerebrospinal fluid, saliva, or urine.

[00560] FAA levels in a biological sample are assayed, e.g., by liquid chromatography tandem-mass spectrometry (LC-MS/MS). Increased assay reproducibility is achieved by spiking biological samples with a known amount of an isotopically labeled FAA, which serves as an internal standard for the FAA to be assayed. The level of the FAA can also be determined using spectrophotometric techniques (e.g., a fluorometric method). Alternatively, the level of the FAA can

be determined using a biological assay. In some embodiments, the level of the FAA is determined using a combination of the aforementioned techniques. Any of the foregoing assays for FAA levels can be partly or fully automated for high throughput. Details of this and other FAA assays, as well as methods for analyzing changes in FAA levels are known in the art. See, e.g., Quistad et al. (2002), *Toxicology and Applied Pharmacology* 179: 57-63; Quistad et al. (2001), *Toxicology and Applied Pharmacology* 173, 48-55; Boger et al. (2000), *Proc. Natl. Acad. Sci. U.S.A.* 97, 5044-49; Cravatt et al. *Proc. Natl. Acad. Sci. U.S.A.* 98, 9371-9376 (2001); Ramarao et al. (2005) *Anal. Biochem.* 343: 143-51. See also U.S. Pat. No. 6,096,784, U.S. Pat. Publication No. 2004/0127518, U.S. Pat. Application No. 10/681,858, International Patent Publication No. WO 98/24396, and WO 04/033422.

Example 4. Compound Screening for Inhibition of FAAH Activity - FAAH LC-MS/MS Screening Assay:

[00561] In one embodiment, inhibition of FAAH activity is determined using LC-MS/MS. The following are combined in a 5-mL glass tube: anandamide (5 μ L of 200 μ g/mL), 960 μ L of 50 mM ammonium phosphate buffer (pH 7.4) containing 0.125% BSA (w/v), 10 μ L of DMSO without (control) or with a FAAH inhibitor (1 μ g/mL), and 25 μ L of human liver microsomes (31.3 μ g). Prior to incubation, a 100 μ L aliquot is transferred to a 96-well plate containing 0.25 mL of acetonitrile and D₄ (deuterated) anandamide (0.2 μ M). Each 5-mL tube is capped and placed in a shaking water bath maintained at 37 °C for 60 minutes. After a 60 minute incubation, a second 100 μ L aliquot is transferred to a 96-well plate as performed earlier. The 96-well plate is then capped, vortex mixed, and placed on an HPLC for liquid chromatography/tandem mass spectrometry (LC/MS/MS) analyses. HPLC is carried out on a Waters 2790 Alliance system (Milford, MA). Separation was performed on a Phenomenex C18 column (2 mm x 50 mm, 4 μ ; Torrance, CA) using an isocratic mobile phase of acetonitrile:water:formic acid (80:20:0.1, v/v/v) at a flow rate of 0.3 mL min⁻¹ and a column temperature of 45 °C. The HPLC system was interfaced with a Micromass Ultima tandem MS (Beverly, MA). The samples are analyzed using an electrospray probe in the positive ionization mode with the cone voltage set at 40 V and capillary at 3.2 kV. The source and desolvation temperature settings are 130 °C and 500 °C, respectively. The voltage of the CID chamber is set at -20 eV. Multiple reaction monitoring is used for the detection of anandamide as [M+H] (m/z 348 > 62) and D₄ anandamide (internal standard) as [M+H] (m/z 352 > 66). An area ratio response (anandamide area response / D₄ anandamide area response) was determined for each sample. Percent anandamide hydrolysis of each sample is determined by the following equation, [(T=60 response) – (T=0 response)/T=0 response] * 100. The percent hydrolysis normalized to control is determined by dividing the % hydrolysis of test sample by the % hydrolysis of the control sample.

[00562] For determining IC₅₀ values for candidate FAAH inhibitor compounds, the above method is used with an adjusted FAAH inhibitor concentration. In the IC₅₀ assay, the FAAH inhibitor is added at a concentration range of approximately 3 μ M to 0.03 nM. The final calculation of IC₅₀ is determined by first transforming the concentrations by “X=log(X)” and then analyzing the data with a sigmoidal dose-response curve (no constraints) using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com).

Example 5. Compound Screening for Inhibition of FAAH Activity - FAAH Fluorescent Screening Assay:

[00563] To a black 96-well plate (Nunc, cat #267342) is added 180 μ L of arachidonyl 7-amino,4-methylcoumarin amide (AAMCA, 3 μ M), 20 μ L of a FAAH inhibitor (0.05 μ g/mL in DMSO) and 50 μ L of human liver microsomes (0.25 mg/mL). The diluent for the AAMCA and human liver microsomes is fatty acid free BSA (1.4 mg/mL) in

HEPES/EDTA (50 mM/lmM) at pH 7.4. The plate is read at excitation 355 nm and emission 460 nm at T=0 on a fluorescence plate reader (SpectraMax GeminiXS, Molecular Devices) and incubated for 30 minutes at 37 °C. After the 30 minute incubation, the plate is read a final time and % hydrolysis (normalized to control) was determined. The calculation for % hydrolysis is $[(T=30 - T=0)/T=0] * 100$. The percent hydrolysis normalized to control is determined by dividing the % hydrolysis of test sample by the % hydrolysis of the control sample (DMSO).

Example 6. Compound Screening for Inhibition of FAAH Activity - Screening for *in vivo* FAAH Inhibition in Rats:

[00564] Potential FAAH inhibitors are formulated for oral (p.o.), intraperitoneal (i.p.) or intravenous (i.v.) delivery to rats. Formulated compounds are administered and the animals were sacrificed at pre-determined time points post dose. At sacrifice, blood samples are collected into EDTA plasma tubes and whole brains were snap frozen in liquid nitrogen. EDTA plasma was isolated from blood samples after centrifugation. Brain and plasma samples are stored at -80 °C prior to analysis. All samples (brain and plasma) are analyzed for the concentrations of test compound (FAAH inhibitor), metabolites of the test compound and endogenous fatty acid ethanolamide levels (including anandamide, oleoylethanolamide, and palmitoylethanolamide) by LC-MS/MS. Levels of these compounds are compared across time points to determine pharmacokinetic properties of the test compounds and partial pharmacological effects of inhibiting FAAH activity (including changes of fatty acid ethanolamide levels).

[00565] In one embodiment, additional tissues and fluid samples can be collected at sacrifice. In one embodiment, FAAH activity can also be determined in fluid and tissues samples according to the methods disclosed or according to methods known in the art. In one embodiment, metabolites of the test compounds can be determined in fluid and tissue samples.

Example 7: Determination of pharmacokinetics

[00566] The pharmacokinetic properties of compounds provided herein were assessed in rats following oral administration as a solution. To test the oral bioavailability of compounds provided herein, a solution of the test compound was prepared for oral administration as a 10 mg/mL solutions in 80% cremephor and 20% ethanol (w/w) or as a 10 mg/mL solution of 90% PEG-400 and 10% Tween 80 (w/w). The solution of the test compound was administered to rats at a dose of 10 mg/kg via oral gavage.

Animal Models

[00567] Any of a variety of animal models can be used to test the compounds disclosed herein for their effectiveness in reducing inflammation and treating pain. Useful compounds can exhibit effectiveness in reducing inflammation or pain in one or more animal models.

Animal Models for Assessing Anti-inflammatory Activity

Example 8. Carrageenan-Induced Foot Pad Edema Model

[00568] The model is described, for example, by Winter *et al.* (1962 *Proc Soc Exp Biol Med* 111:544). Briefly, rats are fasted with free access to water for 17 to 19 hours before oral treatment with up to three doses of a test compound, indomethacin or celecoxib, or a control vehicle (1% methylcellulose in deionized water). One hour after the last treatment, paw edema is induced by injecting 0.05 ml of a 2% carrageenan solution into the left hindpaw. The left hindpaw volume of each rat is measured using a plethysmometer before oral treatment, at the time of carrageenan

injection and at 1.5 h, 3 h, 4.5 h after the injection of carrageenan. The edema volume of each rat at each time point is expressed as the change from the volume at the time of oral treatment and the anti-inflammatory effect in treated groups is expressed as % inhibition compared to the vehicle only group 1.5 h, 3 h and 4.5 h after the carrageenan injection. The significance of the difference between in edema different groups is assessed by a one-way analysis of variance (ANOVA) followed by the non-paired Dunnett t test. In this model, hyperalgesic response and PGE₂ production can also be measured (Zhang *et al.* 1997 *J Pharmacol and Exp Therap* 283:1069).

Example 9. Complete Freund's Adjuvant (CFA) Induced Arthritis Model

[00569] In this model, arthritis is induced in groups of eight Lewis derived male rats weighing 160±10 g by injecting a well-ground suspension of killed *Mycobacterium tuberculosis* (0.3 mg in 0.1 mL of light mineral oil; Complete Freund's Adjuvant, CFA) into the subplantar region of the right hind paw on Day 1. Hind paw volumes are measured by water displacement on Days 0, 1 and 5 (right hind paw, with CFA), and on Days 0, 14 and 18 (left hind paw, without CFA); rats are weighed on Days 0 and 18. Test compounds, dissolved or suspended in 2% Tween 80, are prepared fresh daily and administered orally twice daily for 5 consecutive days (Day 1 through day 5) beginning one hour before injection of CFA. For CFA-injected vehicle control rats, the increase in paw volume on Day 5 relative to Day 1 (Acute Phase of inflammation) is generally between about 0.7 and about 0.9 mL; and, that on Day 18 relative to Day 14 (Delayed Phase of inflammation) is generally between about 0.2 and about 0.4 mL. Thus, anti-inflammatory activity in this model may be denoted by values calculated during the Acute Phase as well as the Delayed Phase. Animals are also weighed on Day 0 and Day 18; CFA-injected vehicle control animals generally gain between 40 to 60 g body weight over this time period. A 30 percent or more reduction in paw volume relative to vehicle treated controls is considered of significant anti-inflammatory activity. The mean ±SEM for each treatment group is determined and a Dunnett test is applied for comparison between vehicle and treated groups. Differences are considered significant at P<0.05. Polyarthritis of fore paw, tail, nose and ear can be scored visually and noted on the first day and final day, wherein positive (+) sign is for swelling response and negative (-) sign is normal. X-ray radiographies of the hindpaws can also be performed for further radiological index determination of arthritic symptoms. Hyperalgesia can also be measured in this model, allowing determination of analgesic effects of test compounds (Bertorelli *et al.* 1999 *Brit J. Pharmacol* 128:1252).

Example 10. Air-Pouch Model

[00570] This model is described by Masferrer *et al.* (1994 *Proc Natl Acad Sci USA* 91:3228). Briefly, male Lewis rats (175-200 g, Harlan Sprague-Dawley) are subcutaneously injected with 20 mL of sterile air into the intrascapular area of the back to create air cavities. An additional 10 mL of air is injected into the cavity every 3 days to keep the space open. Seven days after the initial air injection, 2 mL of a 1% solution of carrageenan dissolved in sterile saline is injected directly into the pouch to produce an inflammatory response. In treated and untreated animals, the volume of exudate is measured and the number of leukocytes present in the exudate is determined by Wright-Giemsa staining. In addition, PGE₂ and 6-keto-PGF_{1α} are determined in the pouch exudates from treated and untreated animals by specific ELISAs (Cayman Chemicals, Ann Arbor, Mich.).

Animal Models for Assessing Analgesic Activity

Example 11. Carrageenan-Induced Thermal Hyperalgesia

[00571] This model is described by Hargreaves *et al.* (1988 *Pain* 32:77). Briefly, inflammation is induced by subplantar injection of a 2% carrageenan suspension (0.1 mL) into the right hindpaw. Three hours later, the nociceptive threshold is evaluated using a thermal nociceptive stimulation (plantar test). A light beam (44% of the maximal intensity) is focused beneath the hindpaw and the thermal nociceptive threshold is evaluated by the paw flick reaction latency (cut-off time: 30 sec). The pain threshold is measured in ipsilateral (inflamed) and in contralateral (control) hindpaws, 1 hour after the oral treatment with the test compound or a control. The results can be expressed as the nociceptive threshold in seconds (sec) for each hindpaw and the percentage of variation of the nociceptive threshold (mean $\pm$ SEM) for each rat from the mean value of the vehicle group. A comparison of the nociceptive threshold between the inflamed paw and the control paw of the vehicle-treated group is performed using a Student's t test, a statistically significant difference is considered for $P < 0.05$. Statistical significance between the treated groups and the vehicle group is determined by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) using SigmaStat Software.

Example 12. Phenylbenzoquinone-Induced Writhing Model

[00572] This model is described by Siegmund *et al.* (1957 *Proc Soc Exp Bio Med* 95:729). Briefly, one hour after oral dosing with a test compound, morphine or vehicle, 0.02% phenylbenzoquinone (PBQ) solution (12.5 mL/kg) is injected by intraperitoneal route into the mouse. The number of stretches and writhings are recorded from the 5th to the 10th minute after PBQ injection, and can also be counted between the 35th and 40th minute and between the 60th and 65th minute to provide a kinetic assessment. The results are expressed as the number of stretches and writhings (mean $\pm$ SEM) and the percentage of variation of the nociceptive threshold calculated from the mean value of the vehicle-treated group. The statistical significance of any differences between the treated groups and the control group is determined by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) using SigmaStat Software.

Example 13. Kaolin-Induced Arthritis Model

[00573] This model is described by Hertz *et al.* (1980 *Arzneim Forsch* 30:1549). Briefly, arthritis is induced by injection of 0.1 mL of kaolin suspension into the knee joint of the right hind leg of a rat. Test compounds are administered subcutaneously after 15 minutes and again after two hours. Reference compounds can be administered orally or subcutaneously. Gait is assessed every hour from 1.5 hours to 5.5 hours after treatment and is scored as follows: normal gait (0), mild disability (1), intermittent raising of paw (2), and elevated paw (3). Results are expressed as the mean gait score (mean $\pm$ SEM) calculated from individual values at each time point and the percentage of variation of the mean score calculated from the mean value of the vehicle-treated group at 4.5 hours and 5.5 hours after treatment. The statistical significance of differences between the treated groups and the vehicle-treated group is determined by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) at each time point.

Example 14. Peripheral Mononeuropathy Model

[00574] This model is described by Bennett *et al.* (1988 *Pain* 33:87) and can be used to assess anti-hyperalgesic effect of an orally administered test compound in a model of peripheral mononeuropathy. The effect of the test substance can be compared to a no treatment control or reference substance, e.g., morphine. Peripheral mononeuropathy is induced by loose ligation of the sciatic nerve in anaesthetized male Sprague Dawley rats (pentobarbital; 45 mg/kg by intraperitoneal route). Fourteen days later, the nociceptive threshold is evaluated using a mechanical nociceptive stimulation (analgesimeter paw pressure test; Ugo Basile, Italy). The test and reference compounds and the vehicle are

orally administered (10 mL/kg carried 1% methylcellulose). Increasing pressure is applied to the hindpaw of the animal until the nociceptive reaction (vocalization or paw withdrawal) is reached. The pain threshold (grams of contact pressure) is measured in ipsilateral (injured) and in contralateral (non injured) hindpaws, 60 minutes after treatment. The results are expressed as: the nociceptive threshold (mean $\pm$ SEM) in grams of contact pressure for the injured paw and for the non-injured paw (vehicle-treated group) and the percentage of variation the nociceptive threshold calculated from the mean value of the vehicle-treated group. A comparison of the nociceptive threshold between the non injured paw and the injured paw of the vehicle-treated group is performed using a Student's t test. The statistical significance of the difference between the treated groups and the vehicle group is determined for the injured hindpaw by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) using SigmaStat Software (SigmaStat.RTM. v. 2.0.3 (SPSS Science Software, Erkrath GmbH)).

Example 15. Chung rat model of peripheral neuropathy

[00575] In one embodiment, the effectiveness of a compound provided herein in alleviating neuropathic pain is demonstrated using the well-recognized Chung rat model of peripheral neuropathy. In the Chung rat model, spinal nerve partial ligation of left spinal nerves L-5 and L-6 produces a long-lasting hypersensitivity to light pressure on the affected left foot. The hypersensitivity is similar to the pain experienced by humans with the neuropathic condition of causalgia (Kim and Chung, *Pain* 50:355-363 (1992), which is incorporated herein by reference).

Example 16. Diabetic Neuropathy Paw Pressure Test

[00576] Complete protocol details can be found in Rakieten *et al.* (1963 *Cancer Chemother Rep* 29:91). Briefly, diabetes is induced by intraperitoneal injection of streptozotocin in rats. Three weeks later, the nociceptive threshold is measured using the paw pressure test to assess hyperalgesia. Test compound or controls are administered intraperitoneally 30 minutes prior to pain measurement.

Example 17. Acetic Acid Writhing Test

[00577] Briefly, a test compound is administered orally one hour before intraperitoneal injection of acetic acid (0.5%, 10 ml/kg) in rats. Reduction in the number of writhes by 50 percent or more (≥ 50) per group of animals observed during the 5 to 11 minute period after acetic acid administration, relative to a vehicle treated control group, indicates possible analgesic activity. This assay is based on that described in Inoue, K. *et al.* (1991 *Arzneim. Forsch./Drug Res.* 41: 235).

Example 18. Formalin Test

[00578] Complete protocol details can be found in Hunskaar *et al.* (1985 *Neurosci. Meth.* 14:69). Briefly, 30 minutes after intraperitoneal administration of a test compound or a control, 20 μ L of a 5% formalin solution is injected by subplantar route into the right hindpaw of the rat. Hindpaw licking time is recorded during the early phase and the later phase after formalin injection.

Example 19. Tail Flick Test

[00579] Complete protocol details can be found in D'Amour and Smith (1941 *J Pharmacol. Exp Ther.* 72:74). Briefly, 30 minutes after intraperitoneal administration of a test compound or a control, a light beam is focused onto the tail of the rat. The nociceptive reaction latency, characterized by tail withdrawal, is recorded. The cutoff time is set to 15 seconds.

Example 20. Tail Immersion Test

[00580] In this test the tail of the rat is immersed into a 50-60 °C. water bath. The nociceptive reaction latency, characterized by tail withdrawal, is measured (Haubrich *et al.* 1990 *J Pharmacol Exp Ther* 255:511 and Lichtman *et al.* 2004 *Pain* 109:319).

Example 21. Hot Plate Test

[00581] Complete protocol details can be found in Eddy *et al.* (1950 *J. Pharmacol. Exp. Ther.* 98:121). Briefly, 30 minutes after intraperitoneal administration of a test compound or a control, the mouse is placed on a metallic hot plate maintained at 52 °C. The nociceptive reaction latency, characterized by a licking reflex of the forepaws or by a jumping off the hot plate is recorded. The cut-off time is set to 30 seconds.

Assays for Assessing Anxiolytic Activity

[00582] Compounds provided herein that inhibit FAAH activity, and thus modulate fatty acid amide levels, may also have anxiolytic activity. Animal models to assess anxiolytic activity include:

Example 22. Elevated Plus Maze

[00583] The elevated plus maze consists of four maze arms that originate from a central platform, effectively forming a plus sign shape as described in van Gaalen and Steckler (2000 *Behavioural Brain Research* 115:95). The maze can be made of plexiglas and is generally elevated. Two of the maze arms are unwallled (open) and two are walled (closed). The two open arms are well lit and the two enclosed arms are dark (Crawley 2000 *What's Wrong With My Mouse?: Behavioral Phenotyping of Transgenic and Knockout Mice.* Wiley-Liss, New York). The test is premised on the naturalistic conflict between the tendency of an animal to explore a novel environment and the aversive properties of a brightly lit, open area (Pellow *et al.* 1985 *J. Neuroscience Methods.* 14:149).

[00584] Complete protocol details can be found in Fedorova *et al.* (2001 *J. Pharm. Exp. Ther.* 299: 332). Briefly, 15 minutes following intraperitoneal administration of test compound or control, an animal is placed individually on the central platform, facing one of the open arms opposite to the observer. The number of open and closed arm entries, and the time spent in the different compartments of the maze by the animal (central platform, open and closed arms) is scored (as described in Gaalen *et al.* (*supra*)). An arm visit is recorded when an animal moves all four paws into the arm as described in Simonin *et al.* (1998 *EMBO J.* 17: 886). Behavior is scored by an observer and/or via a video camera over a 5-minute test session. A greater amount of time spent or entries made by the animal in the open versus the closed arms is an indicator of anxiolytic activity.

Example 23. Elevated Zero Maze

[00585] The elevated zero maze is a modification of the elevated plus maze. The elevated zero maze consists of a plexiglas apparatus in the shape of a circle (i.e., a circular runway of 46 cm diameter and 5.5 cm runway width) with two open and two wall-enclosed sectors of equal size. It is elevated up to a meter above the ground. This apparatus is described in Simonin *et al.* (*supra*) and Crawley (*supra*).

[00586] Complete protocol details can be found in Kathuria *et al* (2003 *Nature Medicine* 9: 76). Briefly, 30 minutes following intraperitoneal administration of test compound or control, an animal is placed on one open sector in front of an enclosed sector. Time in a new sector is recorded as entry with all four paws. Behavior will be scored by an observer

and/or via a video camera over a 5-minute test session. A greater amount of time spent or entries made by the animal in the open versus the walled sector is an indicator of anxiolytic activity.

Example 24. Isolation-induced ultrasonic emission test

[00587] In another animal model, the isolation-induced ultrasonic emission test, compounds provided herein are tested for their anti-anxiety effects. The isolation-induced ultrasonic emission test measures the number of stress-induced vocalizations emitted by rat pups removed from their nest (Insel, T. R. *et al.*, *Pharmacol. Biochem. Behav.*, 24, 1263-1267 (1986); Miczek, K. A. *et al.*, *Psychopharmacology*, 121, 38-56 (1995); Winslow, J. T. *et al.*, *Biol. Psychiatry*, 15, 745-757 (1991); U.S. 6,326,156).

Assays for Assessing Antinociception Mechanism

[00588] Compounds can be tested to determine if they influence pathways involved in nociception. The results of such assays can be used to investigate the mechanism by which a test compound mediates its antinociceptive effect.

Example 25. Elevation of 3 α ,5 α -THP

[00589] 3 α -hydroxy-5 α -pregnan-20-one (3 α ,5 α -THP or allopregnanolone) is a pregnane steroid that acts as an agonist of the inhibitory GABA_A receptor subtype and is known to have both anxiolytic and analgesic effects in a variety of animal systems, with supportive evidence for a similar role in humans. Thus, compounds that elevate 3 α ,5 α -THP may have an antinociceptive effect. The level of 3 α ,5 α -THP in the brain of animals treated with a test compound can be measured as described by VanDoren *et al.* (1982 *J Neuroscience* 20:200). Briefly, steroids are extracted from individual cerebral cortical hemispheres dissected in ice-cold saline after euthanasia. Cortices are frozen at -80 °C until use. Samples are digested in 0.3 N NaOH by sonication and extracted three times in 3 mL aliquots of 10% (v/v) ethyl acetate in heptane. The aliquots are combined and diluted with 4 mL of heptane. The extracts are applied to solid phase silica columns (Burdick & Jackson, Muskegon, Mich.), washed with pentane, and steroids of similar polarity to 3 α ,5 α -THP are eluted off of the column by the addition of 25% (v/v) acetone in pentane. The eluant is then dried under N₂ and steroids are redissolved in 20% (v/v) isopropanol RIA buffer (0.1 M NaH₂PO₄, 0.9 M NaCl, 0.1% w/v BSA, pH 7.0). Extraction efficiency is determined in 50 μ L of the redissolved extract by liquid scintillation spectroscopy and the remaining sample is used in the determination of 3 α ,5 α -THP by radioimmunoassay. Reconstituted sample extracts (75 μ L) and 3 α ,5 α -THP standards (5-40,000 pg in 6.25% v/v ethanol, 31% v/v isopropyl alcohol in RIA buffer) are assayed in duplicate by the addition of 725 μ L of RIA buffer, 100 μ L of [³H] 3 α ,5 α -THP (20,000 dpm), and 100 μ L of anti-3 α ,5 α -THP antibody. Total binding is determined in the absence of unlabeled 3 α ,5 α -THP, and nonspecific binding is determined in the absence of antibody. The antibody-binding reaction is allowed to equilibrate for 120 min at room temperature and is terminated by cooling the mixture to 4 °C. Bound 3 α ,5 α -THP is separated from unbound 3 α ,5 α -THP by incubation with 300 μ L of cold dextran coated charcoal (DCC; 0.04% dextran, 0.4% powdered charcoal in double-distilled H₂O) for 20 min. DCC is removed by centrifugation at 2000xg for 10 min. Bound radioactivity in the supernatant is determined by liquid scintillation spectroscopy. Sample values are compared to a concurrently run 3 α ,5 α -THP standard curve and corrected for extraction efficiency.

Example 26. Evaluation of Anti-depressive effects

[00590] In one embodiment, compounds provided herein are evaluated for anti-depressive effects in animal models. The chronic mild stress induced anhedonia model is based on the observation that chronic mild stress causes a gradual

decrease in sensitivity to rewards, for example consumption of sucrose, and that this decrease is doses-dependent and reversed by chronic treatment with antidepressants. The method has previously been described by Willner, Paul, *Psychopharmacology*, 1997, 134, 319-329.

[00591] Another test for antidepressant activity is the forced swimming test (*Nature* 266, 730-732, 1977). In this test, animals are administered the compound preferably by the intraperitoneal route or by the oral route 30 or 60 minutes before the test. The animals are placed in a crystallizing dish filled with water and the time during which they remain immobile is clocked. The immobility time is then compared with that of the control group treated with distilled water. Imipramine (25 mg/kg) may be used as the positive control. The antidepressant compounds decrease the immobility time of the mice thus immersed.

[00592] Another test for antidepressant activity is the caudal suspension test on the mouse (*Psychopharmacology*, 85, 367-370, 1985). In this test, animals are preferably treated with a compound provided herein by the intraperitoneal route or by the oral route 30 minutes to 6 hours before the test. The animals are then suspended by the tail and their immobility time is automatically recorded by a computer system. The immobility times are then compared with those of a control group treated with vehicle. Imipramine (25 mg/kg) may be used as the positive control. Antidepressant compounds decrease the immobility time of the mice.

[00593] Antidepressant effects of the compounds provided herein can be tested in the DRL-72 TEST. This test, carried out according to the protocol of Andrews et al "Effects of imipramine and mirtazapine on operant performance in rats" *Drug Development Research* 32, 5 8-66 (1994), gives an indication of antidepressant-like activity. The effects of the compounds provided herein also may be examined in serotonin disorders and bipolar disorders, such as described in U.S. 6,403,573 and 5,952,315, incorporated herein by reference.

Example 27. Evaluation of Anticovulsant effects

[00594] In another embodiment, compounds provided herein are examined for anticonvulsant activity in animal models, as described in U.S. 6,309,406 and 6,326,156.

Example 28. Effects of Compounds on Appetite behaviour

[00595] In one embodiment, compounds provided herein are administered to a rat in order to measure the effect on appetite behavior. The effect of the administered compound is assessed by examining the intake of a sucrose solution by the rat. This method is taught in W. C. Lynch *et al.*, *Physiol. Behav.*, 1993, 54, 877-880. Male Sprague-Dawley rats weighing about 190 g to about 210 g are under a normal light cycle (from 7 am to 7 pm) and receive water and food ad libitum. For 6 days, between 11 am and 3 pm, the food and the water bottles are withdrawn and the rats are given a 5% sucrose solution to drink. Rats drinking less than 3 g of sucrose solution are eliminated. On the seventh day the test is carried out according to the following procedure: 9 am: withdrawal of food, 10 am: administration of either a compound provided herein or vehicle to the test animals; 11 am = T0: introduction of bottles containing a weighed sucrose solution; T0+1 hour, T0+2 hours, T0+3 hours, T0+4 hours: measurement of the sucrose consumption by weighing of the bottles. Followed by comparison of the experimental (administered a compound provided herein) and control groups' intake of the sucrose solution. Animals can be, for example, obese or normal guinea pigs, rats, mice, or rabbits. Suitable rats include, for example, Zucker rats. Suitable mice include, for example, normal mice, ALS/LtJ, C3.5W-H-2b/SnJ,

(NON/LtJ x NZO/H1J)F1, NZO/H1J, ALR/LtJ, NON/LtJ, KK.Cg-AALR/LtJ, NON/LtJ, KK.CgAy/J, B6.HRS(BKS)-Cpefat/+, B6.129P2-GcktmLEfr, B6.V-Lepob, BKS.Cg-m +1+ Leprdb, and C57BL/6J with Diet Induced Obesity.

[00596] In another test, the effect of a compound of the invention on the consumption of an alcohol solution can be shown in mice. For instance, male C 57 BL 6 mice are isolated on the day of their arrival in an animal housing under a reverse cycle (night from 10 am to 10 pm) with 2 bottles filled with water. After 1 week, one of the bottles of water is replaced with a bottle filled with a 10% alcohol solution for 6 hours of the test. Each day, 30 minutes before the bottle of alcohol is introduced, the mice are treated with a compound of the invention. The amounts of alcohol and water consumed are measured after 6 hours. The test is repeated for 4 days. The results for an experimental and a control or vehicle are compared.

Example 29. Reduction of body weight, body fat, and liver steatosis

[00597] The effects of inhibiting FAAH activity on body weight, body fat, triglyceride levels, cholesterol levels can be determined in APOE*3-Leiden transgenic (E3L) mice, an animal model of hyperlipidemia. E3L mice express a mutated variant of human apoE, apoE*3-Leiden, that has impaired binding of apoE to the LDL receptor. Consequently, E3L mice exhibit a decreased clearance rate of apoB-containing lipoproteins and elevated serum lipid levels. See van Vlijmen *et al.* (1994), *J. Clin Invest.*, 93:1403-1410. Upon high fat and cholesterol feeding, these mice develop various stages of atherosclerotic lesions depending on plasma total cholesterol levels and resembling those found in humans. See Groot *et al.* (1996), *Arterioscler. Thromb. Vasc. Biol.*, 16:926-933; Verschuren *et al.* (2005), *Arterioscler. Thromb. Vasc Biol.*, 25:161-167; and Lutgens *et al.* (1999), *Circulation*; 99(2):276-283). Thus, the E3L mouse is a suitable model for the investigation of the efficacy of anti-atherosclerotic drugs.

[00598] E3L mice are fed a high cholesterol (1% w/w) diet (HC diet) for a period of four weeks. Animals are then matched based on their plasma cholesterol levels, and are divided into five groups, each of which was maintained on an HC diet. Every day for the remainder of the study (four weeks), a “control” group receives food with no additives, a “fenofibrate” group receives food containing fenofibrate (0.04% w/w), an “oral vehicle” group receives an oral suspension of vehicle, an “oral OEA” group receives an oral suspension of OEA at a dose of 500 mg/kg, and an “oral Carbamate” group receives an oral suspension of a compound provided herein at a dose of 10 mg/kg.

[00599] Blood samples are collected at days 0, 14, and 28 of the treatment period. At the end of the treatment period, animals are sacrificed, and various tissues and organs are analyzed.

Example 30. Cannabinoid Receptor Binding

[00600] Compounds may exert an antinociceptive effect via binding to either or both of the cannabinoid receptors CB₁ and CB₂. CB₁ is expressed in the brain (Matsuda *et al.* 1990 *Nature* 346:561), and CB₂ is expressed by macrophages and in the spleen (Munro *et al.* 1993 *Nature* 365:61). Both of these receptors have been implicated in mediating analgesic effects through binding of agonists (see, for example, Clayton *et al.* 2002 *Pain* 96:253). Thus, test compounds can be assayed to determine whether they bind to one or both human cannabinoid receptors. An assay for CB₁ binding is described by Matsuda *et al.* (supra). This assay employs recombinant cells expressing CB₁. Binding to CB₂ can be determined in the same manner using recombinant cells expressing CB₂. Briefly, to measure the ability of a test compound to bind to CB₁, the binding of a labelled CB₁ ligand, e.g., [³H]WIN 55212-2 (2 nM for CB₁ and 0.8 nM for CB₂) to membranes isolated from HEK-293 cells expressing recombinant CB₁ is measured in the presence and absence

of a compound. Non-specific binding is separately determined in the presence of several-fold excess of unlabelled WIN 55212-2 (5 μ M for CB₁ and 10 μ M for CB₂). The specific ligand binding to the receptors is defined as the difference between the total binding and the non-specific binding determined in the presence of an excess of unlabelled WIN 55212-2. The IC₅₀ values and Hill coefficients (n_H) are determined by non-linear regression analysis of the competition curves using Hill equation curve fitting. The inhibition constants (K_i) are calculated from the Cheng Prusoff equation ($K_i = IC_{50} / (1 + (L/K_D))$), where L=concentration of radioligand in the assay, and K_D =affinity of the radioligand for the receptor).

Example 31: Pharmaceutical Compositions

Example 31a: Parenteral Composition

[00601] To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a water-soluble salt of a compound described herein is dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection.

Example 31b: Oral Composition

[00602] To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound described herein is mixed with 750 mg of starch. The mixture is incorporated into an oral dosage unit for, such as a hard gelatin capsule, which is suitable for oral administration.

Example 31c: Sublingual (Hard Lozenge) Composition

[00603] To prepare a pharmaceutical composition for buccal delivery, such as a hard lozenge, mix 100 mg of a compound described herein, with 420 mg of powdered sugar mixed, with 1.6 mL of light corn syrup, 2.4 mL distilled water, and 0.42 mL mint extract. The mixture is gently blended and poured into a mold to form a lozenge suitable for buccal administration.

Example 31d: Inhalation Composition

[00604] To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a compound described herein is mixed with 50 mg of anhydrous citric acid and 100 mL of 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

Example 31e: Rectal Gel Composition

[00605] To prepare a pharmaceutical composition for rectal delivery, 100 mg of a compound described herein is mixed with 2.5 g of methylcellulose (1500 mPa), 100 mg of methylparaben, 5 g of glycerin and 100 mL of purified water. The resulting gel mixture is then incorporated into rectal delivery units, such as syringes, which are suitable for rectal administration.

Example 31f: Topical Gel Composition

[00606] To prepare a pharmaceutical topical gel composition, 100 mg of a compound described herein is mixed with 1.75 g of hydroxypropyl cellulose, 10 mL of propylene glycol, 10 mL of isopropyl myristate and 100 mL of purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topical administration.

Example 31g: Ophthalmic Solution Composition

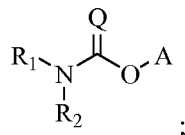
[00607] To prepare a pharmaceutical ophthalmic solution composition, 100 mg of a compound described herein is mixed with 0.9 g of NaCl in 100 mL of purified water and filtered using a 0.2 micron filter. The resulting isotonic solution is then incorporated into ophthalmic delivery units, such as eye drop containers, which are suitable for ophthalmic administration.

[00608] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

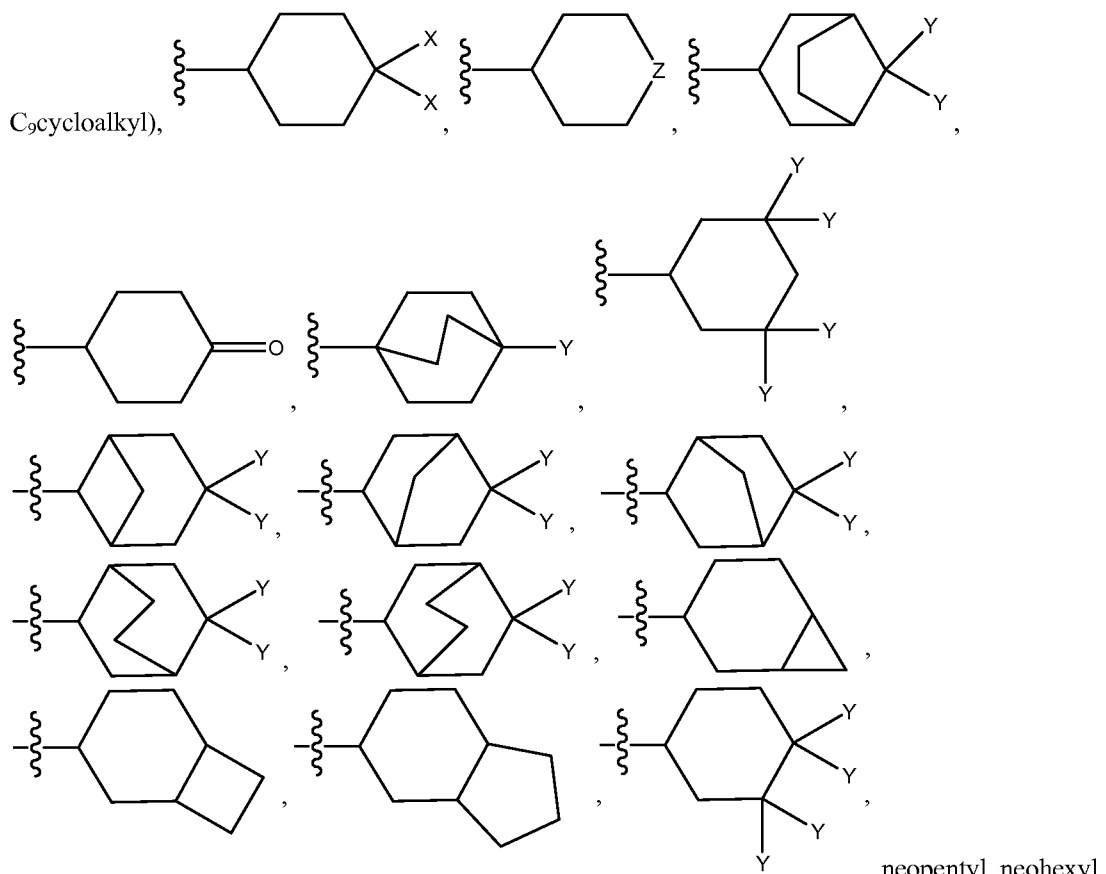
CLAIMS

WHAT IS CLAIMED IS:

1. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

O-A is a deprotonated form of a hydroxy containing endocannabinoid or a deprotonated form of a hydroxy containing derivative of a cannabinoid; and

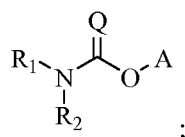
pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

2. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 1.
3. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient.
4. A compound of formula (I):

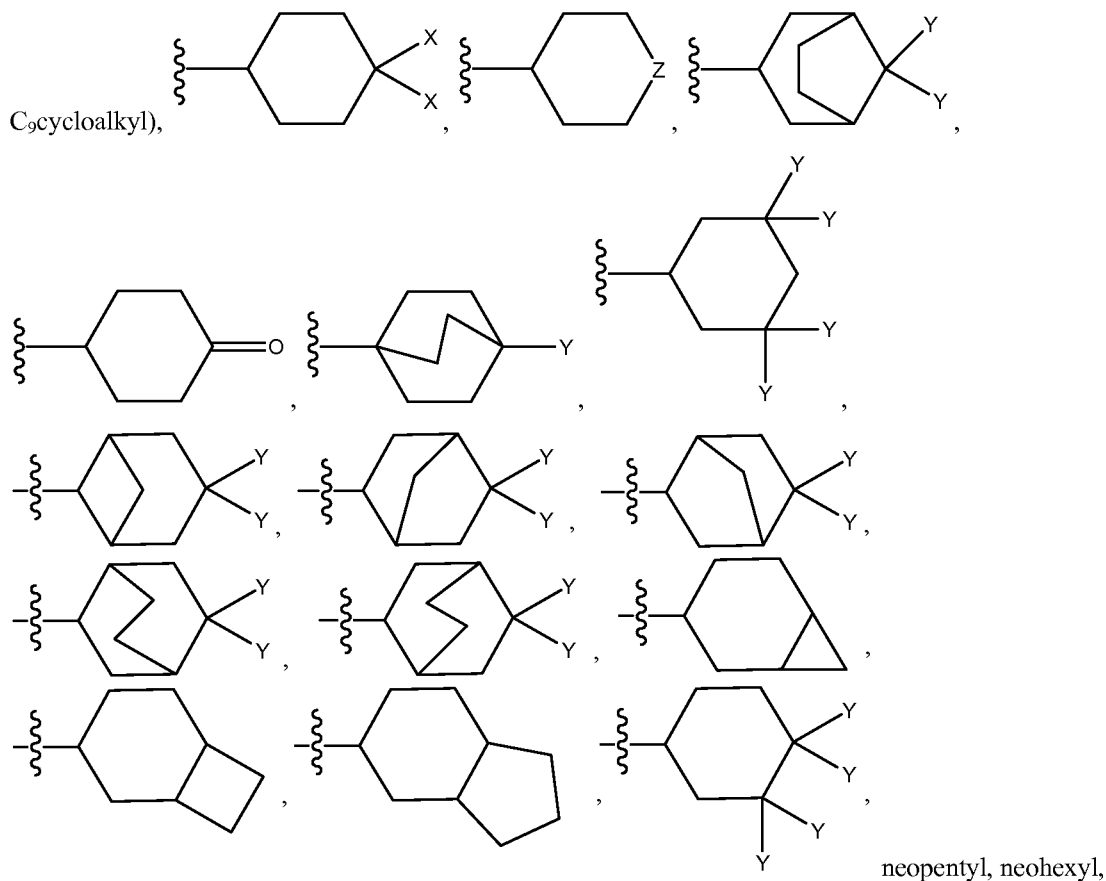
O-A is a deprotonated form of a hydroxy containing cannabinoid or a deprotonated form of a hydroxy containing derivative of a cannabinoid; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

5. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 4.
6. A pharmaceutical composition comprising a compound of claim 4 and a pharmaceutically acceptable excipient.
7. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

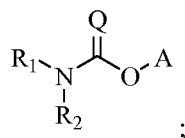
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

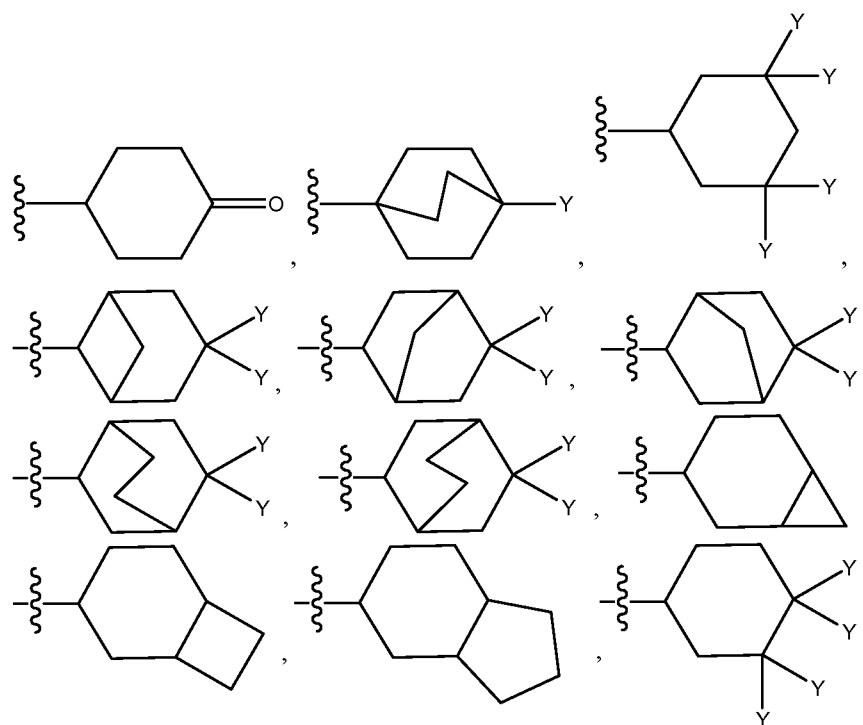
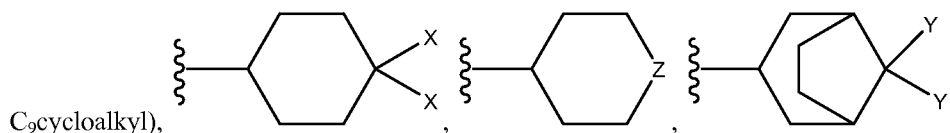
O-A is a deprotonated form of a hydroxy containing FAAH inhibitor or a deprotonated form of a hydroxy containing derivative of a FAAH inhibitor; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

8. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 7.
9. A pharmaceutical composition comprising a compound of claim 7 and a pharmaceutically acceptable excipient.
10. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



neopentyl, neohexyl,

methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

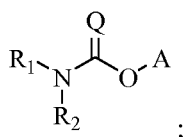
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

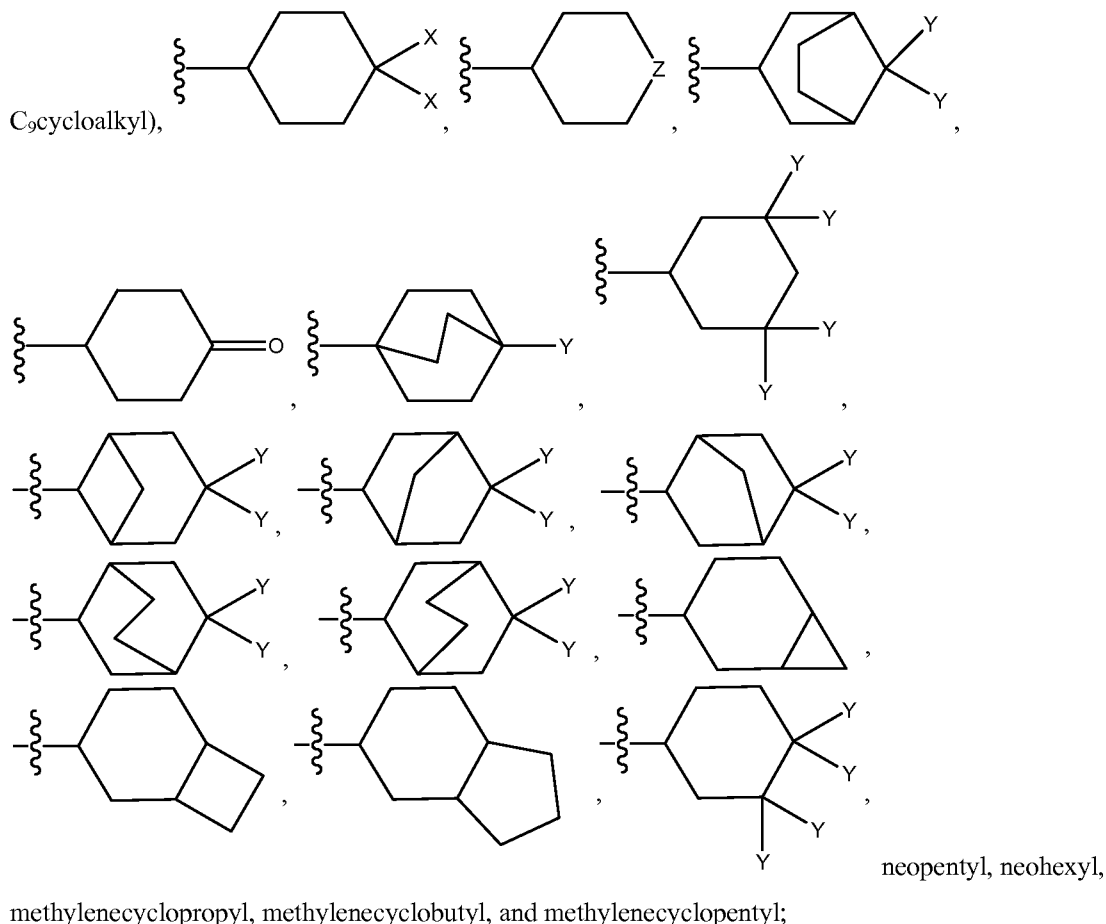
O-A is a deprotonated form of a hydroxy containing anandamide membrane transport inhibitor or a deprotonated form of a hydroxy containing derivative of an anandamide membrane transport inhibitor ; and

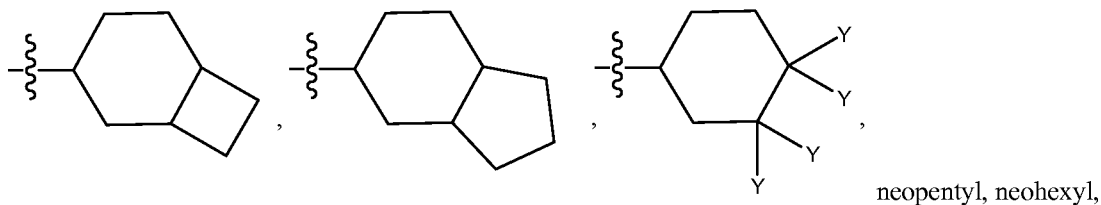
pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

11. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 10.
12. A pharmaceutical composition comprising a compound of claim 10 and a pharmaceutically acceptable excipient.
13. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-





methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R_2 is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

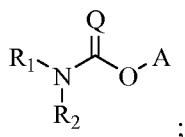
Z is O, N-(C_1 - C_6 alkyl), or SO_2 ;

Q is O or S; and

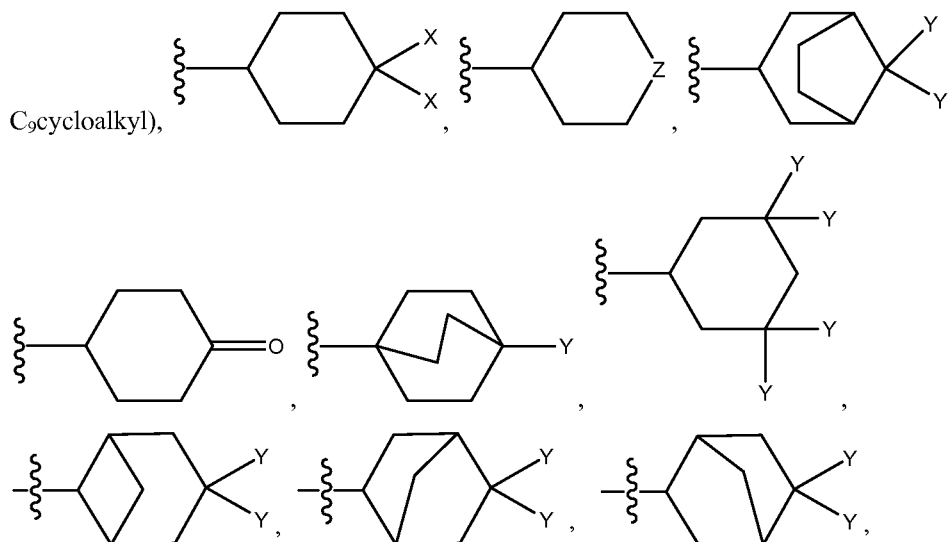
HO-A is serotonin or a serotonin-like compound; and

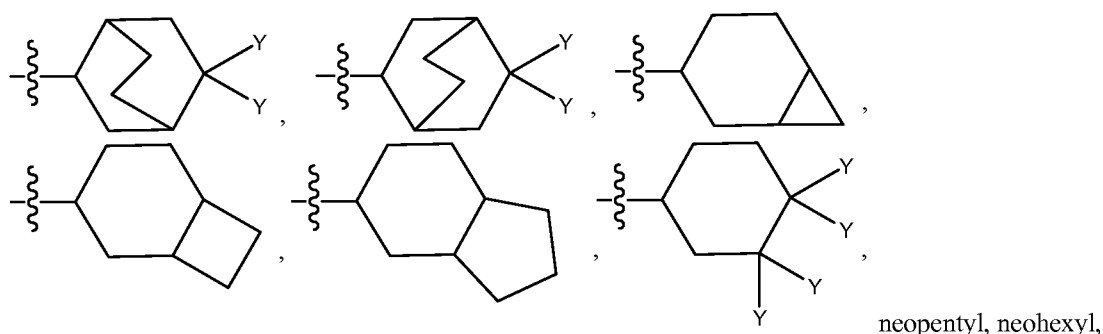
pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

17. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 16.
18. A pharmaceutical composition comprising a compound of claim 16 and a pharmaceutically acceptable excipient.
19. A compound of formula (I):



wherein R_1 is an optionally substituted group selected from among C_1 - C_8 alkyl, C_3 - C_9 cycloalkyl, C_1 - C_4 alkyl-(C_3 -





methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

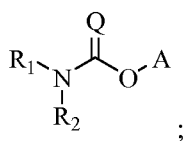
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

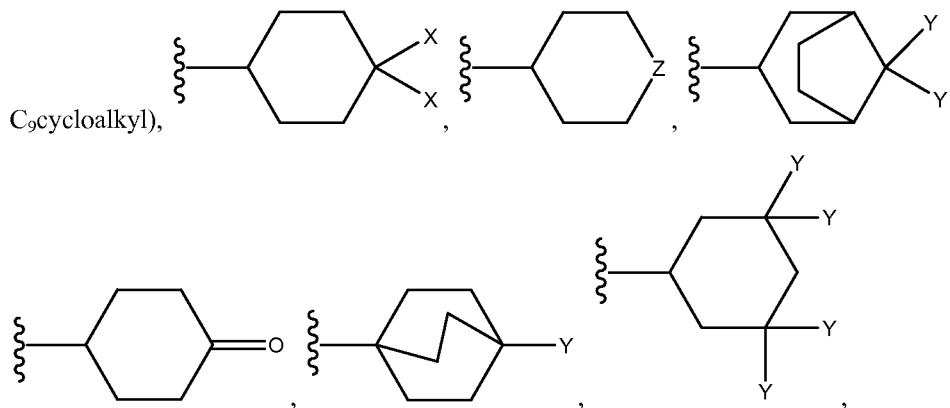
HO-A is tyrosine or a tyrosine-like compound; and

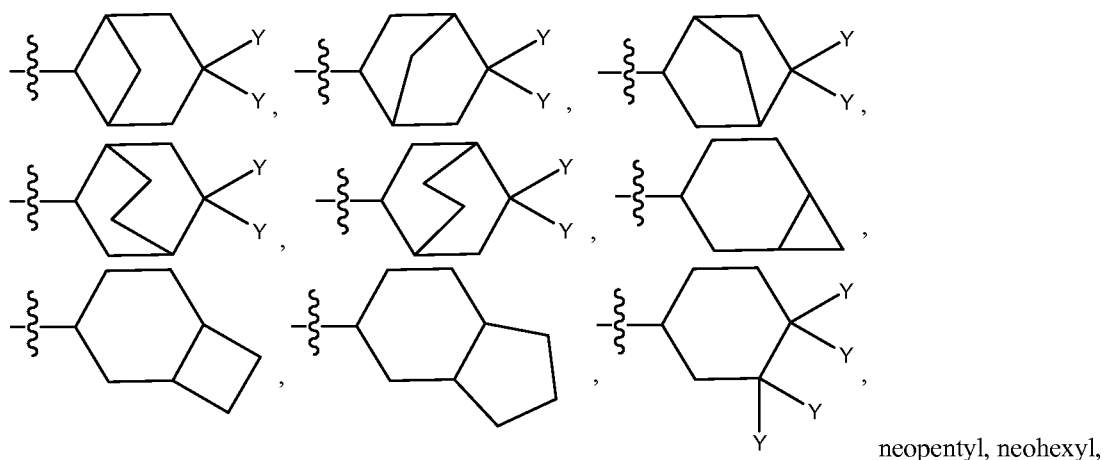
pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

20. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 19.
21. A pharmaceutical composition comprising a compound of claim 19 and a pharmaceutically acceptable excipient.
22. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-





methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R_2 is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

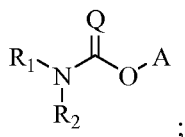
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

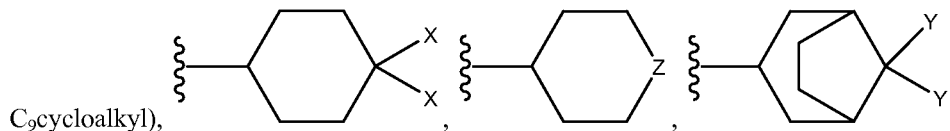
HO-A is acetaminophen or an acetaminophen-like compound; and

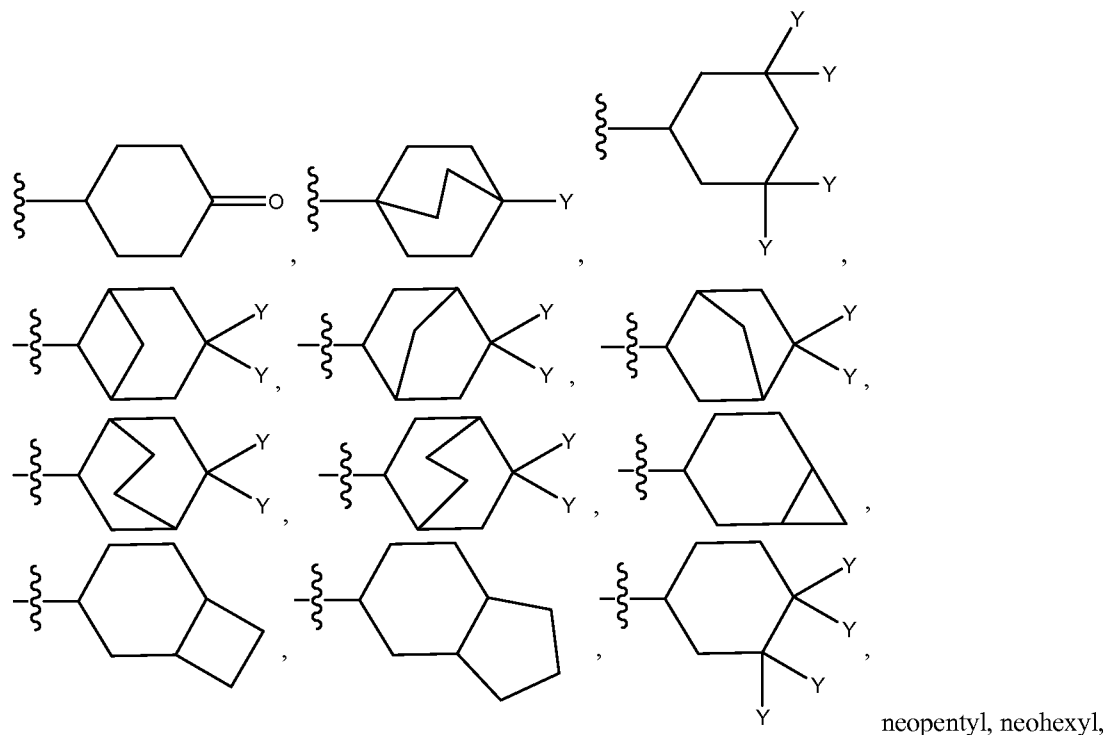
pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

23. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 22.
24. A pharmaceutical composition comprising a compound of claim 22 and a pharmaceutically acceptable excipient.
25. A compound of formula (I):



wherein R_1 is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-





R_2 is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

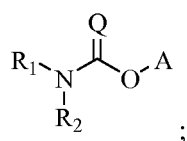
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

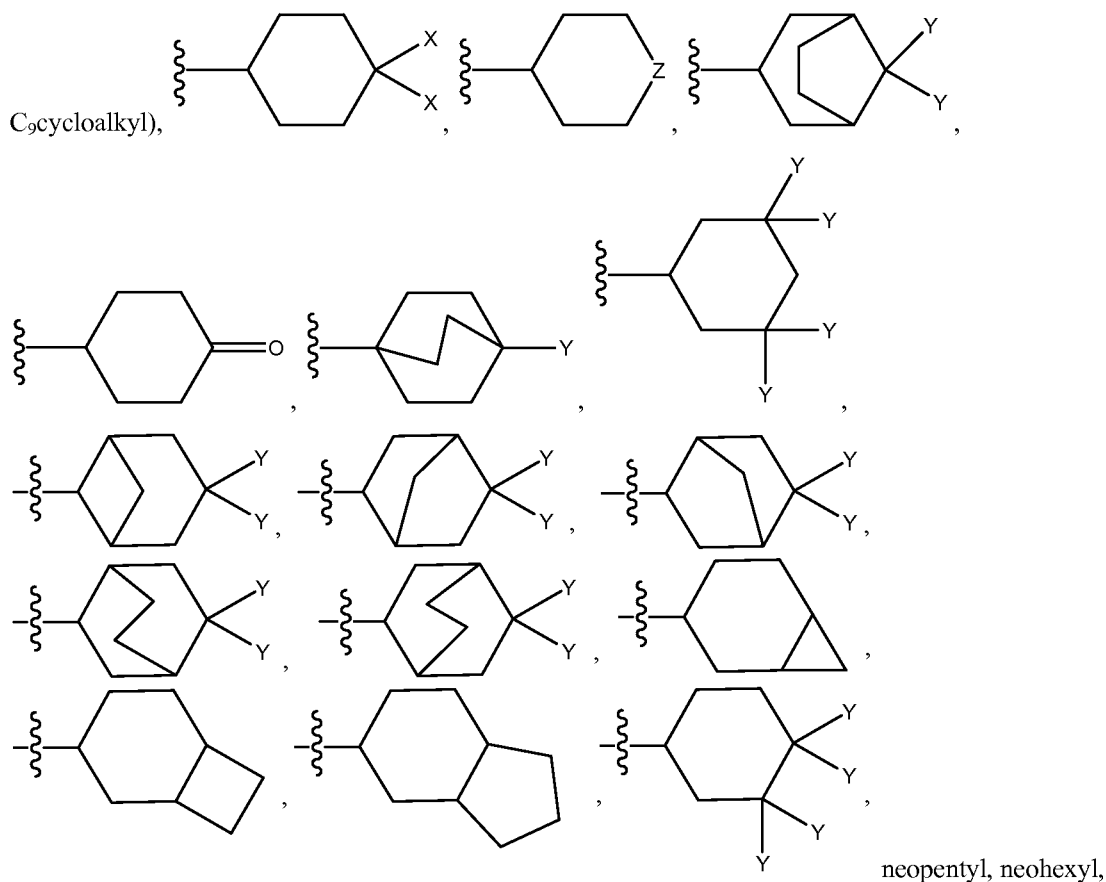
O-A is a deprotonated form of a hydroxy containing opioid or a deprotonated form of a hydroxy containing derivative of an opioid; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

26. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 25.
27. A pharmaceutical composition comprising a compound of claim 25 and a pharmaceutically acceptable excipient.
28. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

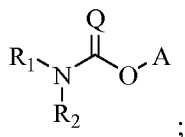
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

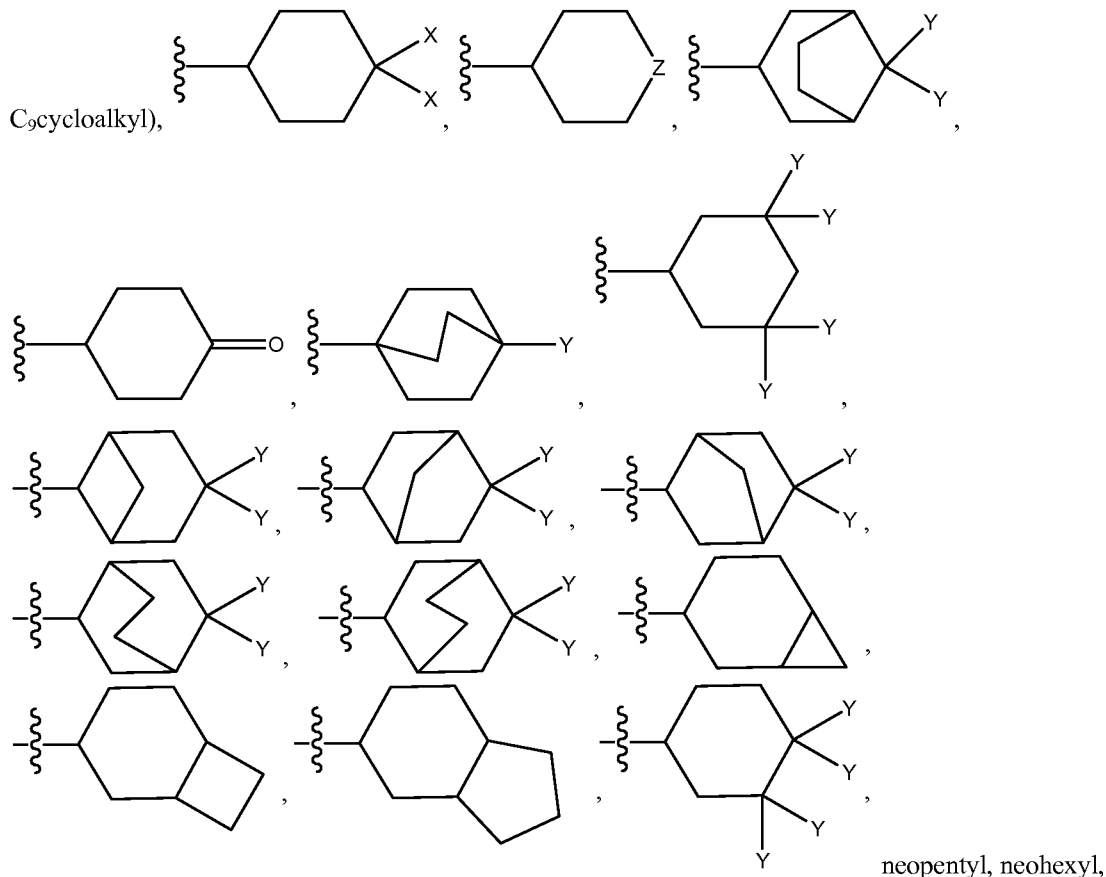
O-A is a deprotonated form of a hydroxy containing NSAID or a deprotonated form of a hydroxy containing derivative of an NSAID; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

29. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 28.
30. A pharmaceutical composition comprising a compound of claim 28 and a pharmaceutically acceptable excipient.
31. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

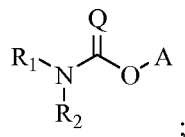
O-A is a deprotonated form of a hydroxy containing anesthetic agent or a deprotonated form of a hydroxy containing derivative of an anesthetic agent; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

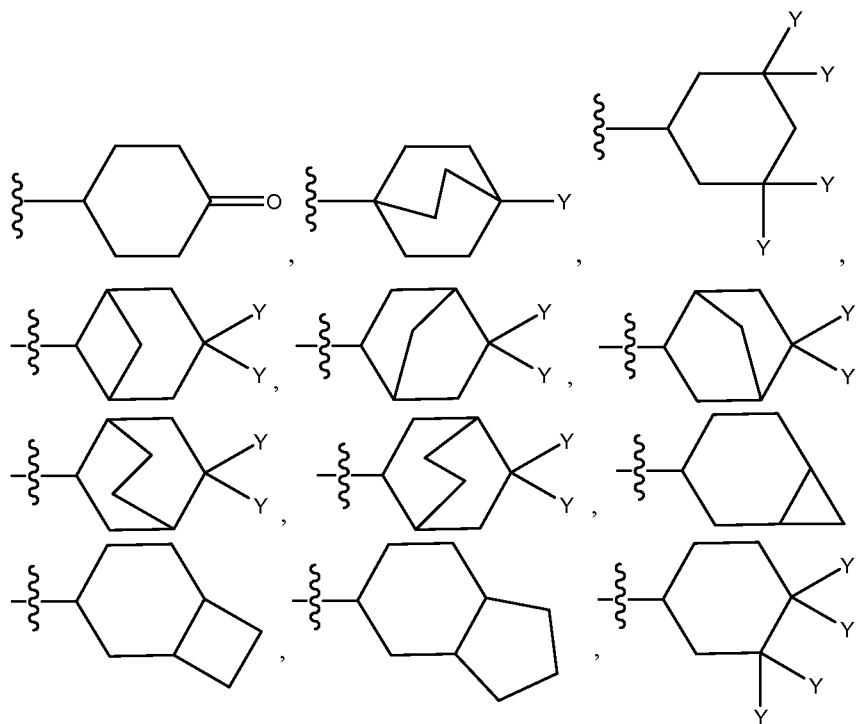
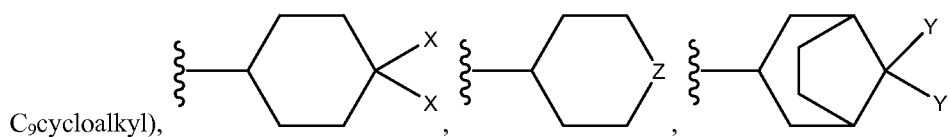
32. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 31.

33. A pharmaceutical composition comprising a compound of claim 31 and a pharmaceutically acceptable excipient.

34. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



neopentyl, neohexyl,

methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

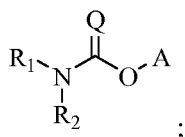
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

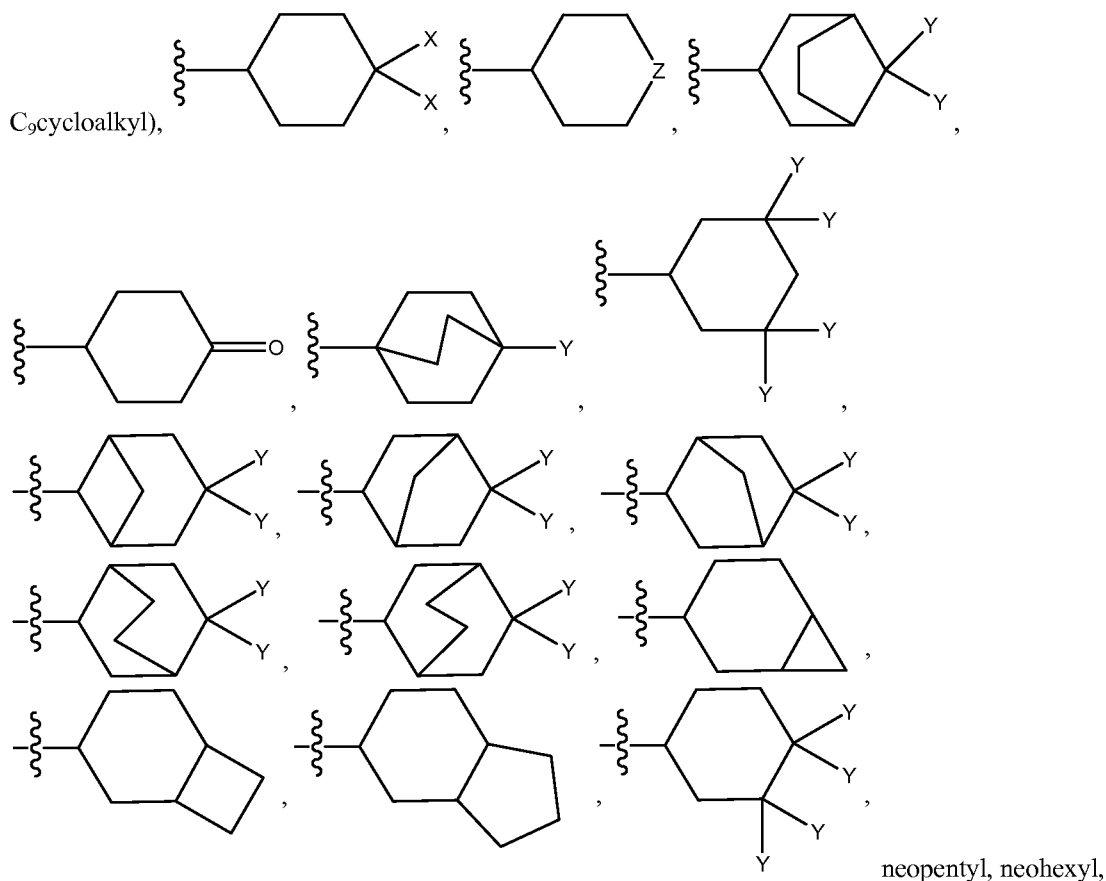
O-A is a deprotonated form of a hydroxy containing agent used to treat metabolic disorders or a deprotonated form of a hydroxy containing derivative of an agent used to treat metabolic disorders; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

35. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 34.
36. A pharmaceutical composition comprising a compound of claim 34 and a pharmaceutically acceptable excipient.
37. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

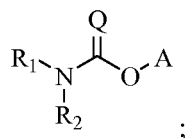
O-A is a deprotonated form of a hydroxy containing antihyperlipidemic agent or a deprotonated form of a hydroxy containing derivative of an antihyperlipidemic agent; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

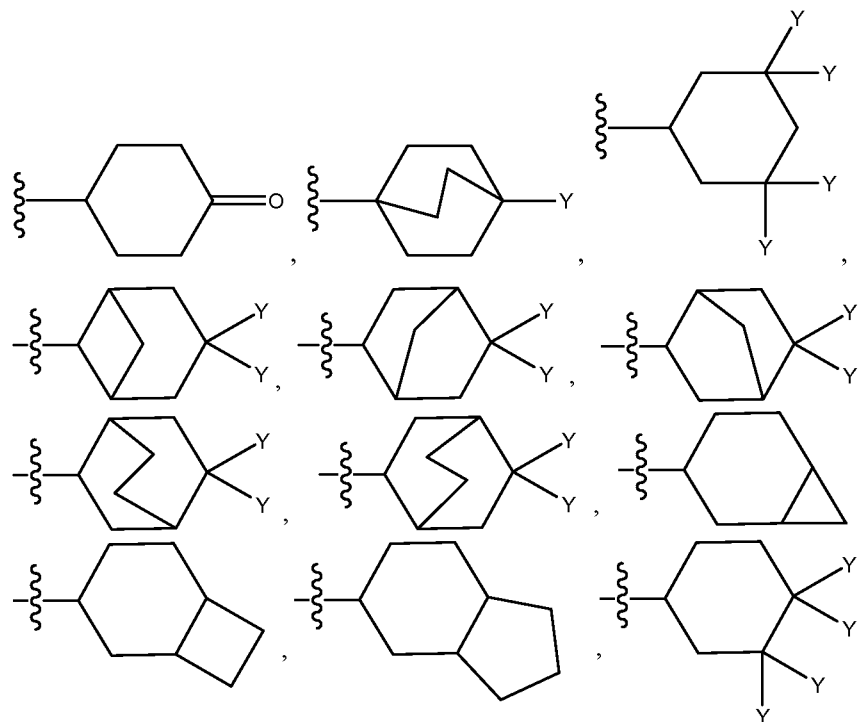
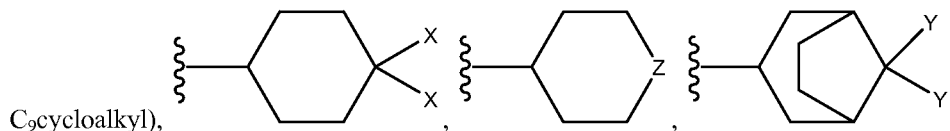
38. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 37.

39. A pharmaceutical composition comprising a compound of claim 37 and a pharmaceutically acceptable excipient.

40. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



neopentyl, neohexyl,

methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

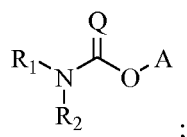
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

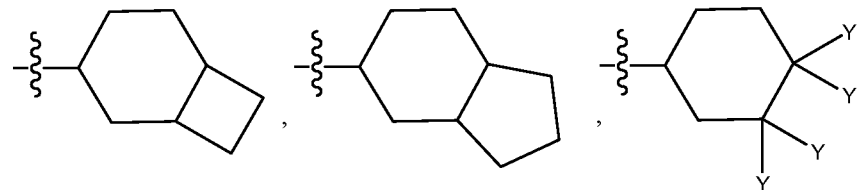
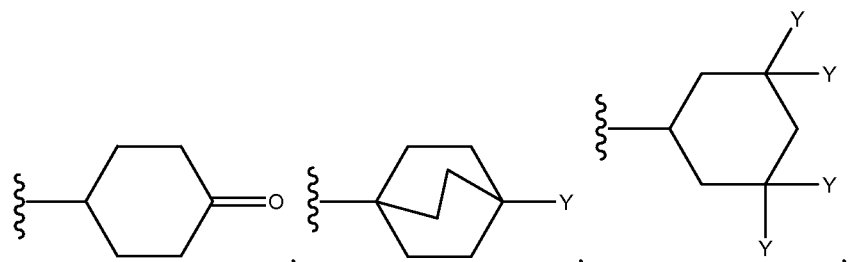
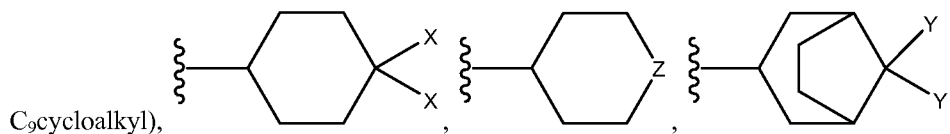
O-A is a deprotonated form of a hydroxy containing statin or a deprotonated form of a hydroxy containing derivative of a statin; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

41. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 40.
42. A pharmaceutical composition comprising a compound of claim 40 and a pharmaceutically acceptable excipient.
43. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



neopentyl, neohexyl,

methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

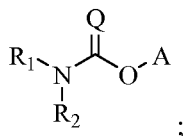
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

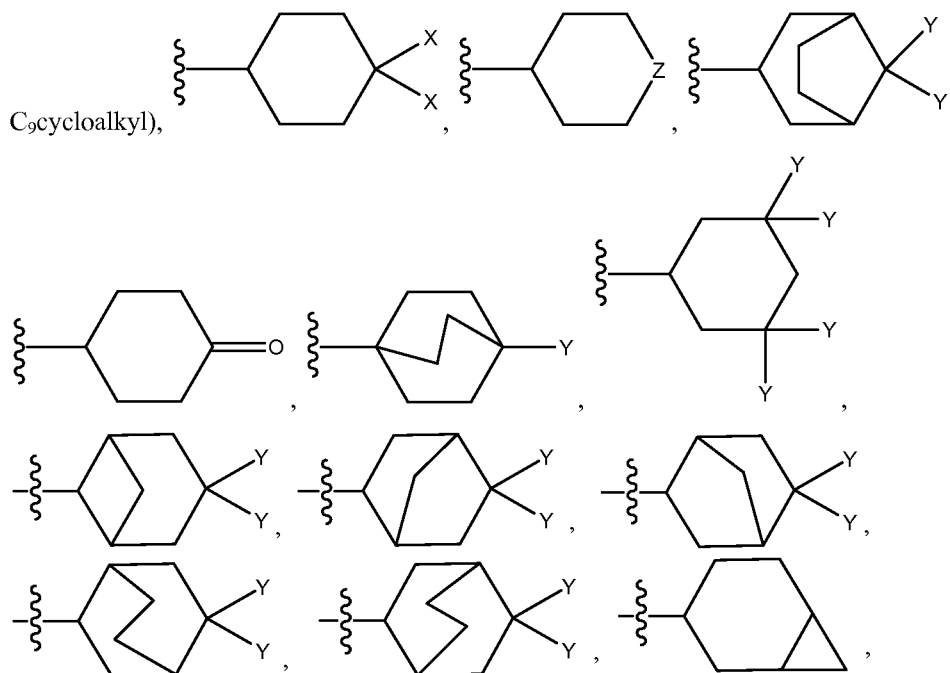
O-A is a deprotonated form of a hydroxy containing PPAR agonist or a deprotonated form of a hydroxy containing derivative of a PPAR agonist; and

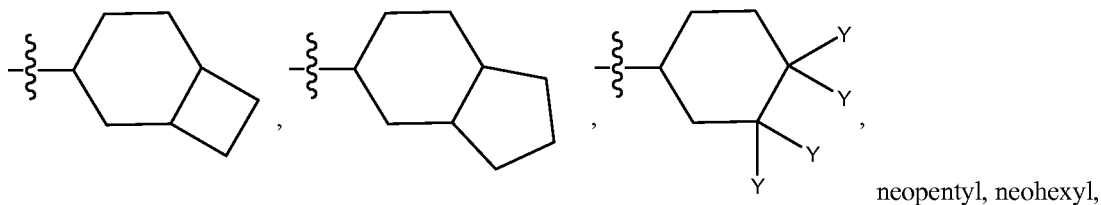
pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

44. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 43.
45. A pharmaceutical composition comprising a compound of claim 43 and a pharmaceutically acceptable excipient.
46. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-





methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

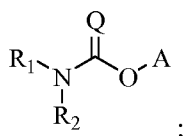
O-A is a deprotonated form of a hydroxy containing PPAR γ agonist or a deprotonated form of a hydroxy containing derivative of a PPAR γ agonist; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

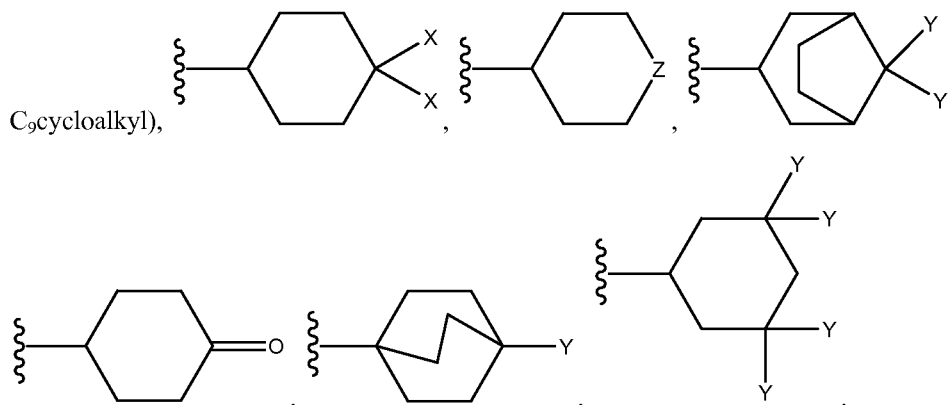
47. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 46.

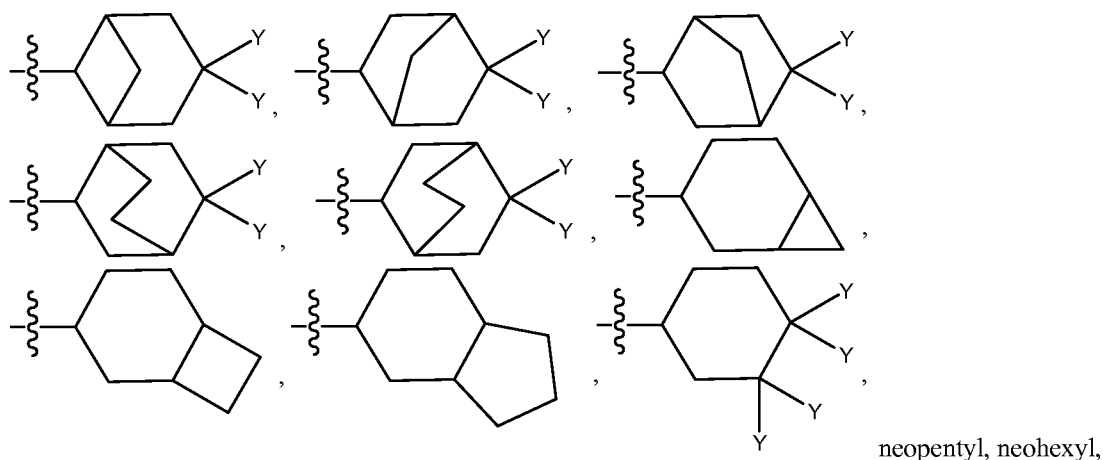
48. A pharmaceutical composition comprising a compound of claim 46 and a pharmaceutically acceptable excipient.

49. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-





methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

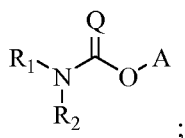
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

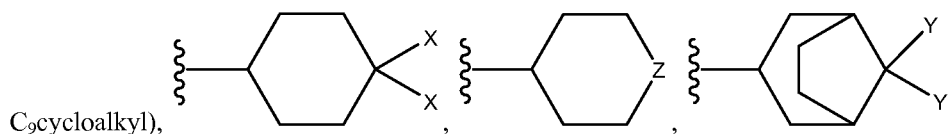
O-A is a deprotonated form of a hydroxy containing PPAR α agonist or a deprotonated form of a hydroxy containing derivative of a PPAR α agonist; and

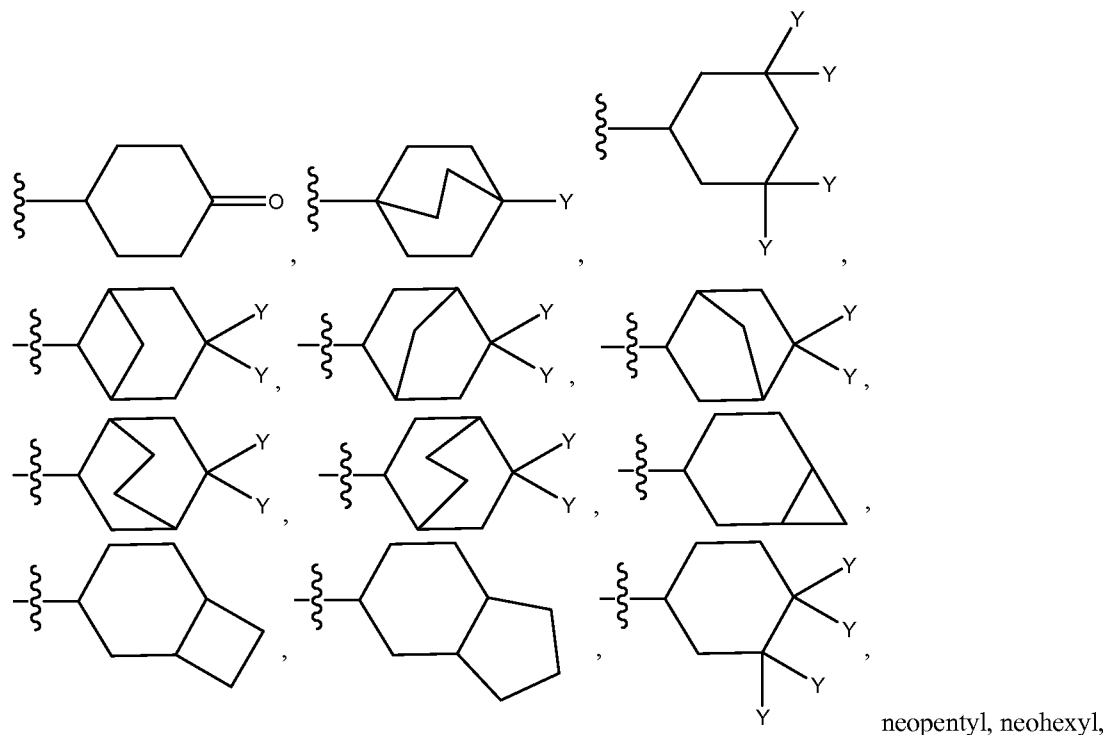
pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

50. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 49.
51. A pharmaceutical composition comprising a compound of claim 49 and a pharmaceutically acceptable excipient.
52. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-





methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

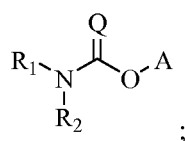
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

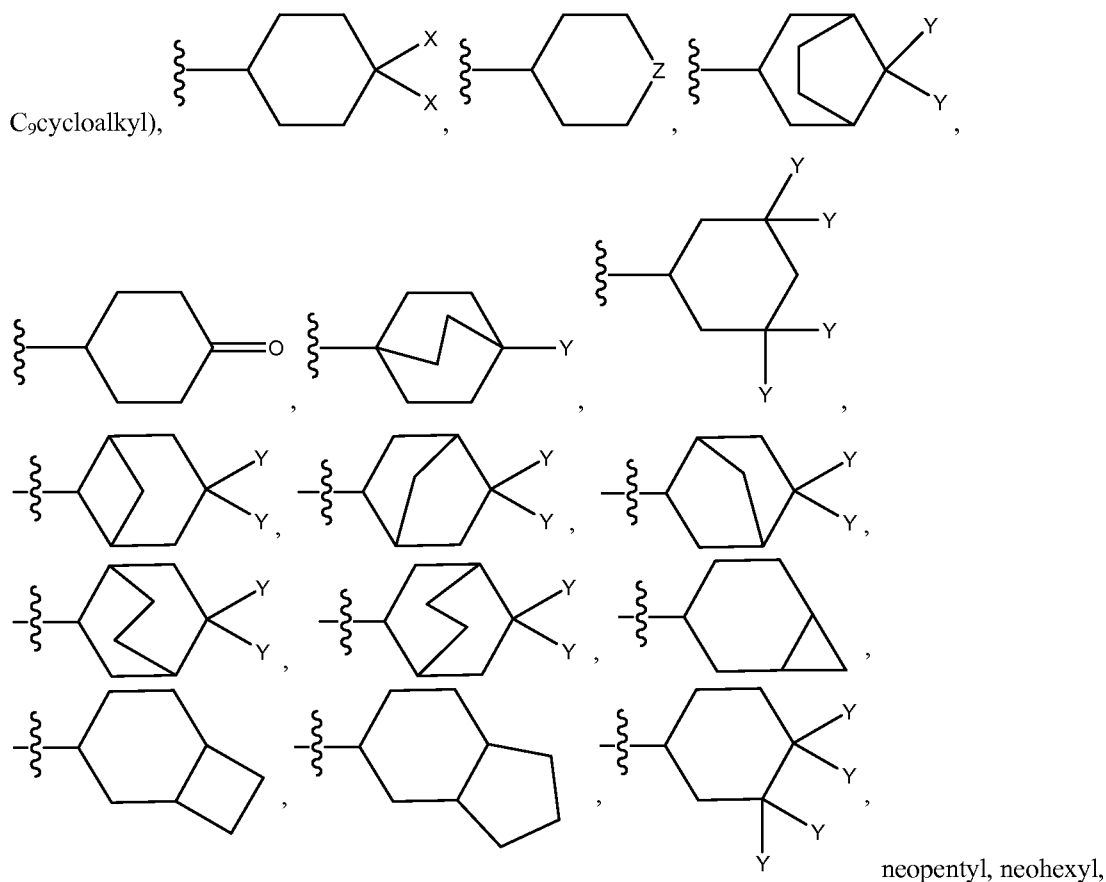
O-A is a deprotonated form of a hydroxy containing hypolipidemic agent or a deprotonated form of a hydroxy containing derivative of a hypolipidemic agent; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

53. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 52.
54. A pharmaceutical composition comprising a compound of claim 52 and a pharmaceutically acceptable excipient.
55. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

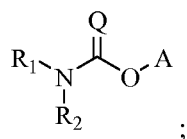
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

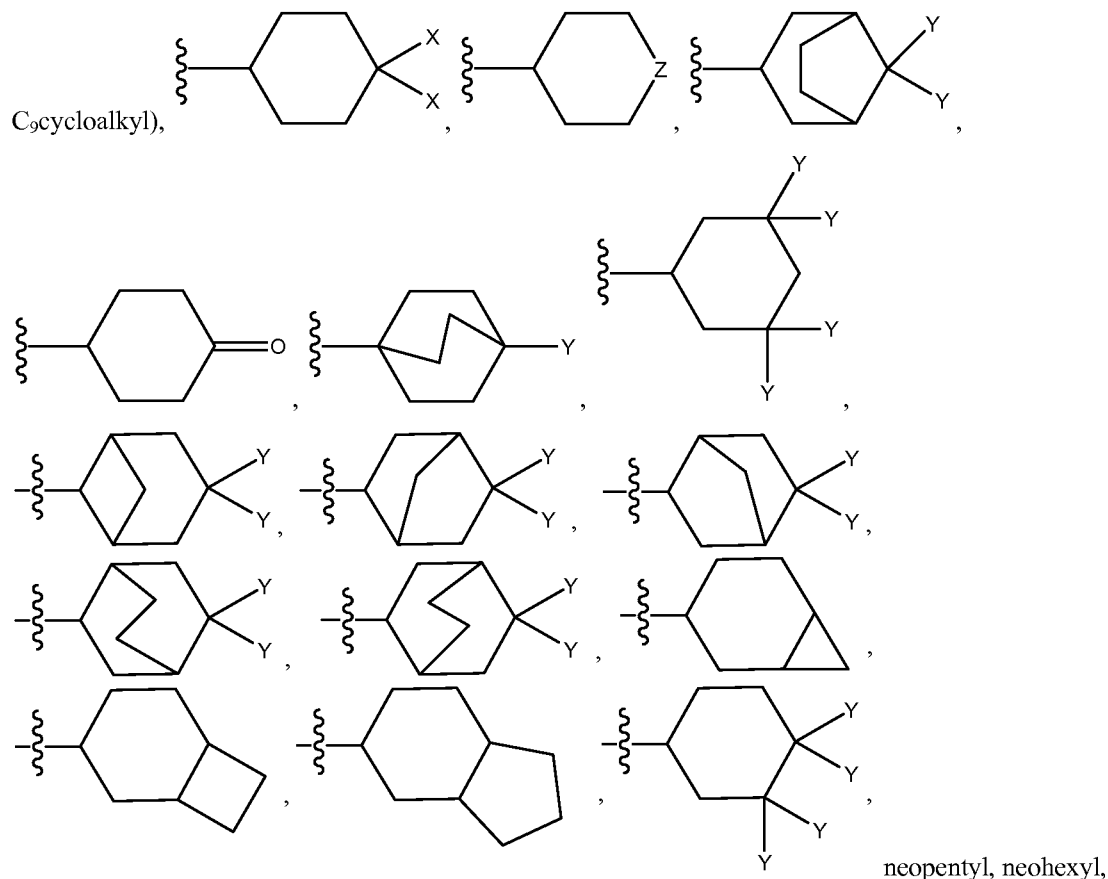
O-A is a deprotonated form of a hydroxy containing anti-diabetic agent or a deprotonated form of a hydroxy containing derivative of an anti-diabetic agent; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

56. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 55.
57. A pharmaceutical composition comprising a compound of claim 55 and a pharmaceutically acceptable excipient.
58. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

HO-A is ezetimibe or an ezetimibe-like compound; and

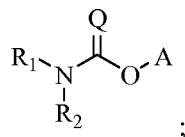
pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites,

pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

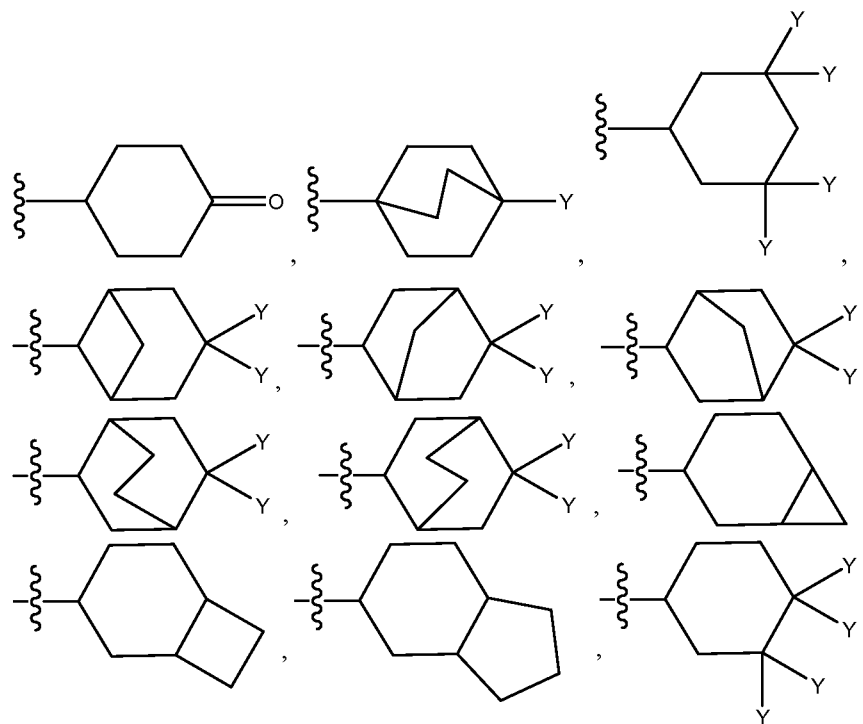
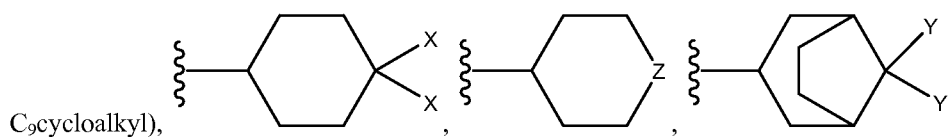
59. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 589.

60. A pharmaceutical composition comprising a compound of claim 58 and a pharmaceutically acceptable excipient.

61. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



neopentyl, neohexyl,

methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

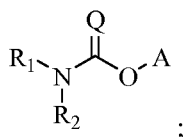
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

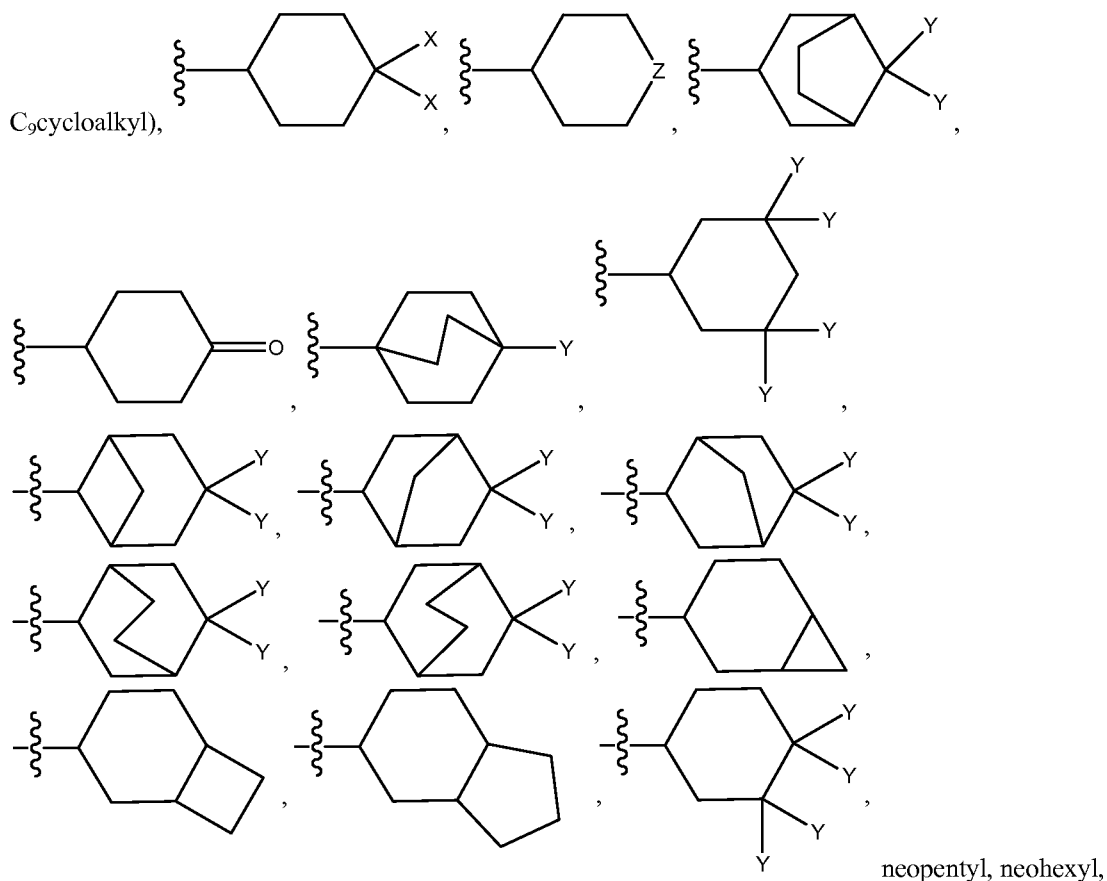
O-A is a deprotonated form of a hydroxy containing anti-hypertensive agent or a deprotonated form of a hydroxy containing derivative of an anti-hypertensive agent; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

62. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 61.
63. A pharmaceutical composition comprising a compound of claim 61 and a pharmaceutically acceptable excipient.
64. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

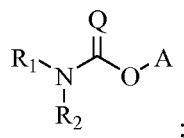
O-A is a deprotonated form of a hydroxy containing decongestant agent or a deprotonated form of a hydroxy containing derivative of a decongestant agent; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

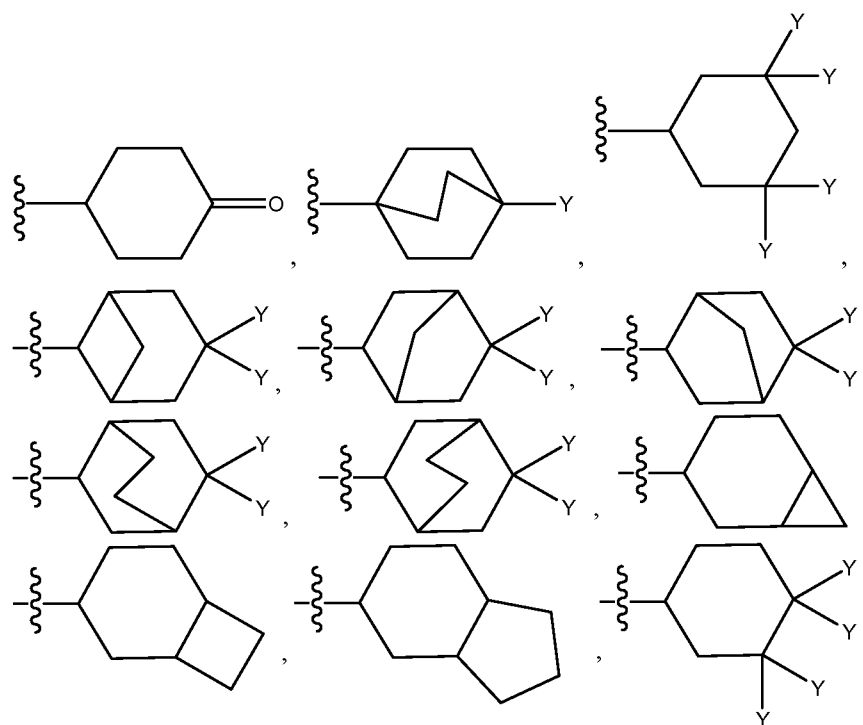
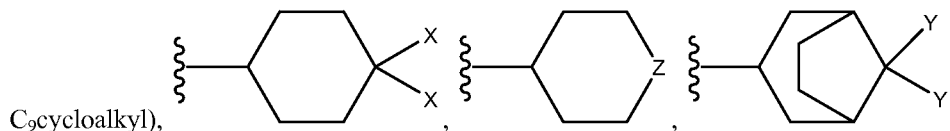
65. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 64.

66. A pharmaceutical composition comprising a compound of claim 64 and a pharmaceutically acceptable excipient.

67. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



neopentyl, neohexyl,

methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

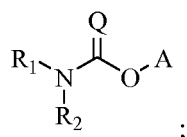
O-A is a deprotonated form of a hydroxy containing phytochemical or a deprotonated form of a hydroxy containing derivative of a phytochemical; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

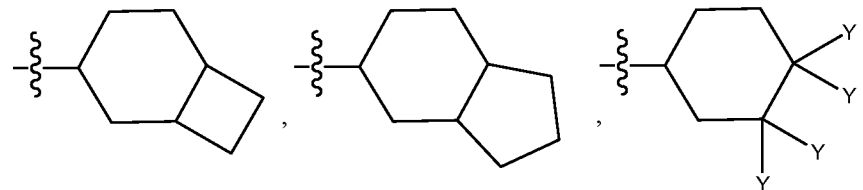
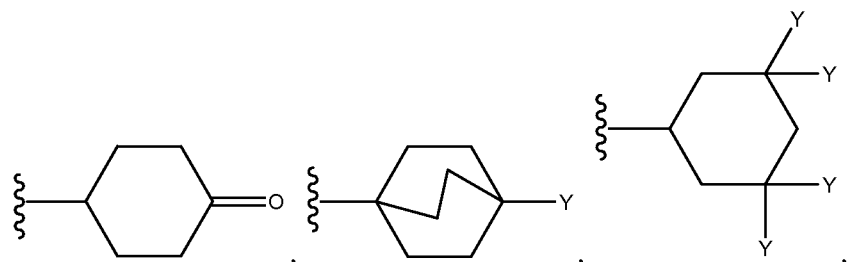
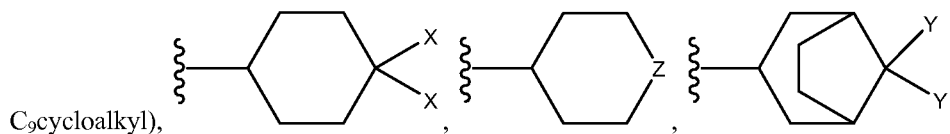
68. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 67.

69. A pharmaceutical composition comprising a compound of claim 67 and a pharmaceutically acceptable excipient.

70. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



neopentyl, neohexyl,

methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

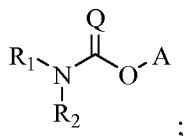
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

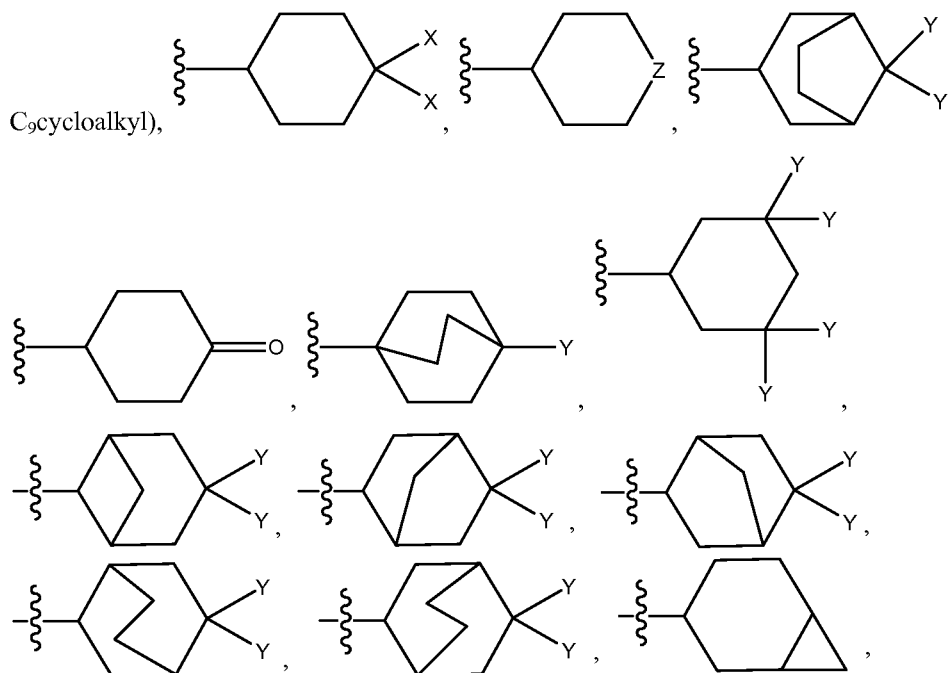
O-A is a deprotonated form of a hydroxy containing phenethylamine or a deprotonated form of a hydroxy containing derivative of a phenethylamine; and

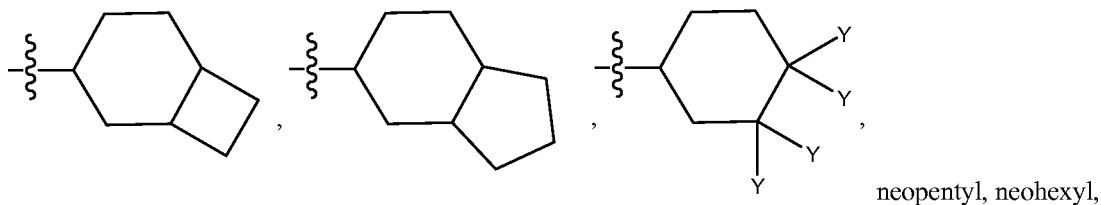
pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

71. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 70.
72. A pharmaceutical composition comprising a compound of claim 70 and a pharmaceutically acceptable excipient.
73. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-





methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R_2 is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

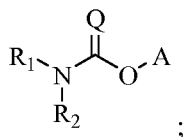
Z is O, N-(C_1 - C_6 alkyl), or SO_2 ;

Q is O or S; and

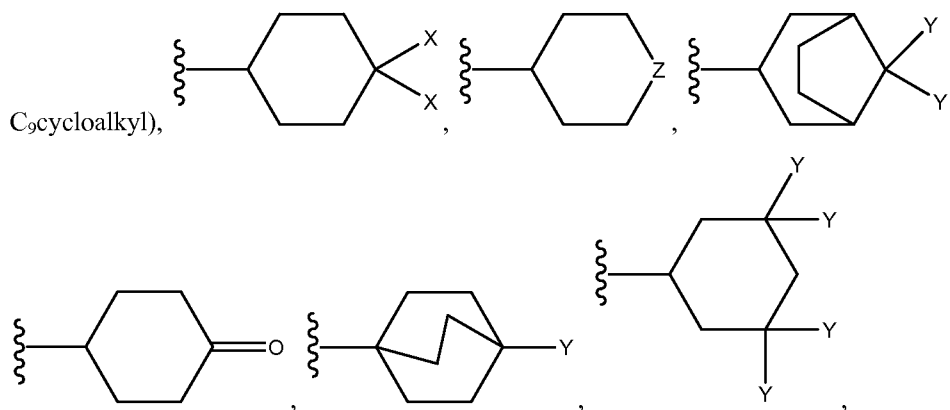
O-A is a deprotonated form of a hydroxy containing anti-oxidant or a deprotonated form of a hydroxy containing derivative of an anti-oxidant; and

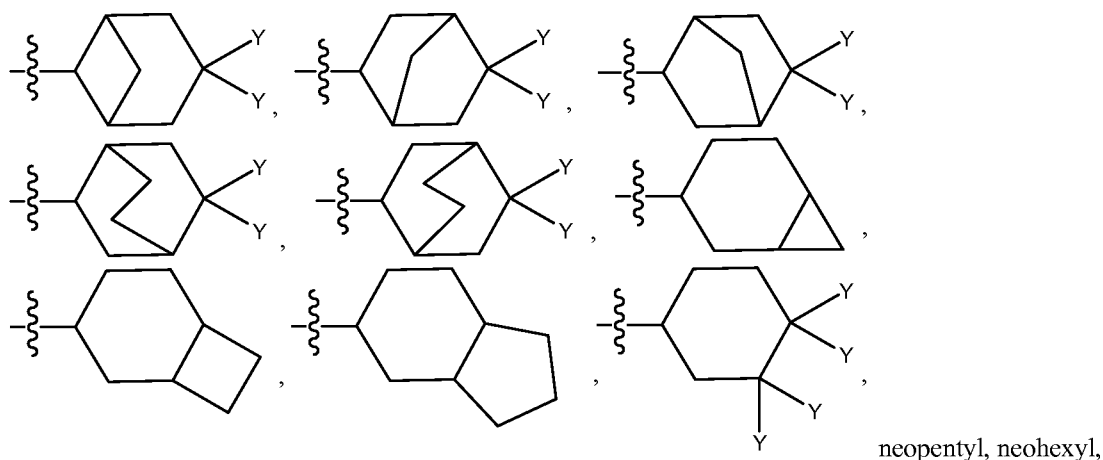
pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

74. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 73.
75. A pharmaceutical composition comprising a compound of claim 73 and a pharmaceutically acceptable excipient.
76. A compound of formula (I):



wherein R_1 is an optionally substituted group selected from among C_1 - C_8 alkyl, C_3 - C_9 cycloalkyl, C_1 - C_4 alkyl-(C_3 -





methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R_2 is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C_1 - C_6 alkyl), or SO_2 ;

Q is O or S; and

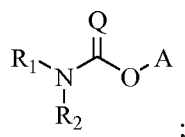
O-A is a deprotonated form of a hydroxy containing vitamin or a deprotonated form of a hydroxy containing derivative of a vitamin; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

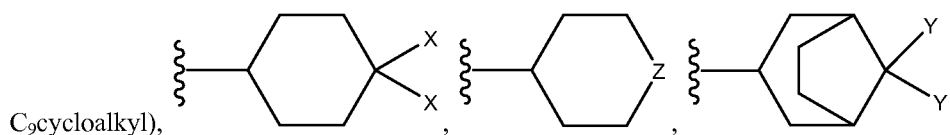
77. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 76.

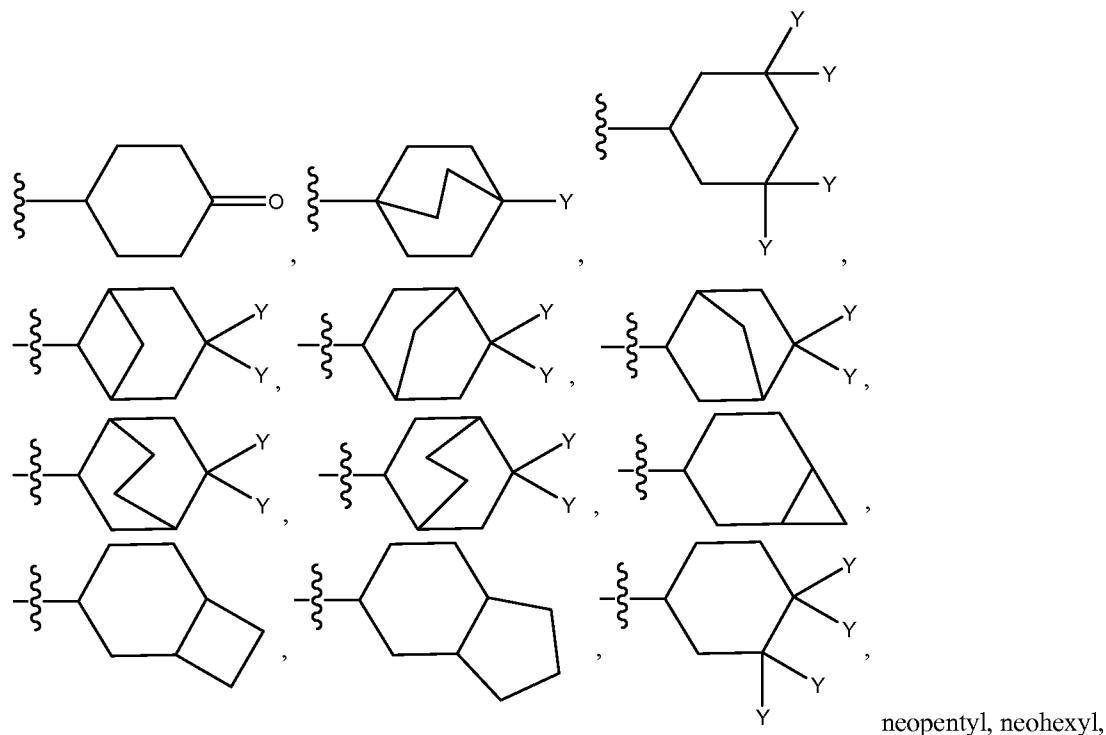
78. A pharmaceutical composition comprising a compound of claim 76 and a pharmaceutically acceptable excipient.

79. A compound of formula (I):



wherein R_1 is an optionally substituted group selected from among C_1 - C_8 alkyl, C_3 - C_9 cycloalkyl, C_1 - C_4 alkyl-(C_3 -





methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

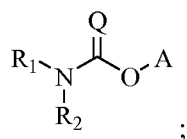
Q is O or S; and

O-A is a deprotonated form of a hydroxy containing agent as provided in Section **aa** or a deprotonated form of a

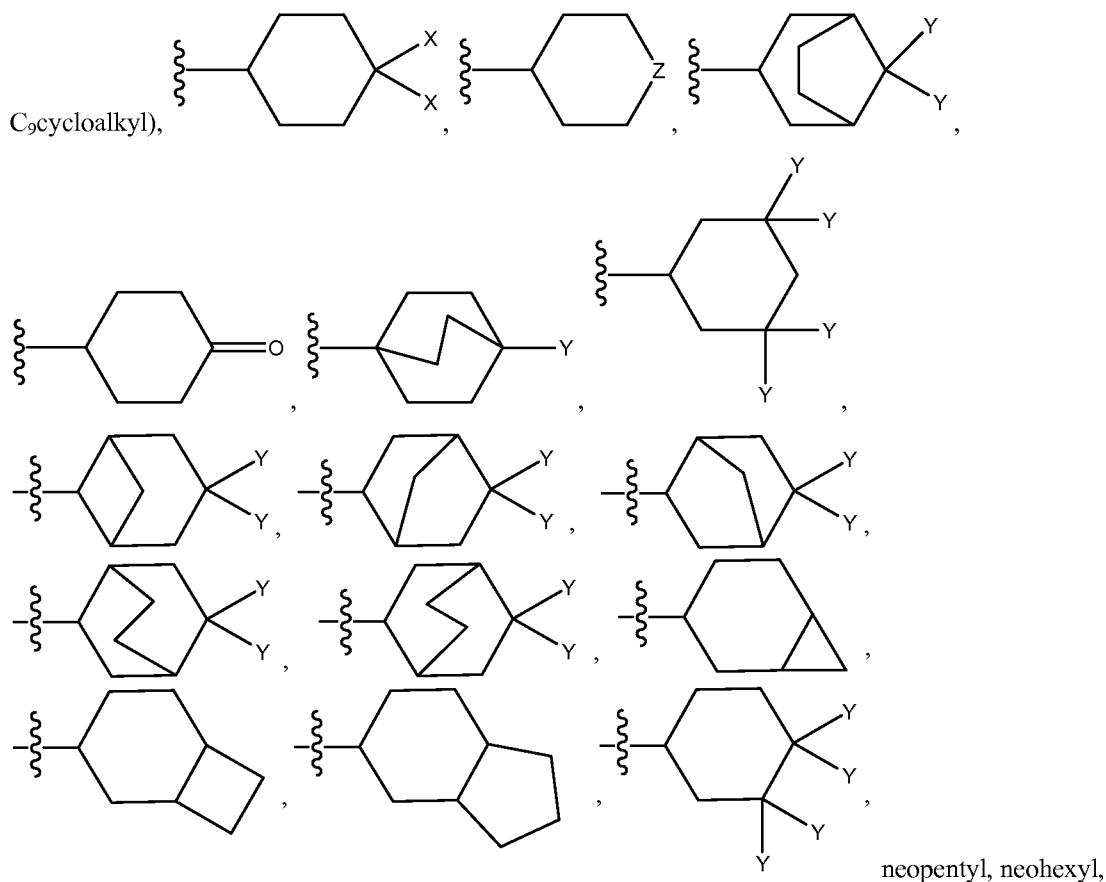
hydroxy containing derivative of a therapeutic agent as provided in Section **aa**; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

80. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 79.
81. A pharmaceutical composition comprising a compound of claim 79 and a pharmaceutically acceptable excipient.
82. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

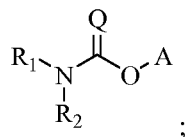
Q is O or S; and

O-A is a deprotonated form of a hydroxy containing agent as provided in Figures 1-4 or a deprotonated form of a

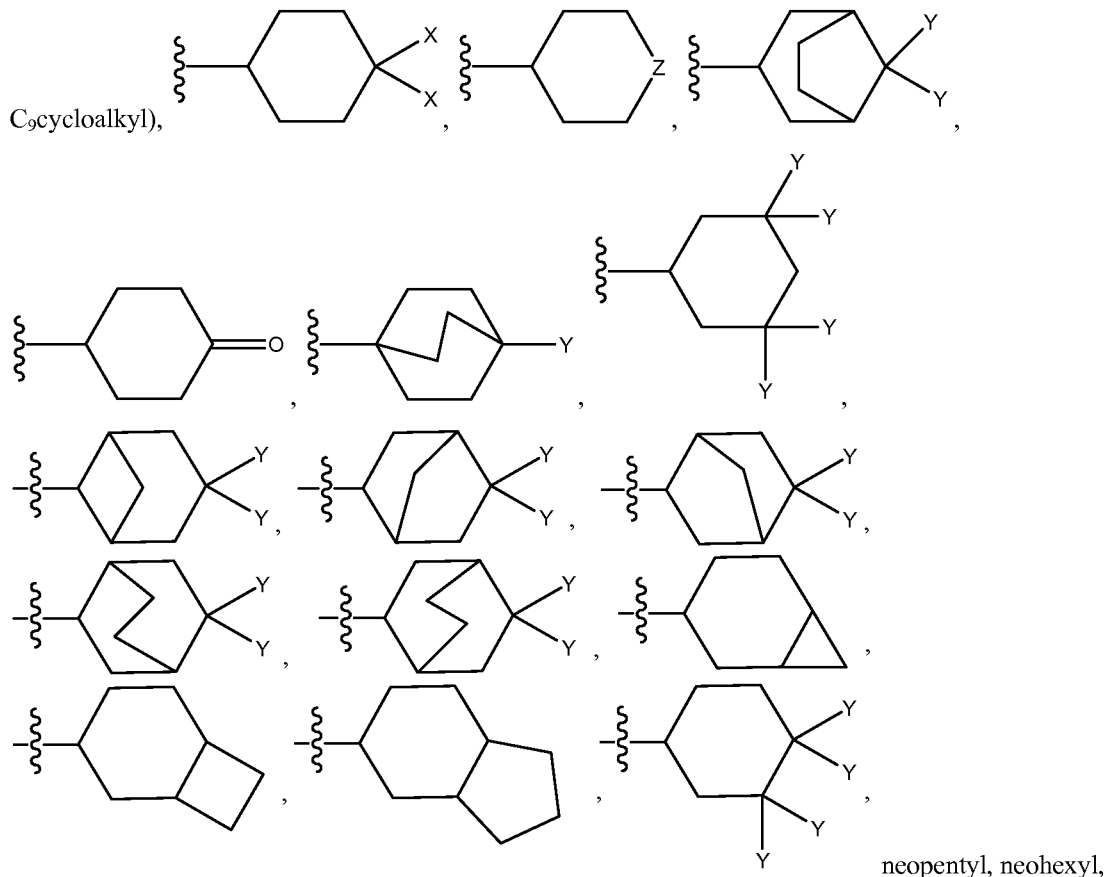
hydroxy containing derivative of an agent as provided in Figures 1-4; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

83. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 82.
84. A pharmaceutical composition comprising a compound of claim 82 and a pharmaceutically acceptable excipient.
85. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

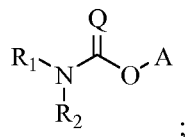
O-A is a deprotonated form of a hydroxy containing anti-depressive agent or a deprotonated form of a hydroxy containing derivative of an anti-depressive agent; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

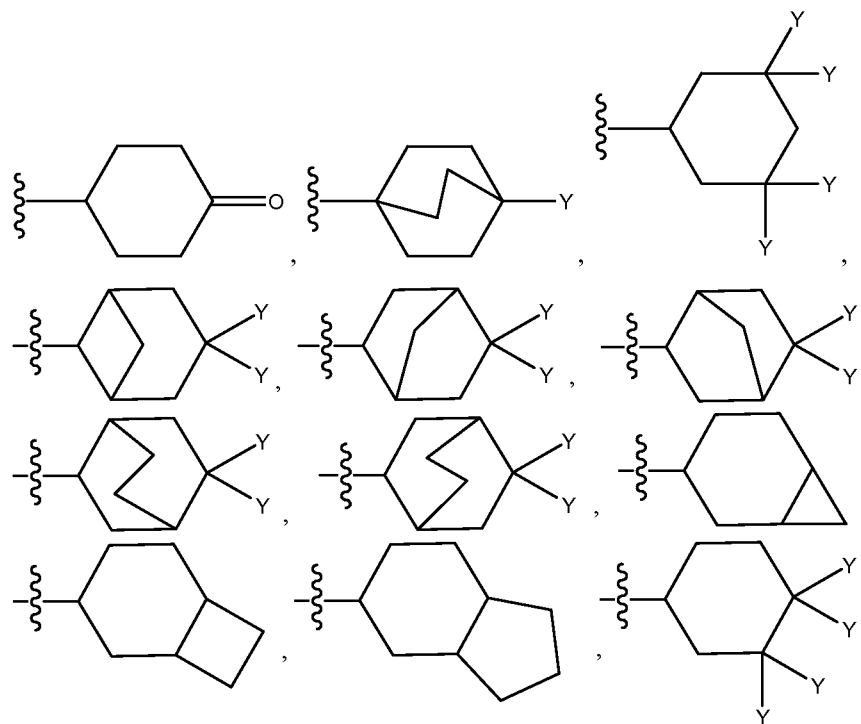
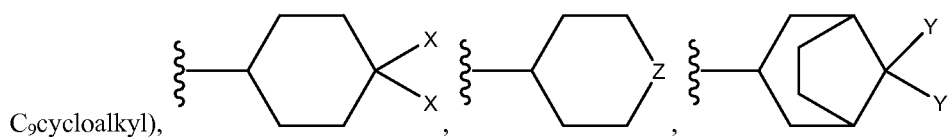
86. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 85.

87. A pharmaceutical composition comprising a compound of claim 85 and a pharmaceutically acceptable excipient.

88. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



neopentyl, neohexyl,

methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

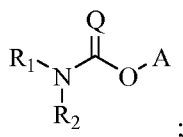
Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

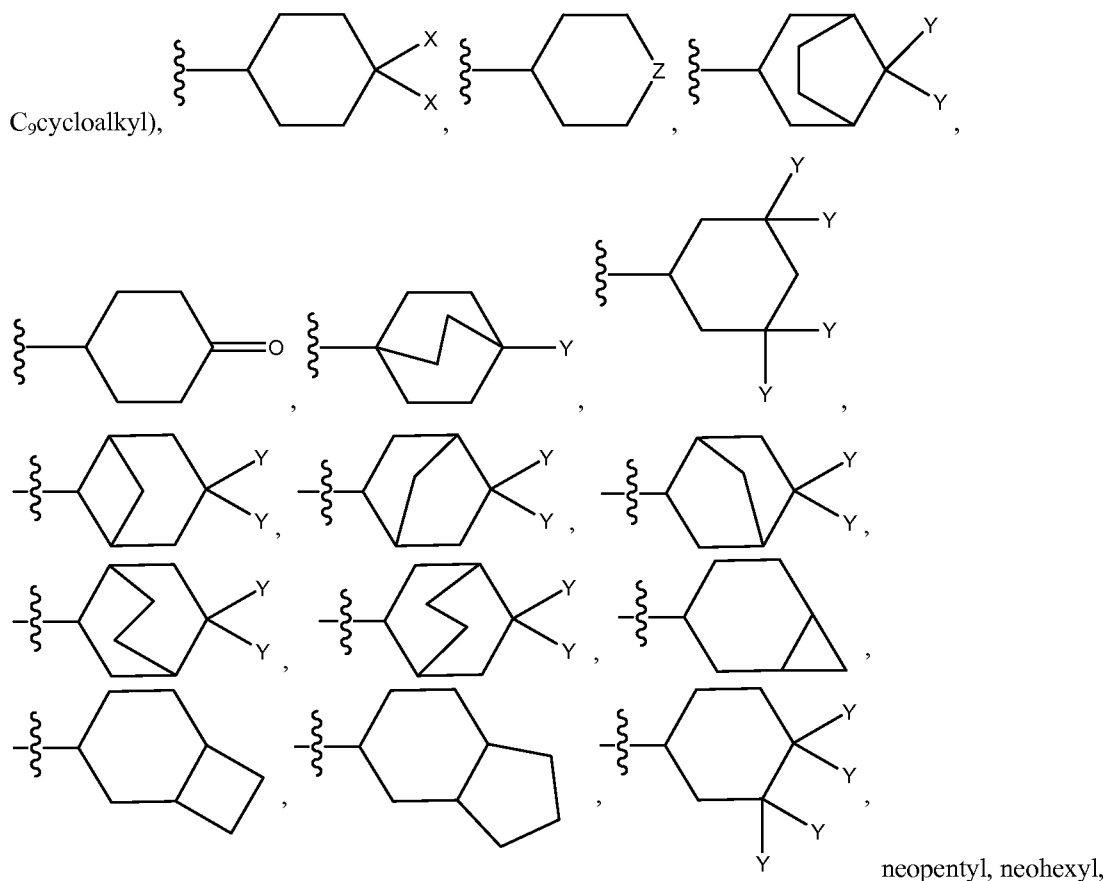
O-A is a deprotonated form of a hydroxy containing anxiolytic agent or a deprotonated form of a hydroxy containing derivative of an anxiolytic agent; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

89. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 88.
90. A pharmaceutical composition comprising a compound of claim 88 and a pharmaceutically acceptable excipient.
91. A compound of formula (I):



wherein R₁ is an optionally substituted group selected from among C₁-C₈ alkyl, C₃-C₉ cycloalkyl, C₁-C₄alkyl-(C₃-



methylenecyclopropyl, methylenecyclobutyl, and methylenecyclopentyl;

R₂ is H or an optionally substituted alkyl;

each X is independently halogen, methyl, fluoromethyl; or

each X taken together can form a 3-, 4-, or 5-membered carbocyclic group;

each Y is independently H, halogen, methyl, fluoromethyl; or

each Y taken together can form a 3-, 4-, or 5-membered carbocyclic group;

Z is O, N-(C₁-C₆ alkyl), or SO₂;

Q is O or S; and

O-A is a deprotonated form of a hydroxy containing neuroprotective agent or a deprotonated form of a hydroxy containing derivative of a neuroprotective agent; and

pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

92. A method of treating a patient in need comprising administering to the patient a therapeutically effective amount of the compound of claim 91.
93. A pharmaceutical composition comprising a compound of claim 91 and a pharmaceutically acceptable excipient.

FIGURE 1

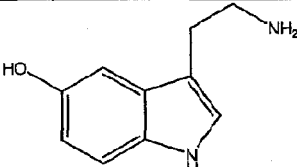
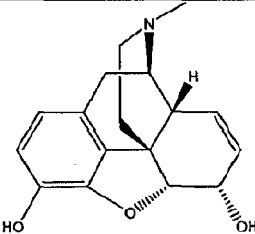
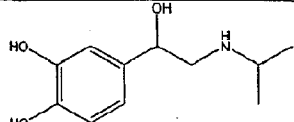
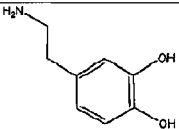
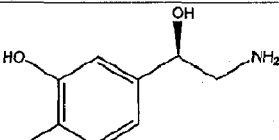
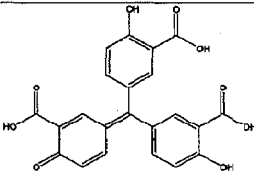
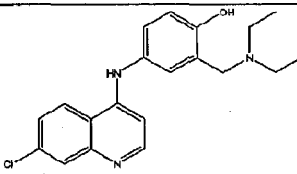
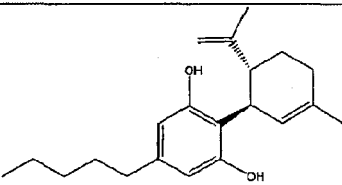
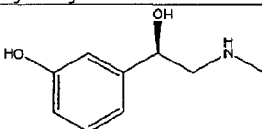
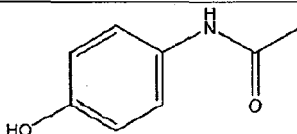
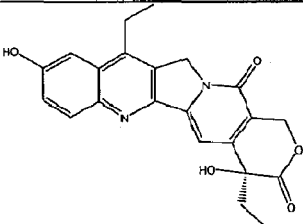
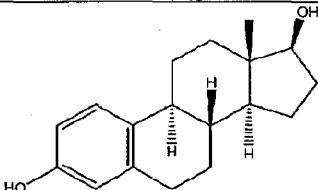
 Drug Name 5-Hydroxytryptamine, Serotonin, 5-HT Chemical Name 3-(2-Aminoethyl)-5-hydroxy-1H-indole	 Drug Name Morphine Chemical Name (5α,6α)-4,5-Epoxy-7,8-didehydro-17-methylmorphinan-3,6-diol	 Drug Name Isoproterenol hydrochloride, Isoprenaline hydrochloride, Isuprel hydrochloride, Vapo-Iso, Norisodrine Chemical Name 4-[1-Hydroxy-2-(isopropylamino)ethyl]benzene-1,2-diol hydrochloride
 Drug Name Dopamine Chemical Name 4-(2-Aminoethyl)-1,2-benzenediol	 Drug Name Norepinephrine, Noradrenaline Chemical Name (-)-4-[2-Amino-1(R)-hydroxyethyl]-1,2-benzenediol	 Drug Name Aurintricarboxylic acid Chemical Name 5-[(3-Carboxy-4-hydroxyphenyl)(3-carboxy-4-oxo-2,5-cyclohexadien-1-ylidene)methyl]-2-hydroxybenzoic acid
 Drug Name Amodiaquine, SN-10751, Camoquin, Flavoquin Chemical Name 4-(7-Chloroquinolin-4-ylamino)-2-(diethylaminomethyl)phenol	 Drug Name Cannabidiol, CBD, Nabidiolex Chemical Name 2-[6(R)-Isopropenyl-3-methyl-2-cyclohexen-1(R)-yl]-5-pentyl-1,3-benzenediol	 Drug Name Phenylephrine hydrochloride, SLV-325, Biomydrin, Alcon Efrin, Mydrin, Nostril, Neo-Synephrine hydrochloride, Incostop Chemical Name (-)-3-[1(R)-Hydroxy-2-(methylamino)ethyl]phenol hydrochloride
 Drug Name Acetaminophen, Paracetamol, Efferalgan, Febrectal, Dolgesic, Tylenol, Perfalgan, Feverall, Fensum, Melabon, Calonal Chemical Name N-(4-Hydroxyphenyl)acetamide	 Drug Name SN-38 Chemical Name 7-Ethyl-10-hydroxycamptothecin; 4(S),11-Diethyl-4,9-dihydroxy-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14-dione	 Drug Name Estradiol, 17beta-Estradiol, NSC-9895, S-21400, SL-1100, Diogyn, Aerodiol, Bio-E-Gel, Estrace, Vagifem, Diogynets, Progynon, Aquadiol, Evorel, Estring Chemical Name (17beta)-Estra-1,3,5(10)-triene-3,17-diol

FIGURE 1 cont.

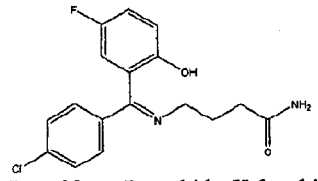
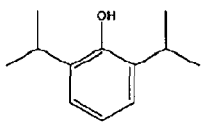
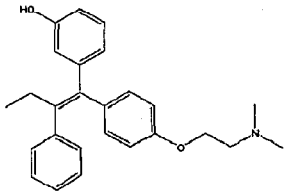
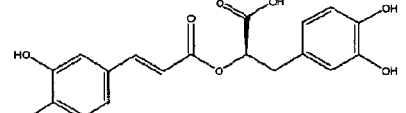
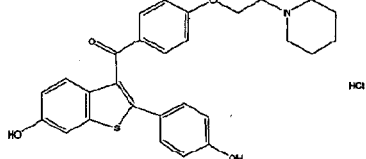
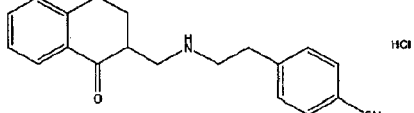
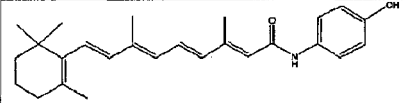
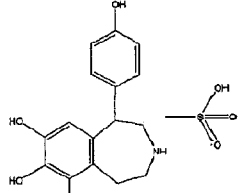
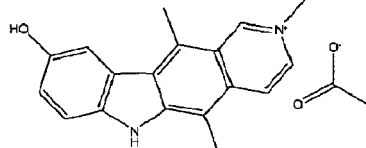
 Drug Name Progabide, Halogabide, SL-76002, Gabrene Chemical Name 4-[[alpha-(p-Chlorophenyl)-5-fluoro-2-hydroxybenzylidene]amino]butyramide	 Drug Name Propofol, Disoprofol, AM-149 (New formulation), ICI-35868, ZD-0859, Ampofol, Disoprivan, Propofol IDD-D, Diprivan Chemical Name 2,6-Bis(1-methylethyl)phenol	 Drug Name Droloxifene, K-21060E, FK-435, K-060 Chemical Name (E)-1-[4'-(2-Dimethylaminoethoxy)phenyl]-1-(3'-hydroxyphenyl)-2-phenylbut-1-ene; (E)-alpha-[p-[2-(Dimethylamino)ethoxy]phenyl]-alpha'-ethyl-3-stilbenol; (E)-3-[1-[4-[2-(Dimethylamino)ethoxy]phenyl]-2-phenyl-1-butenyl]phenol
 Drug Name Rosmarinic acid Chemical Name R(+)-2-(3,4-Dihydroxycinnamoyloxy)-3,4-dihydroxyphenylpropionic acid; R(+)-alpha-[[3-(3,4-Dihydroxyphenyl)-1-oxo-2-propenyl]oxy]-3,4-dihydroxybenzenepropanoic acid	 Drug Name Raloxifene hydrochloride, Keoxifene hydrochloride, LY-139481 (free base), LY-156758, CDT-Raloxifene, Loxifen, Optruma, Evista Chemical Name 1-[6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-1-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride; 6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]benzo[b]thiophene hydrochloride	 Drug Name BE-2254, HEAT Chemical Name 2-[beta-(Hydroxyphenyl)ethylaminomethyl]tetralone hydrochloride; 3,4-Dihydro-2-[[[2-(4-hydroxyphenyl)ethyl]amino]methyl]-1(2H)-naphthalenone hydrochloride; 3,4-Dihydro-2-[[p-(hydroxyphenethyl)amino]methyl]-1(2H)-naphthalenone hydrochloride
 Drug Name Fenretinide, 4-HPR, HPR, McN-R-1967, NSC-374551 Chemical Name N-(4-Hydroxyphenyl)-all-trans-retinamide	 Drug Name Fenoldopam mesilate, SK&F-82526J, Corlopam Chemical Name 6-Chloro-1-(4-hydroxyphenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-diol methanesulfonate; 6-Chloro-7,8-dihydroxy-1-(4-hydroxyphenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine methanesulfonate	 Drug Name Elliptinium acetate, NSC-264137, HME, Celiptium Chemical Name 9-Hydroxy-2,5,11-trimethyl-6H-pyrido[4,3-b]carbazolium acetate; 9-Hydroxy-2-methylellipticinium acetate

FIGURE 1 cont.

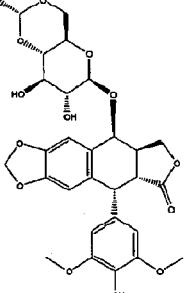
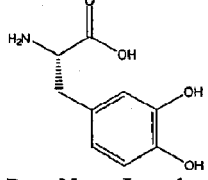
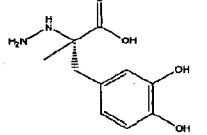
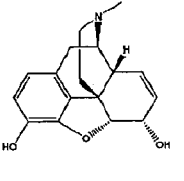
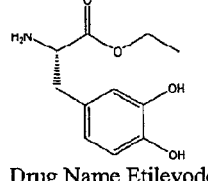
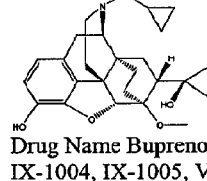
 Drug Name Etoposide, VP-16, EPEG, NSC-141540, VP-16-213, Etopophos, Lastet, Etosid, Etopol, Vepesid, Vepeside Chemical Name 4'-Demethylepipodophyllotoxin 4-(4,6-O-ethylidene-beta-D-glucopyranoside); [5R-[5alpha,5abeta,8aalpha,9beta(R*)]]-9-[(4,6-O-Ethylidene-beta-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one	 Drug Name Levodopa, L-Dopa, Larodopa Chemical Name 3-Hydroxy-L-tyrosine; 2(S)-Amino-3-(3,4-dihydroxyphenyl)propionic acid; 3-(3,4-Dihydroxyphenyl)-L-alanine	 Drug Name Carbidopa Chemical Name (-)-L-alpha-Hydrazino-3,4-dihydroxy-alpha-methylhydrocinnamic acid monohydrate; S-alpha-Hydrazino-3,4-dihydroxy-alpha-methylbenzenepropionic acid monohydrate
 Drug Name Morphine sulphate, Morphine sulfate, PF-402, TA-2620, Oramorph, Astramorph P/F, ReproDose-morphine, Reliadol, Avinza, Moxaxen, Moscontin, Morphelan, Statex SR, M Eslon, Kapanol, Pguard, M-dolor, MS-contin, Skenan LP, Roxanol, Kadian, Mircap SR, AERx-Morphine, Rylomine, Oramorph SR Chemical Name (5alpha,6alpha)-4,5-Epoxy-17-methyl-7,8-didehydromorphinan-3,6-diol sulfate (2:1) pentahydrate	 Drug Name Etilevodopa, Levodopa ethyl ester, L-Dopa ethyl ester, TV-1203 Chemical Name 3-Hydroxy-L-tyrosine ethyl ester; 2(S)-Amino-3-(3,4-dihydroxyphenyl)propionic acid ethyl ester	 Drug Name Buprenorphine hydrochloride, IX-1004, IX-1005, V-1003, CL-112302, TSN-09 (tape), IX-1003, UM-952, NIH-8805, Probuphine, Subutex, Temgesic, Transtec, Buprex, Buprenax Chemical Name 21-Cyclopropyl-7alpha-[2(S)-hydroxy-3,3-dimethyl-2-butyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine hydrochloride; 17-(Cyclopropylmethyl)-4,5alpha-epoxy-7alpha-[1(S)-hydroxy-1,2,2-trimethylpropyl]-6beta-methoxy-6,14-ethanomorphinan-3-ol hydrochloride; 21-Cyclopropyl-7alpha-[1(S)-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine hydrochloride

FIGURE 1 cont.

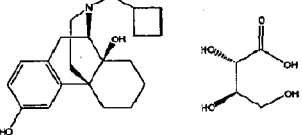
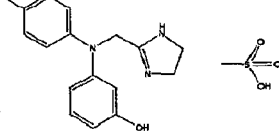
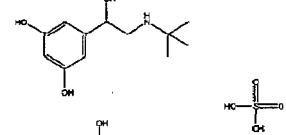
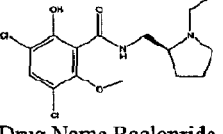
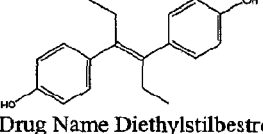
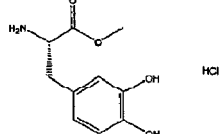
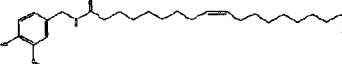
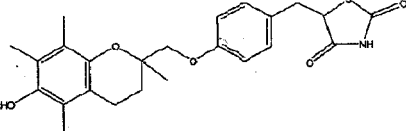
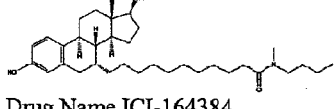
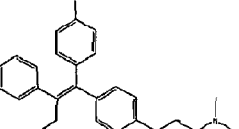
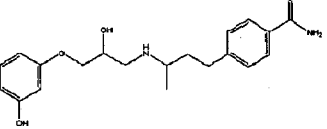
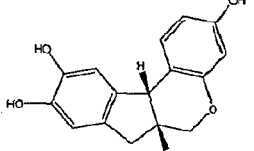
 Drug Name Butorphanol tartrate, levo-BC-2627 (free base), Stadol NS, Stadol Chemical Name (-)-17-(Cyclobutylmethyl)morphinan-3,14-diol D-tartrate	 Drug Name Phentolamine mesilate, Regitin, Z-Max, Vasofem, Vasomax Chemical Name 3-[N-(2-Imidazolin-2-ylmethyl)-N-(4-methylphenyl)amino]phenol methanesulfonate	 Drug Name Terbutaline sulfate, KWD-2019, Chronodyne, Brethine, Bricanyl, Brethaire Chemical Name 5-[2-(tert-Butylamino)-1-hydroxyethyl]-1,3-benzenediol sulfate (2:1)
 Drug Name Raclopride, A-40664 (tartrate) Chemical Name (S)-3,5-Dichloro-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-6-methoxybenzamide	 Drug Name Diethylstilbestrol, Vagestrol, Stilbetin Chemical Name 4,4'-(1,2-Diethyl-1,2-ethenediyl)bisphenol; alpha,alpha'-Diethyl-(E)-stilbenediol	 Drug Name Melevodopa hydrochloride, Levodopa methyl ester hydrochloride, L-Dopa methyl ester hydrochloride, LDME, NSC-295453 (free base), CHF-1301, ST-41769, Levomet Chemical Name 2(S)-Amino-3-(3,4-dihydroxyphenyl)propionic acid methyl ester hydrochloride
 Drug Name Olvanil, NE-19550 Chemical Name N-Vanillyl-9(Z)-octadecenamide	 Drug Name Troglitazone, GR-92132X, CI-991, CS-045, Noscil, Romozin, Prelay, Rezulin Chemical Name (±)-5-[4-[(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy]benzyl]thiazolidine-2,4-dione; (±)-5-[4-(3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-ylmethoxy)benzyl]thiazolidine-2,4-dione	 Drug Name ICI-164384 Chemical Name N-Butyl-11-[3,17beta-dihydroxy-estra-1,3,5(10)-trien-7alpha-y]-N-methylundecanamide
 Drug Name (E)-4-Hydroxytamoxifen, trans-4-Hydroxytamoxifen Chemical Name 1-[4-(2-Dimethylaminoethoxy)phenyl]-1-(4-hydroxyphenyl)-2-phenylbut-1(E)-ene	 Chemical Name 4-[3(R)-[2-Hydroxy-3-(hydroxyphenoxy)propylamino]butyl]benzamide	 Drug Name Brazilin Chemical Name 6a,11b-cis-6,6a,7,11b-Tetrahydrobenz[b]indeno[1,2-d]pyran-3,6a,9,10-tetraol

FIGURE 1 cont.

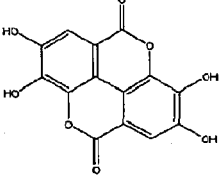
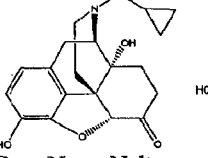
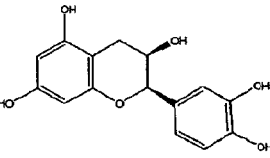
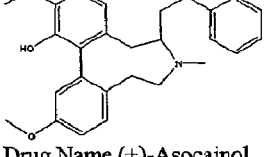
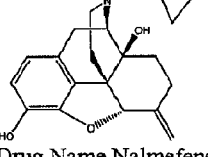
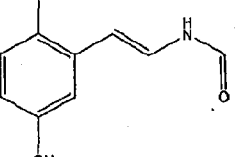
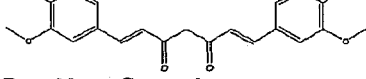
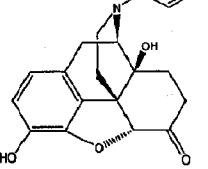
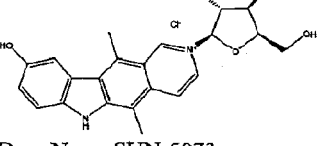
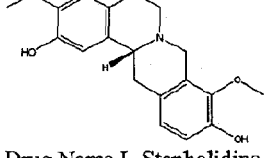
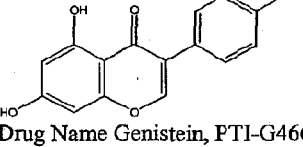
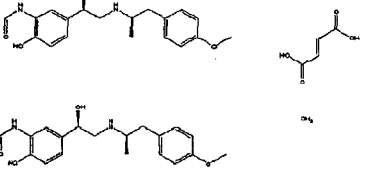
 Drug Name Ellagic acid Chemical Name 2,3,7,8-Tetrahydroxy-1-benzopyrano[5,4,3-cde]-1-benzopyran-5,10-dione	 Drug Name Naltrexone hydrochloride, PTI-901, EN-1639A, Vivitrol, Celupan, Antaxone, ReVia (treatment of alcoholism), Nemexin, Naltrel (Slow Release), Nalorex, Trexan, Vivitrex Chemical Name (-)-17-(Cyclopropylmethyl)-4,5alpha-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride	 Drug Name Epicatechin, (-)-Epicatechin Chemical Name 2(R)-cis-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3,5,7-triol
 Drug Name (±)-Asocainol Chemical Name (±)-2,12-Dimethoxy-7-methyl-6-(2-phenylethyl)-6,7,8,9-tetrahydro-5H-dibenzo[d,f]azonin-1-ol; (R,R;S,S)-2,12-Dimethoxy-1-hydroxy-7-methyl-6-(2-phenylethyl)-5,6,8,9-tetrahydro-7H-dibenzo[d,f]azonine	 Drug Name Nalmefene, Nalmetrene (former INN; USAN), JF-1, NIH-10365 (HCl), ORF-11676, Cessal, Incystene, Cervene, Arthene, Revex (HCl), Alcofene, Soberal Chemical Name N-(Cyclopropylmethyl)-4,5alpha-epoxy-6-methylenemorphinan-3,14beta-diol	 Drug Name Erbatatin, MH-435A Chemical Name (E)-2-(2-Formamidovinyl)-1,4-hydroquinone
 Drug Name Curcumin Chemical Name (E,E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione	 Drug Name Naloxone hydrochloride, Narcan Chemical Name (5alpha,14beta)-17-Allyl-3,14-dihydroxy-4,5-epoxymorphinan-6-one hydrochloride	 Drug Name SUN-5073 Chemical Name 2-beta-D-xylo-Furanosyl-9-hydroxyellipticinium chloride; 9-Hydroxy-5,11-dimethyl-2-beta-D-xylo-furanosyl-6H-pyrido[4,3-b]carbazol-2-ium chloride
 Drug Name L-Stepholidine Chemical Name (S)-5,8,13,13a-Tetrahydro-3,9-dimethoxy-6H-dibenzo[a,g]quinolizine-2,10-diol	 Drug Name Genistein, FTI-G4660, SIPI-9764-I Chemical Name 4',5,7-Trihydroxyisoflavone; 5,7-Dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one	 Drug Name Formoterol fumarate, Eformoterol fumarate, BD-40A (anhydrous), CGP-25827A (free base), YM-08316, Eolus, Broncoral, Oxeze Turbuhaler, Foradil Certihaler, Foradil Aerolizer, Atcock, Foradil, Oxis Turbuhaler Chemical Name (±)-N-[2-Hydroxy-5-

FIGURE 1 cont.

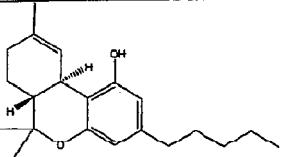
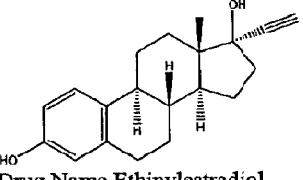
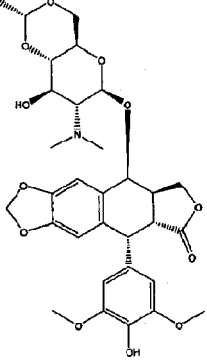
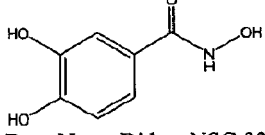
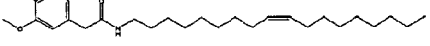
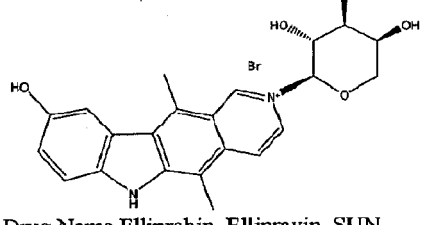
 Drug Name Dronabinol, THC, QCD-84924, DELTA9-THC, Tetranabinex, Deltanyne, Compassia, Marinol Chemical Name (6aR,10aR)-6,6,9-Trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-dibenzo[b,d]pyran-1-ol; DELTA9-Tetrahydrocannabinol	 Drug Name Ethinylestradiol, Ethinyloestradiol, Ethinyl estradiol, NX-201, NSC-10973, Lynoral, Progyonon Chemical Name 19-Nor-17alpha-pregna-1,3,5(10)-trien-20-yne-3,17-diol; 17alpha-Ethinylestradiol	[1(R*)-hydroxy-2-[1(R*)-methyl-2-(4-methoxyphenyl)ethylamino]ethyl]phenyl]formamide fumarate (2:1) monohydrate  Drug Name NK-611 Chemical Name 4-O-[2-Deoxy-2-(dimethylamino)-4:6-O-ethylidene-beta-D-glucopyranosyl]-4'-O-demethyl-1-epipodophyllotoxin; [5R-[5alpha,5abeta,8aa]pha,9beta(R*)]]-9-[[2-Deoxy-2-(dimethylamino)-4,6-O-ethylidene-beta-D-glucopyranosyl]oxy]-5-(4-hydroxy-3,5-dimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one; 2"-Deoxy-2"-[(dimethylamino)etoposide
 Drug Name Didox, NSC-324360 Chemical Name N,3,4-Trihydroxybenzamide; 3,4-Dihydroxybenzohydroxamic acid	 Drug Name NE-28345 Chemical Name (Z)-4-Hydroxy-3-methoxy-N-9-octadecenylphenylacetamide	 Drug Name Elliprabrin, Ellipravin, SUN-4599 Chemical Name 9-Hydroxy-5,11-dimethyl-2-(3alpha,4beta,5beta-trihydroxytetrahydropyran-2beta-yl)-6H-pyrido[4,3-b]carbazolium bromide; 9-Hydroxy-5,11-dimethyl-2-(alpha-L-arabinopyranosyl)-6H-pyrido[4,3-b]carbazolium bromide; 9-Hydroxy-2-(alpha-L-arabinopyranosyl)ellipticinium bromide

FIGURE 1 cont.

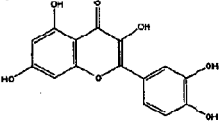
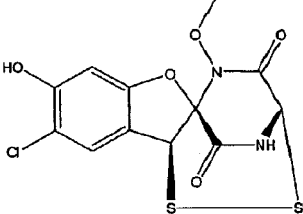
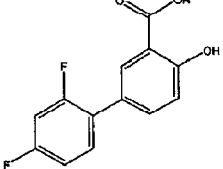
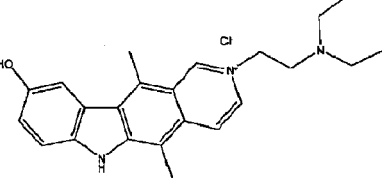
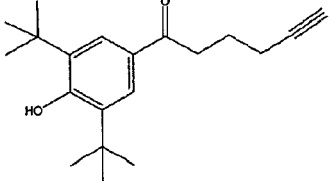
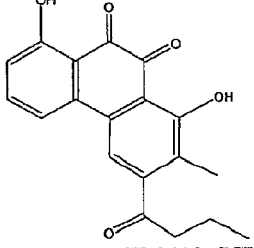
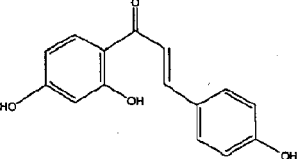
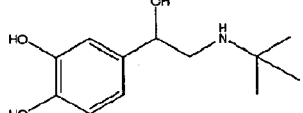
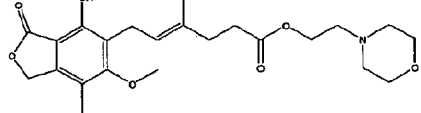
 Drug Name Quercetin Chemical Name 3,3',4',5,7-Pentahydroxyflavone; 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one	 Drug Name Aspirochlorine, A-30641 Chemical Name (1S,9S,12S)-6-chloro-5-hydroxy-15-methoxy-2-oxa-10,11-dithia-13,15-diazatetracyclo[10.2.2.0(1,9).0(3,8)]hexadeca-3,5,7-triene-14,16-dione; (3S,5aS,10bS)-9-Chloro-3,4-dihydro-8-hydroxy-11-methoxy-10bH-5a,3-(iminomethano)-5H-benzofuro[2,3-f]-1,2,4-dithiazepine-5,12-dione	 Drug Name Diflunisal, MK-647, Dolobid Chemical Name 2-Hydroxy-5-(2,4-difluorophenyl)benzoic acid; 2',4'-Difluoro-4-hydroxy-1,1'-biphenyl-3-carboxylic acid
 Drug Name Datelliptinium, Datelliptinium chloride, NSC-311152, DTL, SR-95156B (monoHCl) Chemical Name 2-[2-(Diethylamino)ethyl]-9-hydroxy-5,11-dimethyl-6H-pyrido[4,3-b]carbazolium chloride; 2-[2-(Diethylamino)ethyl]-9-hydroxyellipticininium chloride	 Drug Name Tebufelone, NE-11740 Chemical Name 1-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-5-hexyn-1-one; 3',5'-Di-tert-butyl-4'-hydroxy-5-hexynophenone; 2,6-Di-tert-butyl-4-(5-hexynoyl)phenol	 Drug Name SF-2418, SCH-68631 Chemical Name 3-Butanoyl-1,8-dihydroxy-2-methyl-9,10-dihydrophenanthrene-9,10-dione
 Drug Name Isoliquiritigenin Chemical Name 2',4,4'-Trihydroxychalcone; (E)-1-(2,4-Dihydroxyphenyl)-3-(4-hydroxyphenyl)-2-propen-1-one	 Drug Name Salbutamol, Albuterol, Chemical Name alpha1-[(tert-butylamino)methyl]-4-hydroxy-m-xylene-alpha,alpha'-diol	 Drug Name Mycophenolate mofetil, R-99, ME-MPA, RS-61443, RS-61443-190 (HCl), Munoloc, CellCept Chemical Name Mycophenolic acid 2-(4-morpholinyl)ethyl ester; 6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4(E)-hexenoic acid 2-(4-morpholinyl)ethyl ester

FIGURE 1 cont.

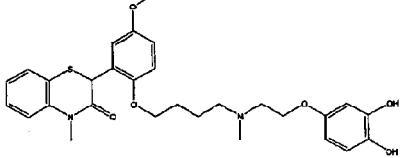
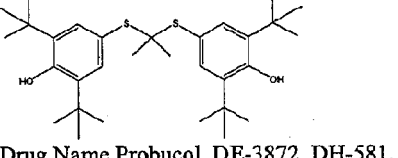
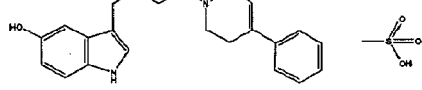
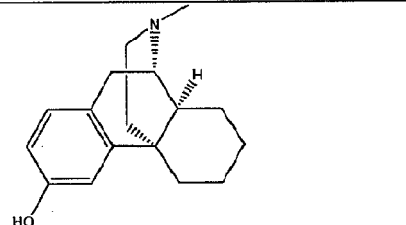
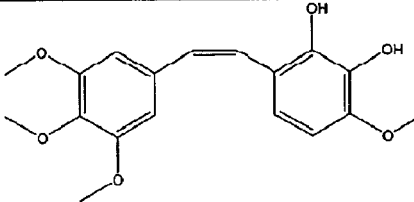
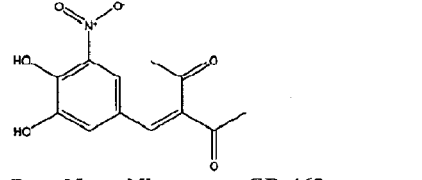
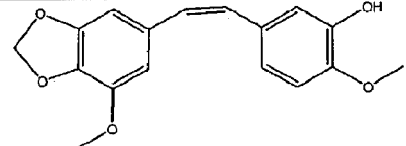
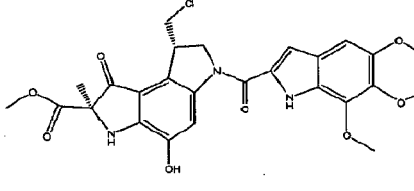
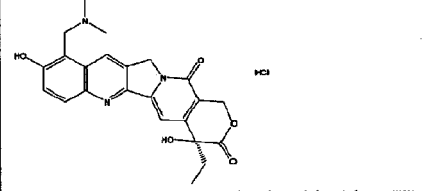
 Chemical Name 2-[2-[4-[N-[2-(3,4-Dimethoxyphenoxy)ethyl]-N-methylamino]butoxy]-5-methoxyphenyl]-4-methyl-3,4-dihydro-2H-1,4-benzothiazin-3-one	 Drug Name Probucol, DE-3872, DH-581, Lorelco, Sinlestal, Panavir (substained release), Lurselle Chemical Name 4,4'-[(Isopropylidenebis(thio))bis[2,6-bis(1,1-dimethylethyl)phenol]]bis(3,5-di-tert-butyl-4-hydroxyphenyl)mercaptole	 Drug Name Roxindole mesilate, EMD-49980, EMD-38362 (HCl), EMD-62100 (free base) Chemical Name 5-Hydroxy-3-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]-1H-indole methanesulfonate
 Drug Name Dextrorphan, DX, Ro-1-6794, Ro-01-6794/706 (HCl) Chemical Name D-3-Hydroxy-N-methylmorphinan; (9alpha,13alpha,14alpha)-3-Hydroxy-17-methylmorphinan	 Drug Name Combretastatin A-1, OXi-4500 Chemical Name 2,3-Dihydroxy-3',4,4',5'-tetramethoxy-(Z)-stilbene	 Drug Name Nitecapone, OR-462 Chemical Name 3-(3,4-Dihydroxy-5-nitrobenzylidene)-2,4-pentanedione
 Drug Name Combretastatin A-2 Chemical Name 3-Hydroxy-3',4-dimethoxy-4',5'-methylenedioxy-(Z)-stilbene	 Drug Name Duocarmycin C2, DC-89A2 Chemical Name 8(S)-(Chloromethyl)-5-hydroxy-2(R)-methyl-1-oxo-6-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-1,2,3,6,7,8-hexahydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylic acid methyl ester	 Drug Name Topotecan hydrochloride, NK-211, E-89/001, SK&F-S-104864-A, NSC-609699, Evotopin, Hycamtin Chemical Name (4S)-10-(Dimethylaminomethyl)-4-ethyl-4,9-dihydroxy-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14-dione monohydrochloride; (S)-9-Dimethylaminomethyl-10-hydroxycamptothecin monohydrochloride

FIGURE 1 cont.

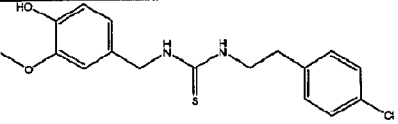
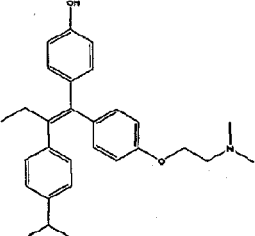
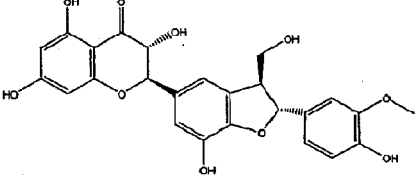
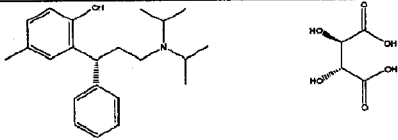
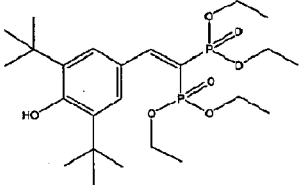
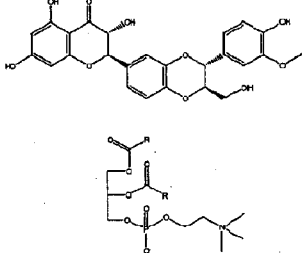
 Chemical Name N-[2-(4-Chlorophenyl)ethyl]-N'-(4-hydroxy-3-methoxybenzyl)thiourea	 Drug Name Miproxifene, DP-TAT-59 Chemical Name (Z)-4-[1-[4-[2-(Dimethylamino)ethoxy]phenyl]-2-[4-(1-methylethyl)phenyl]-1-butenyl]phenol; (Z)-2-[4-[1-(4-Hydroxyphenyl)-2-(4-isopropylphenyl)-1-butenyl]phenoxy]-N,N-dimethylethanamine; 4-Hydroxy-4'-isopropyltamoxifen	 Drug Name Silychristin Chemical Name 3beta,5,7-Trihydroxy-2alpha-[7-hydroxy-2beta-(4-hydroxy-3-methoxyphenyl)-3alpha-(hydroxymethyl)-2,3-dihydrobenzofuran-5-yl]-2,3-dihydro-4H-benzo[b]pyran-4-one
 Drug Name Tolterodine tartrate, Kabi-2234, PNU-200583E, Detrusitol SR, Detrusitol, Detrol LA, Detrol, Urotrol Chemical Name (+)-(R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropylamine L-tartrate (1:1)	 Drug Name SR-12813 Chemical Name 2-(3,5-Di-tert-butyl-4-hydroxyphenyl)ethylidene-1,1-diphosphonic acid tetraethyl ester; 3,5-Di-tert-butyl-4-hydroxystyrene-beta,beta-diphosphonic acid tetraethyl ester	 Drug Name Silipide, Silybin phosphatidylcholine complex, IdB-1016 Chemical Name [2R-[2alpha,3beta,6(2R*,3R*)]]-2-[2,3-Dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl]-2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyran-4-one phosphatidylcholine complex; [2R-[2alpha,3beta,6(2R*,3R*)]]-2-[2,3-Dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl]-2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyran-4-one mixture with soya phosphatidylcholines

FIGURE 1 cont.

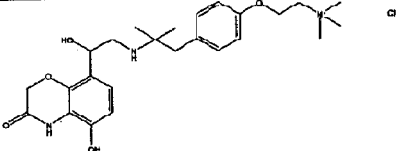
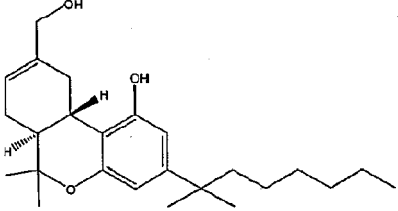
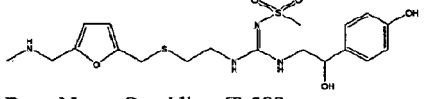
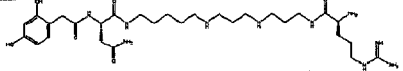
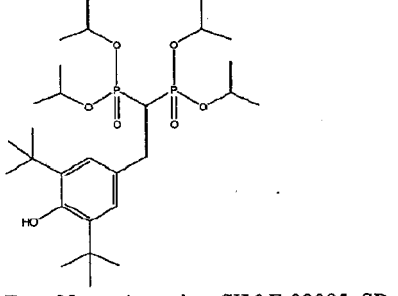
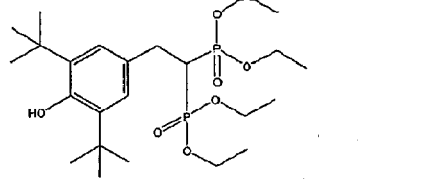
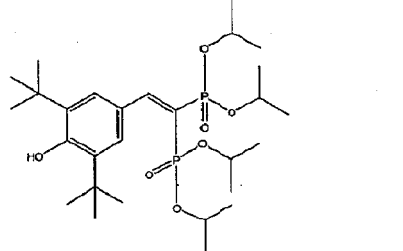
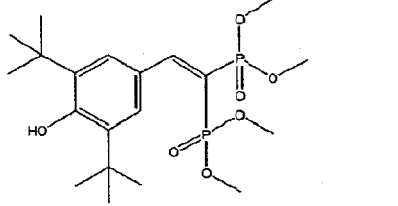
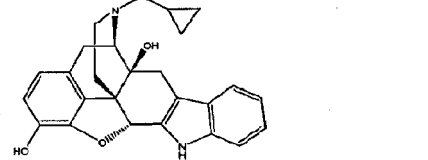
 Chemical Name 8-[2-[1,1-Dimethyl-2-[4-[2-(trimethylammonio)ethoxy]phenyl]ethylamino]-1-hydroxyethyl]-5-hydroxy-3,4-dihydro-2H-1,4-benzoxazin-3-one chloride	 Drug Name Dexanabinol, Dexanabinone, HU-211, PRS-211007 Chemical Name (+)-7-Hydroxy-DELTA6-tetrahydrocannabinol dimethylheptyl homolog; (+)-(S,S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(hydroxymethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran	 Drug Name Osutidine, T-593 Chemical Name (±)-1-[2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-2-(methylsulfonyl)-3-[2-[5-(methylaminomethyl)furan-2-ylmethylthio]ethyl]guanidine
 Drug Name Argiopine, Argiotoxin-636, ARG-636 Chemical Name N1-Arginyl-N13-(2,4-dihydroxyphenylacetyl-asparaginy)-4,8-diazatridecan-1,13-diamine; [S-(R*,R*)]-N1-(16,21-Diamino-21-imino-15-oxo-6,10,14,20-tetraazaheneicos-1-yl)-2-[[[(2,4-dihydroxyphenyl)acetyl]amino]butanedia mide	 Drug Name Apomine, SK&F-99085, SR-9223i, SR-45023A Chemical Name 2-(3,5-Di-tert-butyl-4-hydroxyphenyl)ethylidene-1,1-diphosphonic acid tetraisopropyl ester	 Chemical Name 2-(3,5-Di-tert-butyl-4-hydroxyphenyl)ethylidene-1,1-bis(2-oxo-1,3,2-dioxaphosphorinan)tetraethyl ester
 Chemical Name 2-(3,5-Di-tert-butyl-4-hydroxyphenyl)ethenylidene-1,1-diphosphonic acid tetraisopropyl ester	 Chemical Name 2-(3,5-Di-tert-butyl-4-hydroxyphenyl)ethenylidene-1,1-diphosphonic acid tetramethyl ester	 Drug Name Naltrindole, NTI Chemical Name 17-Cyclopropylmethyl-6,7-dehydro-4,5alpha-epoxy-3,14-dihydroxyindolo[2,3':6,7]morphinan; 15-(Cyclopropylmethyl)-1,5abeta-dihydroxy-4,5,5a,6,11,11bbeta-hexahydro-5beta,12cbeta-(iminoethano)-12cH-benz[3,4]isobenzofuro[1,7-ab]carbazole

FIGURE 1 cont.

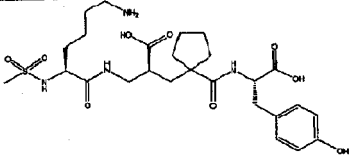
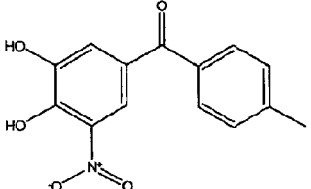
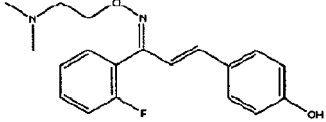
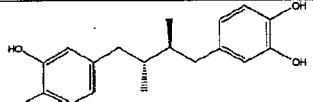
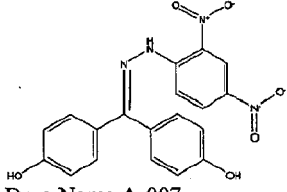
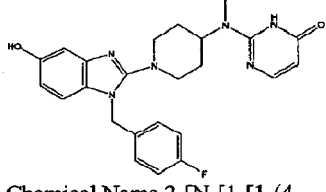
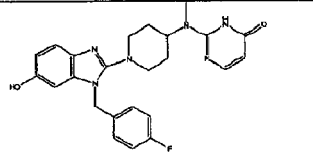
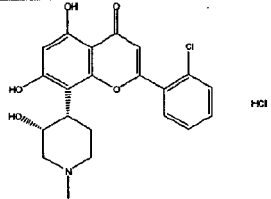
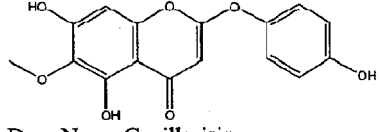
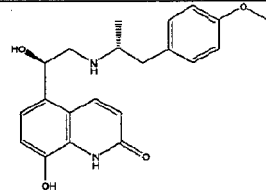
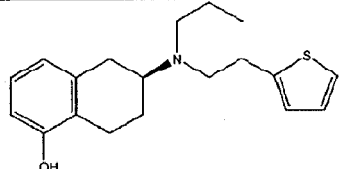
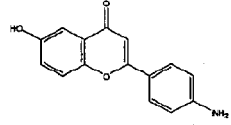
 Drug Name Sampatrilat, UK-81252 Chemical Name N-[1-[2(S)-Carboxy-3-[N2-(methanesulfonyl)-L-lysylamino]propyl]cyclopentyl-1-carbonyl]-L-tyrosine	 Drug Name Tolcapone, Ro-40-7592, Tasmar Chemical Name 3,4-Dihydroxy-4'-methyl-5-nitrobenzophenone	 Drug Name Eplivanserin, SR-46349 Chemical Name 1-(2-Fluorophenyl)-3-(4-hydroxyphenyl)-2(E)-propenone (Z)-O-[2-(dimethylamino)ethyl]oxime; 1(Z)-[2-(Dimethylamino)ethoxyimino]-1-(2-fluorophenyl)-3-(4-hydroxyphenyl)-2(E)-propene
 Drug Name Nordihydroguaiaretic acid, Masoprocol, NDGA, meso-NDGA, CHX-100, Actinex Chemical Name (R*,S*)-4,4'-(2,3-Dimethyl-1,4-butanediyl)-bis[1,2-benzenediol]; meso-4,4'-(2,3-Dimethyltetramethylene)dipyrocatechol; meso-Nordihydroguaiaretic acid	 Drug Name A-007 Chemical Name Bis(4-hydroxyphenyl)methanone (2,4-dinitrophenyl)hydrazone; 4,4'-Dihydrobenzophenone-2,4-dinitrophenylhydrazone	 Chemical Name 2-[N-[1-[1-(4-Fluorobenzyl)-5-hydroxy-1H-benzimidazol-2-yl]piperidin-4-yl]-N-methylamino]pyrimidin-4(3H)-one
 Chemical Name 2-[N-[1-[5-[1-(4-Fluorobenzyl)-6-hydroxy-1H-benzimidazol-2-yl]piperidin-4-yl]-N-methylamino]pyrimidin-4(3H)-one	 Drug Name Flavopiridol, Alvocidib hydrochloride, NSC-649890, L86-8275, MDL-107826A, HMR-1275, HL-275 Chemical Name (-)-cis-2-(2-Chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methylpiperidin-4-yl)-4H-1-benzopyran-4-one	 Drug Name Capillarisin Chemical Name 5,7-Dihydroxy-2-(4-hydroxyphenoxy)-6-methoxy-4H-benzopyran-4-one
 Drug Name Carmoterol hydrochloride, CHF-4226, TA-2005 Chemical Name [R-(R*,R*)]-8-Hydroxy-5-[1-hydroxy-2-[2-(4-methoxyphenyl)-1-methylethylamino]ethyl]-2(1H)-quinolinone hydrochloride	 Drug Name Rotigotine, SPM-936, N-0923, SPM-962 (patch), (-)-N-0437, N-0437 (undefined isomer), Neupro, Rotigotine CDS Chemical Name (-)-(S)-5-[N-Propyl-N-[2-(2-thienyl)ethyl]amino]-5,6,7,8-tetrahydro-1-naphthalenol;	 Chemical Name 2-(4-Aminophenyl)-6-hydroxy-4H-benzo[b]pyran-4-one; 4'-Amino-6-hydroxyflavone

FIGURE 1 cont.

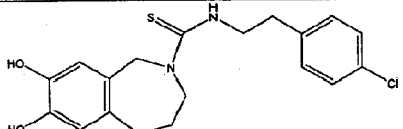
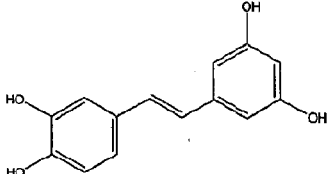
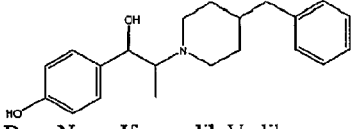
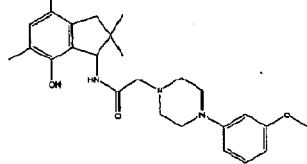
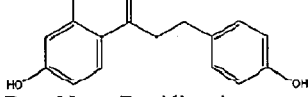
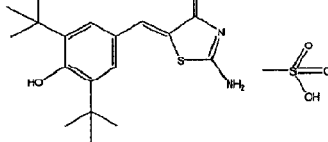
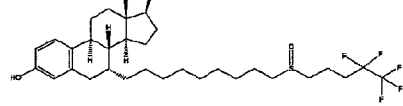
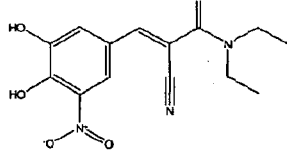
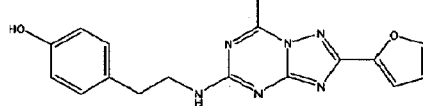
 Drug Name Capsazepine Chemical Name 2-[N-[2-(4-Chlorophenyl)ethyl]thiocarbamoyl]-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-2-benzazepine	(-)-(S)-2-[N-Propyl-N-[2-(2-thienyl)ethyl]amino]-5-hydroxy-1,2,3,4-tetrahydronaphthalene  Drug Name Piceatannol, Astringinine Chemical Name 3,3',4,5'-Tetrahydroxy-trans-stilbene	 Drug Name Ifenprodil, Vadilex Chemical Name 2-(4-Benzylpiperidin-1-yl)-1-(4-hydroxyphenyl)-1-propanol
 Drug Name OPC-14117 Chemical Name 7-Hydroxy-1-[2-[4-(3-methoxyphenyl)piperazin-1-yl]acetamido]-2,2,4,6-tetramethylindan-1-yl)-N-(7-Hydroxy-2,2,4,6-trimethylindan-1-yl)-2-[4-(3-methoxyphenyl)piperazin-1-yl]acetamide	 Drug Name Davidigenin Chemical Name 1-(2,4-Dihydroxyphenyl)-3-(4-hydroxyphenyl)-1-propanone	 Drug Name Darbufelone mesilate, CI-1004, PD-136095-0073 Chemical Name (Z)-2-Amino-5-(3,5-di-tert-butyl-4-hydroxybenzylidene)thiazol-4(5H)-one methanesulfonate
 Drug Name Fulvestrant, ZD-9238, ICI-182780, ZD-182780, ZM-182780, Faslodex Chemical Name 7alpha-[9-(4,4,5,5,5-Pentafluoropentylsulfinyl)nonyl]estra-1,3,5(10)-triene-3,17beta-diol	 Drug Name Entacapone, COM-998, OR-611, Comtess, Comtan Chemical Name (E)-2-Cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)propenamide; (E)-alpha-Cyano-N,N-diethyl-3,4-dihydroxy-5-nitrocinnamamide; (E)-2-Cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide	 Drug Name ZM-241385 Chemical Name 7-Amino-2-(2-furyl)-5-[2-(4-hydroxyphenyl)ethylamino][1,2,4]triazolo[1,5-a][1,3,5]triazine; 4-[2-[7-Amino-2-(2-furyl)[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-ylamino]ethyl]phenol

FIGURE 1 cont.

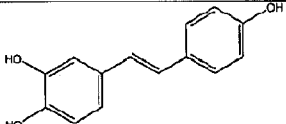
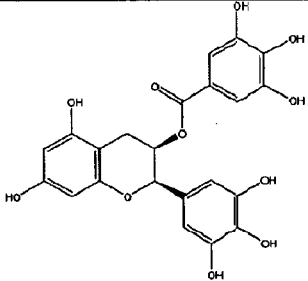
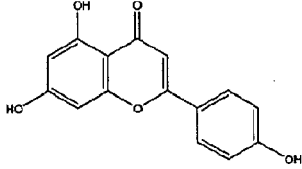
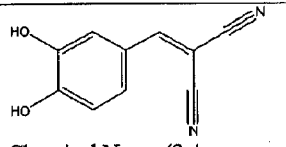
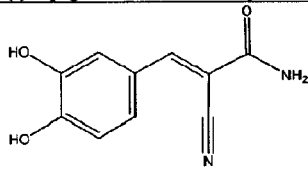
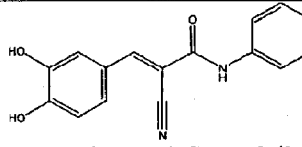
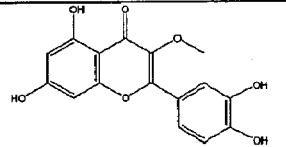
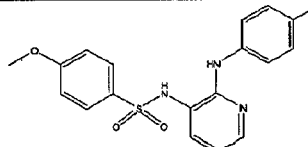
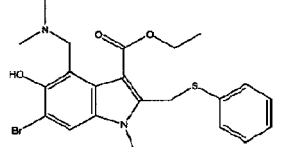
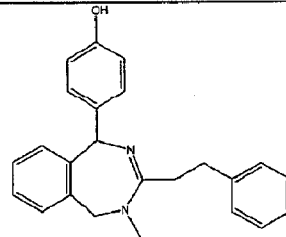
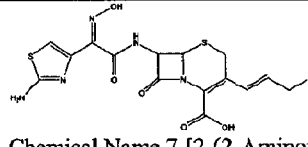
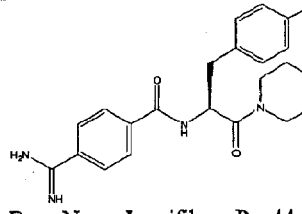
 Chemical Name (E)-3,4,4'-Trihydroxystilbene	 Drug Name (-)-Epigallocatechin gallate, (-)-EGCG, Teavigo Chemical Name (-)-3-O-Galloylepigallocatechin; 3,4,5-Trihydroxybenzoic acid (2R-cis)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl ester; (-)-Epigallocatechin 3-O-gallate	 Drug Name Apigenin Chemical Name 5,7-Dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one; 4',5,7-Trihydroxyflavone
 Chemical Name (3,4-Dihydroxybenzylidene)malononitrile	 Chemical Name 2-Cyano-3-(3,4-dihydroxyphenyl)propenamide	 Chemical Name 2-Cyano-3-(3,4-dihydroxyphenyl)-N-phenylpropenamide
 Drug Name Quercetin-3-O-methyl ether Chemical Name 3',4',5,7-Tetrahydroxy-3-methoxyflavone; 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-methoxy-4H-1-benzopyran-4-one	 Drug Name E-7010, ABT-751 Chemical Name N-[2-(4-Hydroxyphenylamino)-3-pyridyl]-4-methoxybenzenesulfonamide	 Drug Name Arbidol, Arbidol Chemical Name 6-Bromo-4-(dimethylaminomethyl)-5-hydroxy-1-methyl-2-(phenylthiomethyl)-1H-indole-3-carboxylic acid ethyl ester hydrochloride monohydrate
 Chemical Name 1-(4-Hydroxyphenyl)-4-methyl-3-(2-phenylethyl)-4,5-dihydro-1H-2,4-benzodiazepine	 Chemical Name 7-[2-(2-Aminothiazol-4-yl)-2(Z)-(hydroxyimino)acetamido]-3-[3-(3,4-dihydroxybenzoyloxy)-1(E)-propenyl]-3-cephem-4-carboxylic acid	 Drug Name Lamifiban, Ro-44-9883/023 (mono HCl salt), Ro-44-9883/000, Ro-44-9883, Lamstat Chemical Name 2-[1-[N-(4-Amidinobenzoyl)-L-tyrosyl]piperidin-4-yloxy]acetic acid

FIGURE 1 cont.

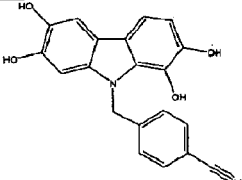
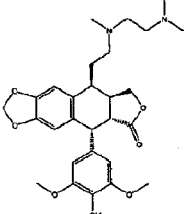
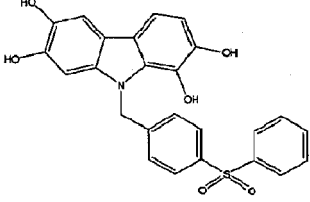
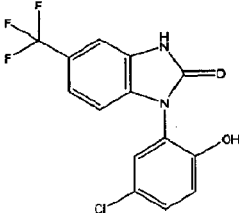
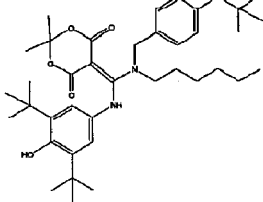
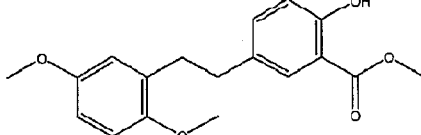
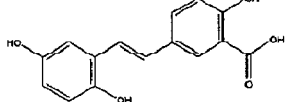
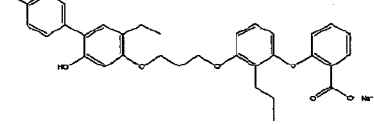
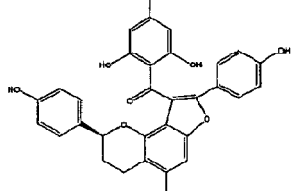
 Chemical Name 9-(4-Cyanobenzyl)-1,2,6,7-tetrahydrocarbazole	 Drug Name TOP-53 Chemical Name [5R-(5α,5β,8α,9β)]-9-[2-[N-[2-(Dimethylamino)ethyl]-N-methylamino]ethyl]-5-(4-hydroxy-3,5-dimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6-one dihydrochloride	 Chemical Name 1,2,6,7-Tetrahydroxy-9-[4-(phenylsulfonyl)benzyl]carbazole
 Drug Name NS-004 Chemical Name 1-(5-Chloro-2-hydroxyphenyl)-5-(trifluoromethyl)-2,3-dihydro-1H-benzimidazol-2-one	 Drug Name Eldacimibe, ACA-147, WAY-ACA-147, WAY-125147 Chemical Name 5-[(3,5-Di-tert-butyl-4-hydroxyphenylamino)[N-[4-(2,2-dimethylpropyl)benzyl]-N-hexylamino]methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione	 Drug Name LAP-977, SDZ-LAP-977, SDZ-281-977 Chemical Name 5-[2-(2,5-Dimethoxyphenyl)ethyl]-2-hydroxybenzoic acid methyl ester
 Chemical Name 5-[2(E)-(2,5-Dihydroxyphenyl)vinyl]-2-hydroxybenzoic acid	 Drug Name Etalocib sodium, LY-293111 Sodium, VML-295, LY-293111Na Chemical Name 2-[3-[3-(5-Ethyl-4'-fluoro-2-hydroxybiphenyl-4-yloxy)propoxy]-2-propylphenoxy]benzoic acid sodium salt	 Drug Name Daphnodorin A Chemical Name (2S)-5-Hydroxy-2,8-bis(4-hydroxyphenyl)-9-(2,4,6-trihydroxybenzoyl)-3,4-dihydro-2H-furo[2,3-h]-1-benzopyran

FIGURE 1 cont.

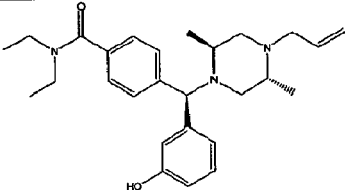
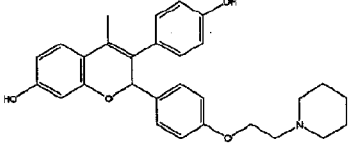
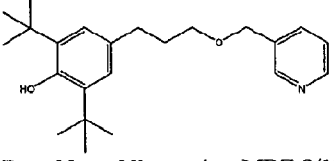
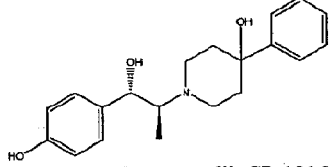
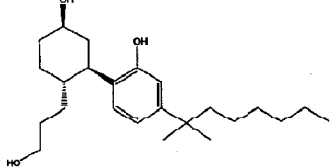
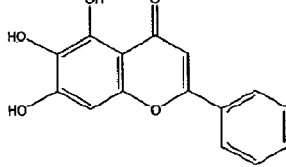
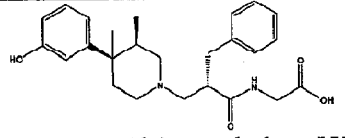
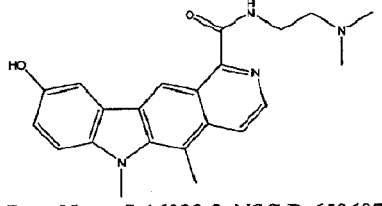
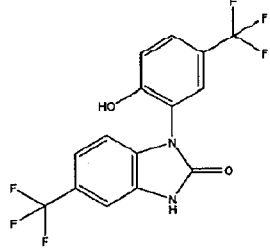
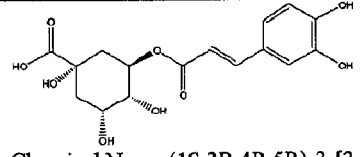
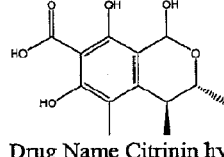
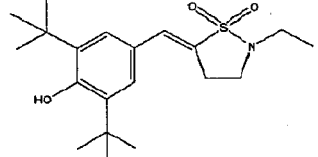
 Drug Name BW-373U86 Chemical Name (±)-4-[α(R*)-[4-Allyl-2(S*),5(R*)-dimethylpiperazin-1-yl]-3-hydroxybenzyl]-N,N-diethylbenzamide	 Drug Name EM-343 Chemical Name 3-(4-Hydroxyphenyl)-4-methyl-2-[4-(2-piperidinoethoxy)phenyl]-2H-1-benzopyran-7-ol	 Drug Name Nicanartine, MRZ-3/124 Chemical Name 2,6-Di-tert-butyl-4-[3-(3-pyridylmethoxy)propyl]phenol
 Drug Name Traxoprodil, CP-101606, CO-98113 (racemate) Chemical Name (+)-(1S,2S)-1-(4-Hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)propan-1-ol	 Drug Name CP-55940 Chemical Name 5-(1,1-Dimethylheptyl)-2-[(1R,2R,5R)-5-hydroxy-2-(3-hydroxypropyl)cyclohexyl]phenol	 Drug Name Baicalein Chemical Name 5,6,7-Trihydroxy-2-phenyl-4H-1-benzopyran-4-one
 Drug Name Alvimopan hydrate, LY-246736 dihydrate, ADL-8-2698, Entereg, Entratereg Chemical Name (+)-2-[2(S)-Benzyl-3-[4(R)-(3-hydroxyphenyl)-3(R),4-dimethylpiperidin-1-yl]propionamido]acetic acid dihydrate	 Drug Name S-16020-2, NSC-D-659687, NSC-659687 Chemical Name N-[2-(Dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide dihydrochloride	 Drug Name NS-1619 Chemical Name 1-[2-Hydroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-1,3-dihydro-2H-benzimidazol-2-one
 Chemical Name (1S,3R,4R,5R)-3-[3-(3,4-Dihydroxyphenyl)-2(E)-propenoyloxy]-1,4,5-trihydroxycyclohexane-1-carboxylic acid	 Drug Name Citrinin hydrate Chemical Name (1S,3R,4S)- and (1R,3R,4S)-1,6,8-Trihydroxy-3,4,5-trimethyl-3,4-dihydro-1H-benzo[c]pyran-7-carboxylic acid mixture	 Drug Name S-2474 Chemical Name (E)-5-(3,5-Di-tert-butyl-4-hydroxybenzylidene)-2-ethylisothiazolidine 1,1-dioxide

FIGURE 1 cont.

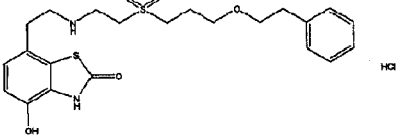
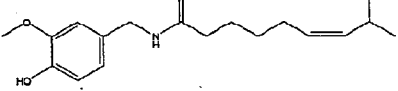
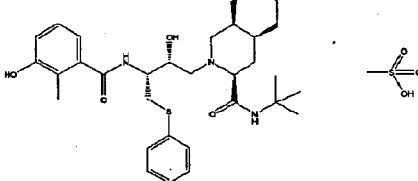
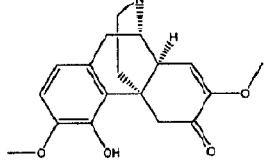
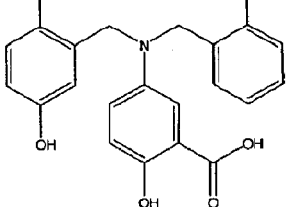
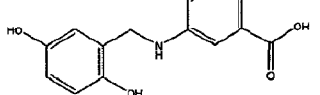
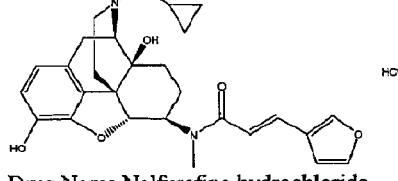
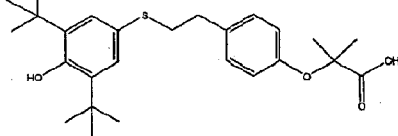
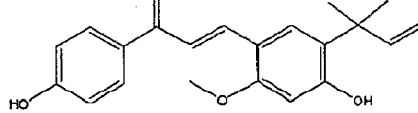
 Drug Name Sildenafil hydrochloride, FPL-68397, AR-C68397XX (free base), AR-C68397AA, Viozan Chemical Name 4-Hydroxy-7-[2-[2-[3-(2-phenylethoxy)propylsulfonyl]ethylamino]ethyl]benzothiazol-2(3H)-one hydrochloride	 Drug Name Capsaicin, (Z)-Capsaicin, Zucapsaicin, WL-1001, WL-1002 Chemical Name N-(4-Hydroxy-3-methoxybenzyl)-8-methyl-6(Z)-nonenamide	 Drug Name Nelfinavir mesilate, AG-1343, LY-312857, AG-1346 (free base), Viracept Chemical Name N-tert-Butyl-2-[2(R)-Hydroxy-3(R)-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylsulfanyl)butyl]decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxamide monomethanesulfonate
 Drug Name Sinomenine, Kukoline, Cucoline Chemical Name (9α,13α,14α)-4-Hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one	 Drug Name Lavendustin A Chemical Name 5-[N-(2,5-Dihydroxybenzyl)-N-(2-hydroxybenzyl)amino]-2-hydroxybenzoic acid	 Chemical Name 5-(2,5-Dihydroxybenzylamino)-2-hydroxybenzoic acid
 Drug Name Nalfurafine hydrochloride, AC-820, TRK-820 Chemical Name N-[17-(Cyclopropylmethyl)-4,5(R)-epoxy-3,14-dihydroymorphinan-5(R)-yl]-3-(3-furyl)-N-methyl-2(E)-propenamide hydrochloride; [4R-(4α,4β,7β,7β,12βS)]-N-[3-(Cyclopropylmethyl)-4a,9-dihydroxy-4,12-methano-2,3,4,4a,5,6,7,7a-octahydro-1H-benzofuro[3,2-e]isoquinolin-7-yl]-3-(3-furyl)-N-methyl-2(E)-propenamide hydrochloride	 Chemical Name 2-[4-[2-(3,5-Di-tert-butyl-4-hydroxyphenylsulfanyl)ethyl]phenoxy]-2-methylpropionic acid	 Drug Name Licochalcone A Chemical Name 3-[5-(1,1-Dimethyl-2-propenyl)-4-hydroxy-2-methoxyphenyl]-1-(4-hydroxyphenyl)-2(E)-propen-1-one

FIGURE 1 cont.

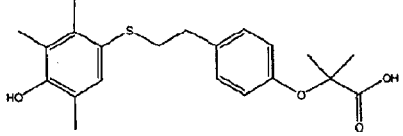
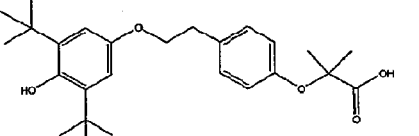
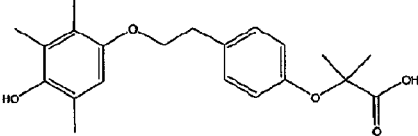
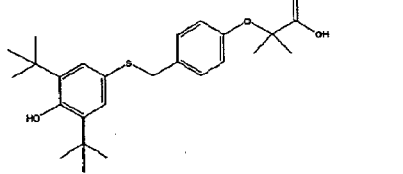
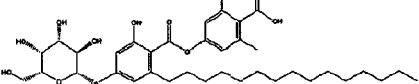
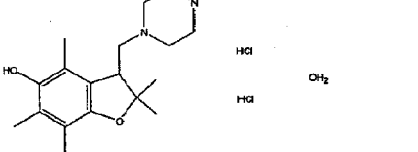
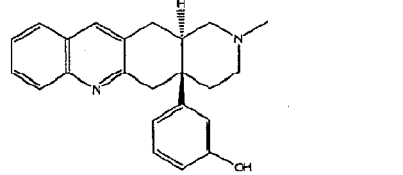
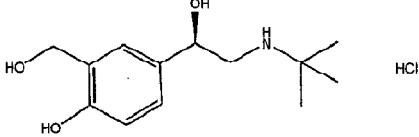
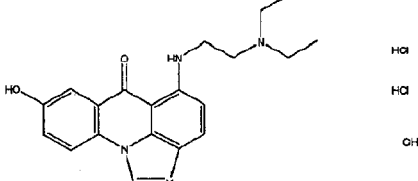
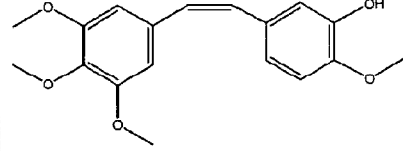
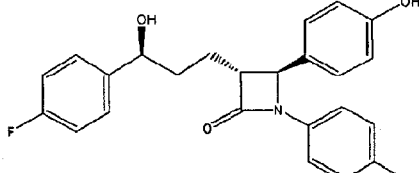
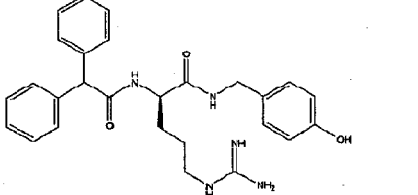
 Chemical Name 2-[4-[2-(4-Hydroxy-2,3,5-trimethylphenylsulfanyl)ethyl]phenoxy]-2-methylpropionic acid	 Chemical Name 2-[4-[2-(3,5-Di-tert-butyl-4-hydroxyphenoxy)ethyl]phenoxy]-2-methylpropionic acid	 Chemical Name 2-[4-[2-(4-Hydroxy-2,3,5-trimethylphenoxy)ethyl]phenoxy]-2-methylpropionic acid
 Chemical Name 2-[4-(3,5-Di-tert-butyl-4-hydroxyphenylsulfanyl)methylphenoxy]-2-methylpropionic acid	 Drug Name Aquastatin A Chemical Name 4-[4-(beta-D-Galactopyranosyloxy)-2-hydroxy-6-pentadecylbenzoyloxy]-2-hydroxy-6-methylbenzoic acid	 Drug Name MDL-75204DA ((-)-enantiomer), MDL-74180DA, MDL-74722DA ((+)-enantiomer) Chemical Name (±)-3-(4-Methyl-1-piperazinylmethyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-ol dihydrochloride monohydrate
 Drug Name TAN-67 Chemical Name (-)-(4aS*,12aR*)-4a-(3-Hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-b]acridine	 Drug Name (-)-Salbutamol hydrochloride, Levosalbutamol hydrochloride, (R)-Albuterol hydrochloride, Levalbuterol hydrochloride, Xopenex HFA (tartrate), Xopenex Chemical Name (-)-(R)-alpha-(tert-Butylaminomethyl)-4-hydroxy-m-xylene-alpha,alpha'-diol hydrochloride; (-)-(R)-alpha 1-(tert-Butylaminomethyl)-4-hydroxy-1,3-benzenedimethanol hydrochloride	 Drug Name Imidazoacridinone, Imidacrine, XLS-002, C-1311, Symadex Chemical Name 5-[2-(Diethylamino)ethylamino]-8-hydroxy-6H-imidazo[4,5,1-de]acridin-5-one dihydrochloride hydrate
 Drug Name Combretastatin A-4, ST-1986, CA-4 Chemical Name (Z)-1-(3,4,5-Trimethoxyphenyl)-2-(3-hydroxy-4-methoxyphenyl)ethene; (Z)-3'-Hydroxy-3,4,4',5'-tetramethoxy stilbene	 Drug Name Ezetimibe, MK-0653, SCH-58235, Ezetrol, Zetia Chemical Name 1-(4-Fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)azetidin-2-one	 Drug Name BIBP-3226 Chemical Name 2,2-Diphenylacetyl-D-arginine 4-hydroxybenzylamide; N2-(2,2-Diphenylacetyl)-N1-(4-hydroxybenzyl)-D-argininamide

FIGURE 1 cont.

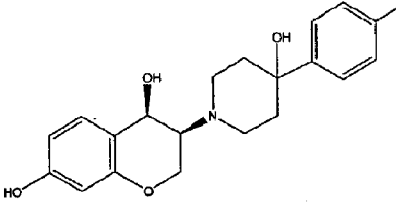
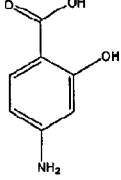
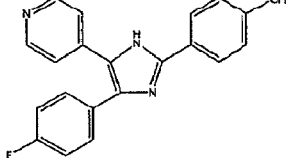
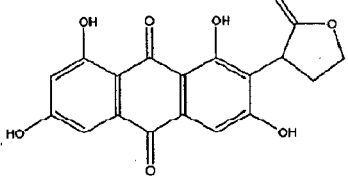
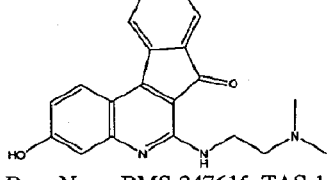
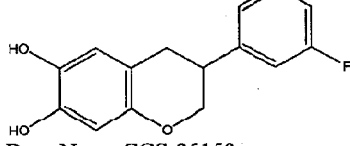
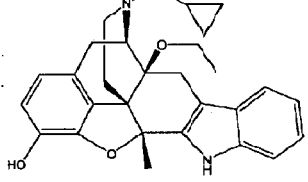
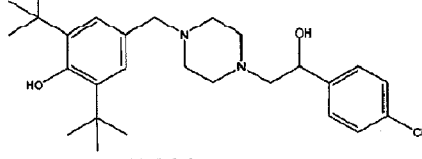
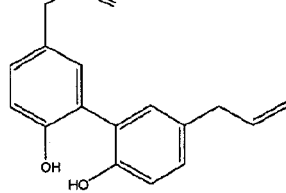
 Chemical Name cis-3-[4-(4-Fluorophenyl)-4-hydroxypiperidin-1-yl]-3,4-dihydro-2H-1-benzopyran-4,7-diol	 Drug Name 4-Aminosalicylic acid, 4-ASA, PASER, Salf-Pas, Pamisyl Chemical Name 4-Amino-2-hydroxybenzoic acid	 Drug Name SB-202190, FHPI Chemical Name 4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)imidazole
 Drug Name Paecilquinine A Chemical Name 1,3,6,8-Tetrahydroxy-2-(2-oxotetrahydrofuran-3-yl)-9,10-anthraquinone	 Drug Name BMS-247615, TAS-103 Chemical Name 6-[2-(Dimethylamino)ethylamino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one dihydrochloride	 Drug Name CGS-25159 Chemical Name 3-(3-Fluorophenyl)-3,4-dihydro-2H-1-benzopyran-6,7-diol
 Drug Name HS-378 Chemical Name 17-(Cyclopropylmethyl)-6,7-dichydro-4,5alpha-epoxy-14-ethoxy-3-hydroxy-5-methylindolo[2',3':6,7]morphinan hydrochloride	 Drug Name AM-36 Chemical Name 4-[4-[2-(4-Chlorophenyl)-2-hydroxyethyl]piperazin-1-ylmethyl]-2,6-bis(tert-butyl)phenol	 Drug Name Magnolol Chemical Name 5,5'-Bis(2-propenyl)biphenyl-2,2'-diol

FIGURE 1 cont.

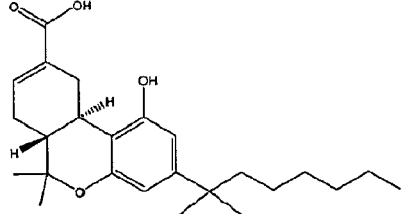
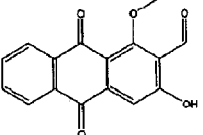
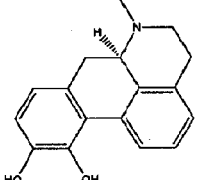
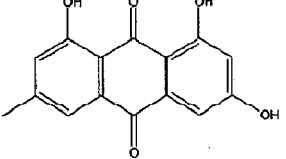
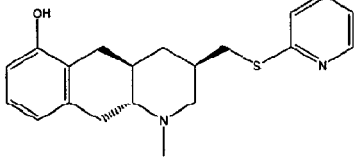
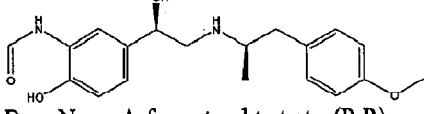
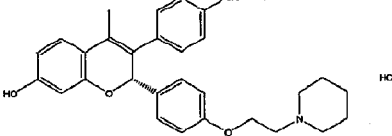
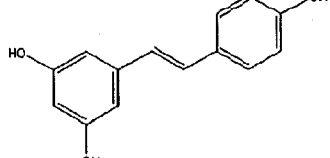
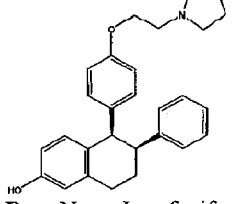
 Drug Name Ajulemic acid, CT-3, IP-751, DMH-THC-11-OIC Chemical Name 1',1'-Dimethylheptyl-DELTA8-tetrahydrocannabinol-11-oic acid; (6aR,10aR)-3-(1,1-Dimethylheptyl)-1-hydroxy-6,6-dimethyl-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran-9-carboxylic acid; (6aR,10aR)-3-(1,1-Dimethylheptyl)-1-hydroxy-6,6-dimethyl-6a,7,10,10a-tetrahydro-6H-benzo[c]chromene-9-carboxylic acid	 Drug Name Damunacantal, Damnacanthal Chemical Name 2-Formyl-3-hydroxy-1-methoxy-9,10-anthraquinone	 Drug Name Apomorphine hydrochloride, VR-040, VR-004, TAK-251, Apokyn, Spontain, Apokinon, Ixense, APO-go, Taluvian, Zydis apomorphine, Apofin, Uprima, Apodref, Britaject Chemical Name (+)-(R)-6-Methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline-10,11-diol hydrochloride hemihydrate
 Drug Name Emodin, Emodol Chemical Name 1,3,8-Trihydroxy-6-methyl-9,10-anthraquinone	 Drug Name GLC-756, SDZ-GLC-756 Chemical Name (-)-(3R,4aR,10aR)-6-Hydroxy-1-methyl-3-(2-pyridylsulfanylmethyl)-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline hydrochloride	 Drug Name Arformoterol tartrate, (R,R)-Formoterol tartrate Chemical Name (-)-N-[2-Hydroxy-5-[1(R)-hydroxy-2-[2-(4-methoxyphenyl)-1(R)-methylethylamino]ethyl]phenyl]formamide tartrate
 Drug Name Acolbifene hydrochloride, EM-652.HCl, SCH-57068.HCl, EM-01538 Chemical Name 3-(4-Hydroxyphenyl)-4-methyl-2(S)-[4-[2-(1-piperidinyloxy)phenyl]-2H-1-benzopyran-7-yl] hydrochloride	 Drug Name Resveratrol Chemical Name 3,4',5-Trihydroxy-trans-stilbene	 Drug Name Lasofoxifene tartrate, CP-336156, Oporia Chemical Name (-)-(5R,6S)-6-Phenyl-5-[4-[2-(1-pyrrolidinyloxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-yl](-)-D-tartrate salt

FIGURE 1 cont.

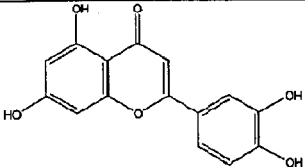
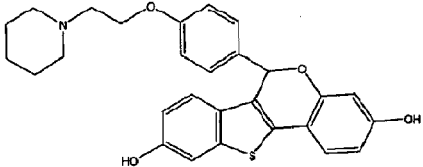
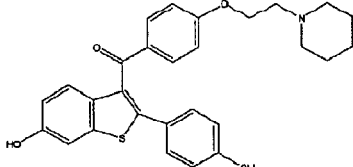
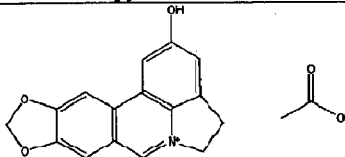
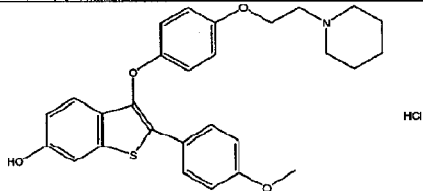
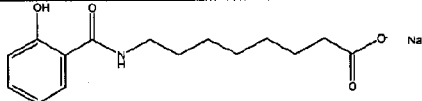
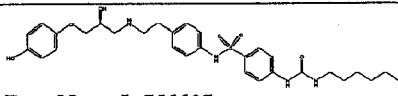
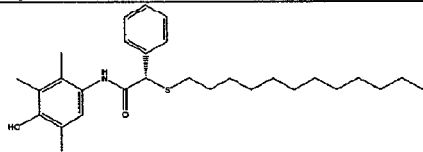
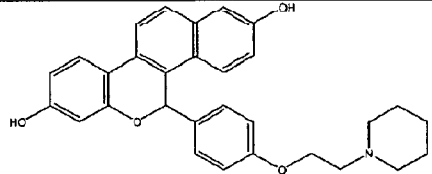
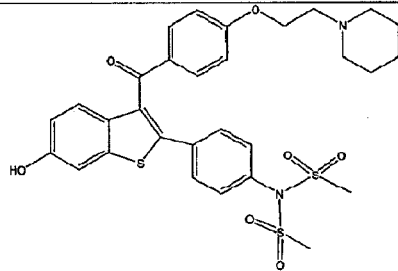
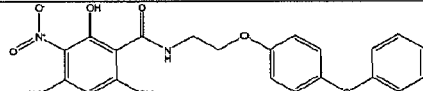
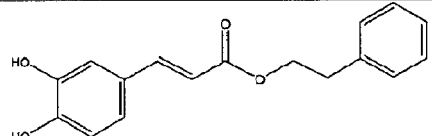
 Drug Name Luteolin Chemical Name 3',4',5,7-Tetrahydroxyflavone; 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one	 Drug Name LY-326391 Chemical Name 3,9-Dihydroxy-6-[4-[2-(1-piperidinyl)ethoxy]phenyl]-6H-[1]benzothieno[3,2-c][1]benzopyran	 Chemical Name [6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone
 Drug Name Ungerimine acetate, Ungerimine acetate, Lycobetaine acetate, AT-1840 Chemical Name 2-Hydroxy-4,5-dihydro[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridinium acetate	 Drug Name Arzoxifene hydrochloride, LY-353381.HCl, SERM 3 Chemical Name 2-(4-Methoxyphenyl)-3-[4-[2-(piperidin-1-yl)ethoxy]phenoxy]benzo[b]thiophen-6-ol hydrochloride	 Drug Name Salcaprozic acid sodium salt, SNAC, E414 (free acid), P414 Chemical Name 8-(2-Hydroxybenzamido)octanoic acid sodium salt
 Drug Name L-755507 Chemical Name 4-(3-Hexylureido)-N-[4-[2-[2(S)-hydroxy-3-(4-hydroxyphenoxy)propylamino]ethyl]phenyl]benzenesulfonamide	 Drug Name Eflucimibe, F-12511 Chemical Name 2-(S)-(Dodecylsulfanyl)-N-(4-hydroxy-2,3,5-trimethylphenyl)-2-phenylacetamide	 Drug Name LY-357489 Chemical Name 2,8-Dihydroxy-5-[4-[2-(1-piperidinyl)ethoxy]phenyl]-5H-benzo[b]naphtho[2,1-d]pyran
 Drug Name LY-329146 Chemical Name N-[4-[6-Hydroxy-3-[4-[2-(4-morpholinyl)ethoxy]benzoyl]-1-benzothien-2-yl]phenyl]-N-(methylsulfonyl)methanesulfonamide	 Drug Name RD2-4039 Chemical Name N-[2-(4-Phenoxyphenoxy)ethyl]-2,4,6-trihydroxy-3-nitrobenzamide	 Drug Name Caffeic acid phenethyl ester, CAPE Chemical Name 3,4-Dihydroxycinnamic acid 2-phenylethyl ester

FIGURE 1 cont.

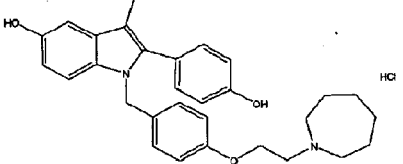
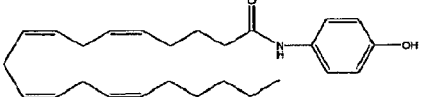
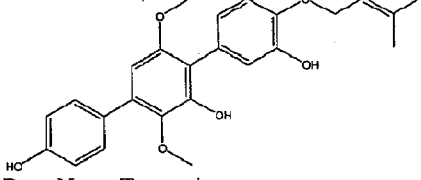
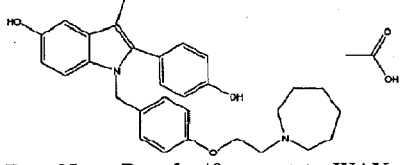
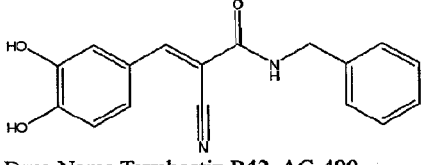
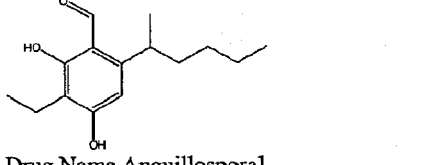
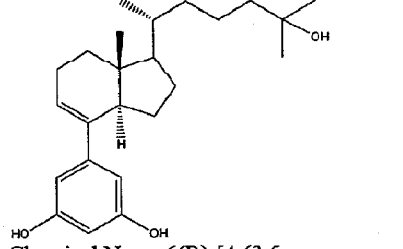
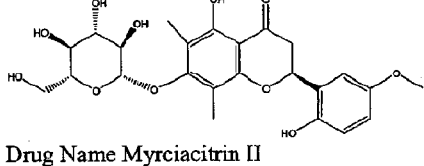
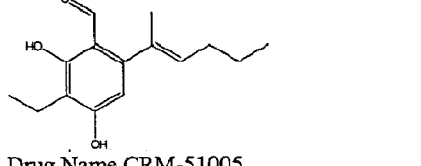
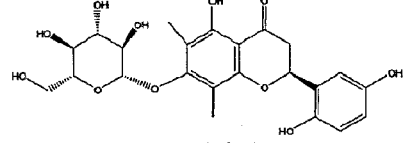
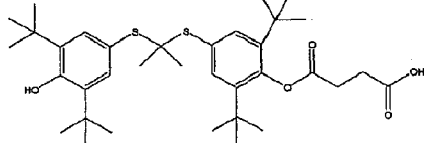
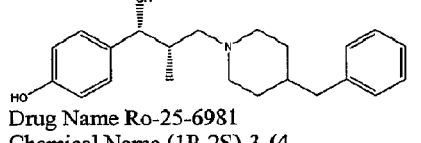
 Drug Name Bazedoxifene hydrochloride Chemical Name 2-(4-Hydroxyphenyl)-3-methyl-1-[4-[2-(perhydroazepin-1-yl)ethoxy]benzyl]-1H-indol-5-yl hydrochloride	 Drug Name AM-404 Chemical Name (all-Z)-N-(4-Hydroxyphenyl)-5,8,11,14-eicosatetraenamide	 Drug Name Terpenin Chemical Name 3',6'-Dimethoxy-4-(3-methyl-2-butenyloxy)-p-terphenyl-2',3,4"-triol
 Drug Name Bazedoxifene acetate, WAY-140424, TSE-424 Chemical Name 2-(4-Hydroxyphenyl)-3-methyl-1-[4-[2-(perhydroazepin-1-yl)ethoxy]benzyl]-1H-indol-5-yl acetate	 Drug Name Tyrphostin B42, AG-490 Chemical Name N-Benzyl-2-cyano-3-(3,4-dihydroxyphenyl)-2-propenamide	 Drug Name Anguillosporal Chemical Name (-)-3-Ethyl-2,4-dihydroxy-6-(1-methylpentyl)benzaldehyde
 Chemical Name 6(R)-[4-(3,5-Dihydroxyphenyl)-7a(R)-methyl-2,3,3a(R),6,7,7a-hexahydro-1H-inden-1-yl]-2-methyl-2-heptanol	 Drug Name Myrciacitrin II Chemical Name 5-Hydroxy-2(S)-(2-hydroxy-5-methoxyphenyl)-7-(beta-D-glucopyranosyloxy)-6,8-dimethyl-3,4-dihydro-2H-pyran-4-one	 Drug Name CRM-51005 Chemical Name (E)-3-Ethyl-2,4-dihydroxy-6-(1-methyl-1-pentenyl)benzaldehyde
 Drug Name Myrciacitrin I Chemical Name 2(S)-2-(2,5-Dihydroxyphenyl)-7-(beta-D-glucopyranosyloxy)-5-hydroxy-6,8-dimethyl-3,4-dihydro-2H-benzopyran-4-one	 Drug Name AGI-1067, AGZ-1067 Chemical Name Succinic acid 2,6-di-tert-butyl-4-[1-(3,5-di-tert-butyl-4-hydroxyphenylsulfanyloxy)-1-methylethylsulfanyloxy]phenyl monoester	 Drug Name Ro-25-6981 Chemical Name (1R,2S)-3-(4-Benzylpiperidin-1-yl)-1-(4-hydroxyphenyl)-2-methyl-1-propanol

FIGURE 1 cont.

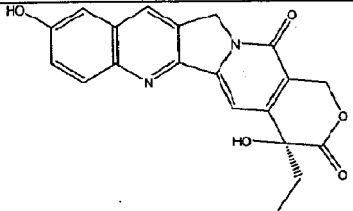
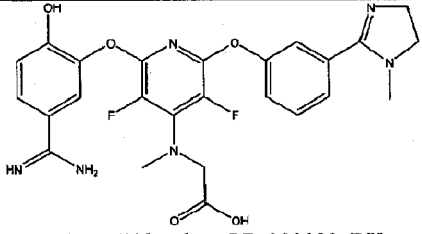
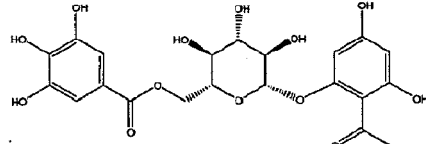
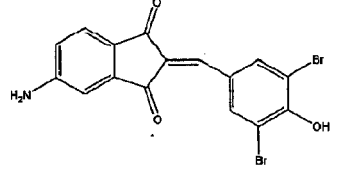
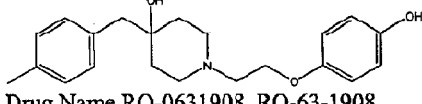
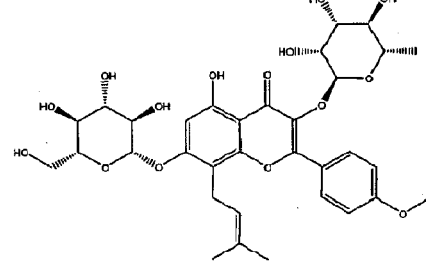
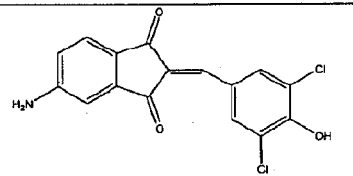
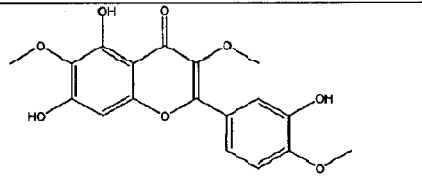
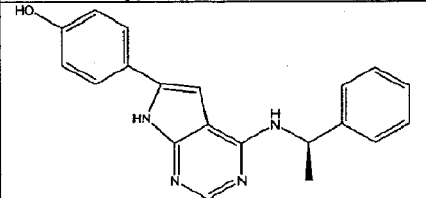
 Drug Name 10-Hydroxycamptothecin, 10-HCPT Chemical Name 4(S)-Ethyl-4,9-dihydroxy-3,4,12,14-tetrahydropyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14-dione	 Drug Name Fidexaban, PD-200022, BX-807834, ZK-807834, CI-1031, ZK-807191 (diHCl) Chemical Name N-[2-(5-Amidino-2-hydroxyphenoxy)-3,5-difluoro-6-[3-(1-methyl-4,5-dihydroimidazol-2-yl)phenoxy]pyridin-4-yl]-N-methylglycine	 Drug Name Myrciaphenone B Chemical Name 3,4,5-Trihydroxybenzoic acid [1-O-(2-acetyl-3,5-dihydroxyphenyl)-beta-D-glucopyranosyl-6-O-yl]ester
 Drug Name R-64777, RWJ-64777 Chemical Name 5-Amino-2(Z)-(3,5-dibromo-4-hydroxybenzylidene)indane-1,3-dione	 Drug Name RO-0631903, RO-63-1908 Chemical Name 1-[2-(4-Hydroxyphenoxy)ethyl]-4-(4-methylbenzyl)piperidin-4-ol	 Drug Name Icariin Chemical Name 3-(6-Deoxy-alpha-L-mannopyranosyloxy)-7-(beta-D-glucopyranosyloxy)-5-hydroxy-2-(4-methoxyphenyl)-8-(3-methyl-2-butenyl)-4H-1-benzopyran-4-one
 Drug Name RWJ-65012, R-65012 Chemical Name 5-Amino-2(Z)-(3,5-dichloro-4-hydroxybenzylidene)indane-1,3-dione	 Drug Name Centaureidin, NSC-106969 Chemical Name 5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-3,6-dimethoxy-4H-chromen-4-one	 Drug Name CGP-75166, PKI-166, PKI-75166 Chemical Name 4-[4-[1(R)-Phenylethylamino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenol

FIGURE 1 cont.

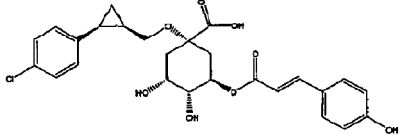
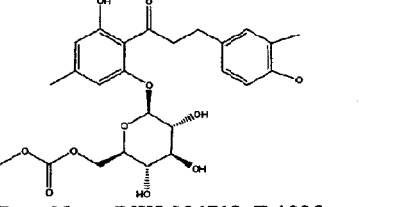
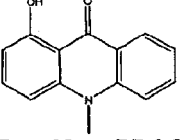
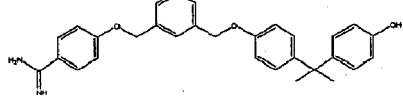
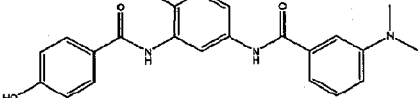
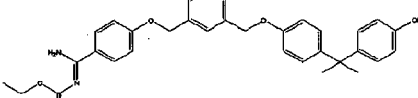
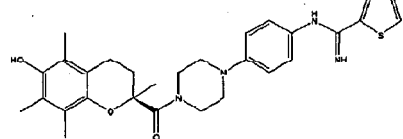
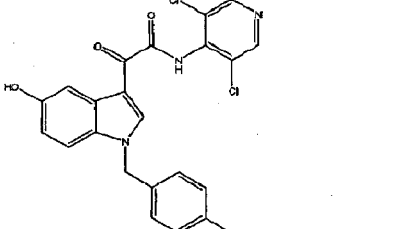
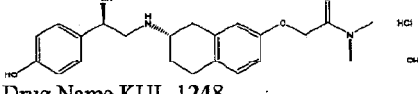
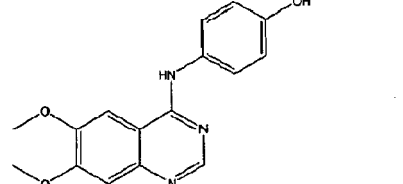
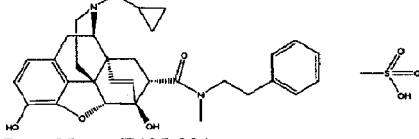
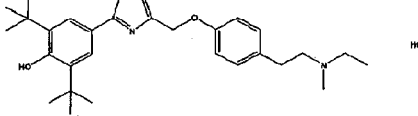
 Drug Name S-3483 Chemical Name (1S,3R,4R,5R)-1-[2(S)-(4-Chlorophenyl)-1(R)-cyclopropylmethoxy]-3,4-dihydroxy-5-[3-(4-hydroxyphenyl)-2(E)-propenoyloxy]cyclohexane-1-carboxylic acid	 Drug Name RWI-394718, T-1095 Chemical Name 3-(5-Benzofuranyl)-1-[2-hydroxy-6-[6-O-(methoxycarbonyl)-beta-D-glucopyranosyloxy]-4-methylphenyl]-1-propanone	 Drug Name RD6-5071 Chemical Name 1-Hydroxy-10-methyl-9(10H)-acridinone
 Drug Name BIIL-260 Chemical Name 4-[3-[4-[1-(4-Hydroxyphenyl)-1-methylethyl]phenoxy]methyl]benzyloxy]benzenecarboximidamide	 Drug Name ZM-336372 Chemical Name N-[5-[3-(Dimethylamino)benzamido]-2-methylphenyl]-4-hydroxybenzamide	 Drug Name Amelubant, BIIL-284 Chemical Name N-(Ethoxycarbonyl)-4-[3-[4-[1-(4-hydroxyphenyl)-1-methylethyl]phenoxy]methyl]benzyloxy]benzenecarboximidamide
 Drug Name BN-80933 Chemical Name N1-[4-[4-[6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-2(S)-ylcarbonyl]piperazin-1-yl]phenyl]thiophene-2-carboxamide	 Drug Name 842470, AWD-12-281, GW-842470 Chemical Name N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide	 Drug Name KUL-1248 Chemical Name (-)-2-[7(S)-[2(R)-Hydroxy-2-(4-hydroxyphenyl)ethylamino]-5,6,7,8-tetrahydro-2-naphthyl]oxy]-N,N-dimethylacetamide hydrochloride monohydrate
 Drug Name Janex-1, HI-P131, DDE-9501, WHI-P131 Chemical Name 4-(4-Hydroxyphenylamino)-6,7-dimethoxyquinazoline; 4-(6,7-dimethoxyquinazolin-4-ylamino)phenol	 Drug Name TAN-821 Chemical Name 17-(Cyclopropylmethyl)-4,5alpha-epoxy-6alpha,14alpha-etheno-3,6beta-dihydroxy-N-methyl-N-(2-phenylethyl)morphinan-7alpha-carboxamide methanesulfonate	 Drug Name LY-382924 Chemical Name 2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-4-[4-[2-(N-ethyl-N-methylamino)ethyl]phenoxy]methyl]oxazole hydrochloride; 2,6-Di-tert-butyl-4-[4-[4-[2-(N-ethyl-N-methylamino)ethyl]phenoxy]methyl]oxazol-2-yl]phenol hydrochloride

FIGURE 1 cont.

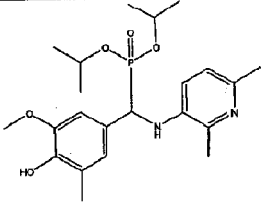
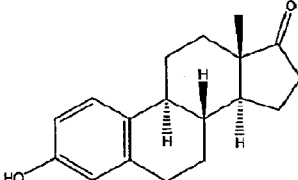
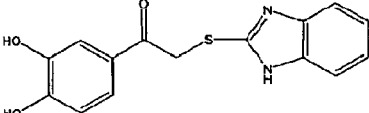
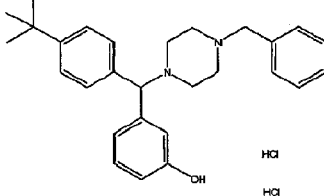
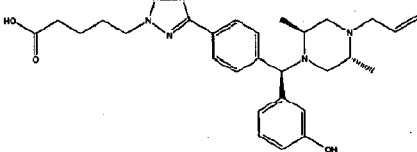
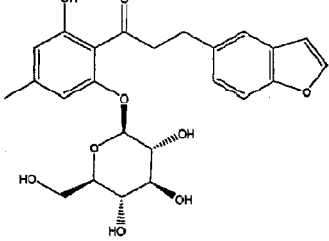
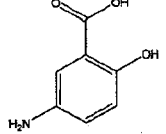
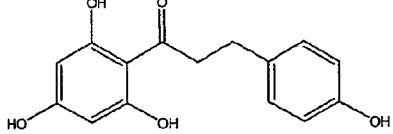
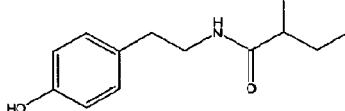
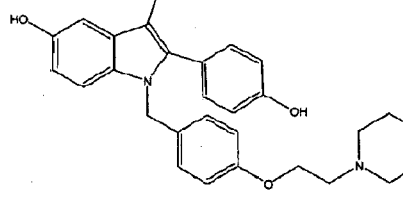
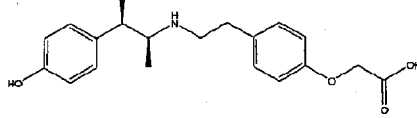
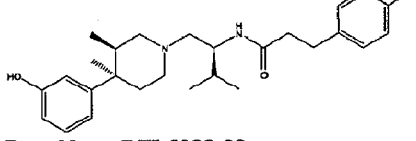
 Drug Name SR-74829i, SB-25314 Chemical Name 1-(2,6-Dimethylpyridin-3-ylamino)-1-(4-hydroxy-3-methoxy-5-methylphenyl)methylphosphonic acid diisopropyl ester	 Drug Name Estrone, Theelin Chemical Name 3-Hydroxyestra-1,3,5(10)-triene-17-one	 Drug Name NNC-92-1687 Chemical Name 2-(1H-Benzimidazol-2-ylsulfanyl)-1-(3,4-dihydroxyphenyl)-1-ethanone
 Drug Name SL-3111 Chemical Name 4-Benzyl-1-(4-tert-butyl-3'-hydroxybenzhydryl)piperazine dihydrochloride	 Drug Name UK-321130 Chemical Name (+)-5-[5-[4-[1(R)-[(2S,5R)-4-Allyl-2,5-dimethylpiperazin-1-yl]-1-(3-hydroxyphenyl)methyl]phenyl]-2H-tetrazol-2-yl]pentanoic acid	 Drug Name T-1095A, T-0115 Chemical Name 3-(Benzofuran-5-yl)-2'-(beta-D-glucopyranosyloxy)-6'-hydroxy-4'-methylpropionophenone
 Drug Name 5-Aminosalicylic acid, Mesalazine, Mesalamine, Z-206, SPD-476, SPD-480, 5-ASA, Mesavance, Asacol, Canasa, Rowasa, Salofalk, Pentasa, Mesalazine MMX Chemical Name 5-Amino-2-hydroxybenzoic acid	 Drug Name Phloretin Chemical Name 3-(4-Hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)-1-propanone	 Drug Name YUA-001 Chemical Name N-[2-(4-Hydroxyphenyl)ethyl]-2-methylbutyramide
 Drug Name Pipendoxifene, ERA-923 Chemical Name 2-(4-Hydroxyphenyl)-3-methyl-1-[4-[2-(1-piperidinyl)ethoxy]benzyl]-1H-indol-5-ol	 Drug Name KUL-7211 Chemical Name (-)-2-[4-[2-[2(R)-Hydroxy-2-(4-hydroxyphenyl)-1(S)-methylethylamino]ethyl]phenoxy]acetic acid	 Drug Name RTI-5989-29 Chemical Name 3-(4-Hydroxyphenyl)-N-[1(S)-[4(R)-(3-hydroxyphenyl)-3(R),4-dimethylpiperidin-1-ylmethyl]-2-methylpropyl]propionamide

FIGURE 1 cont.

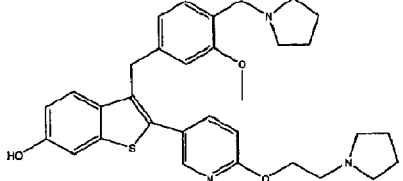
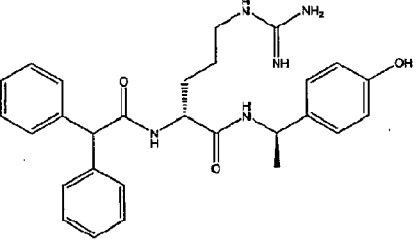
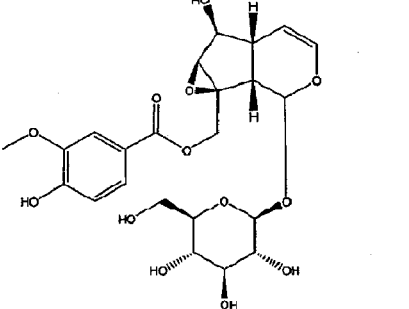
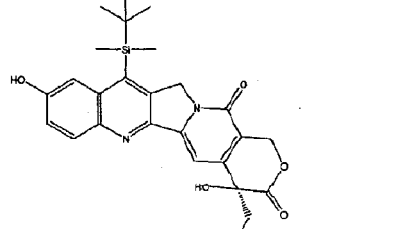
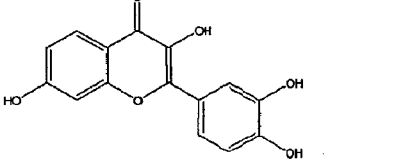
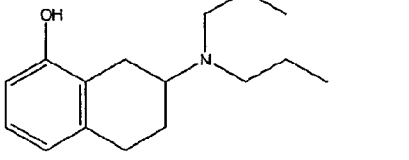
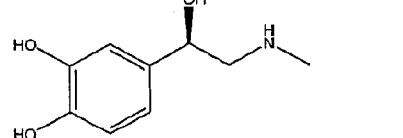
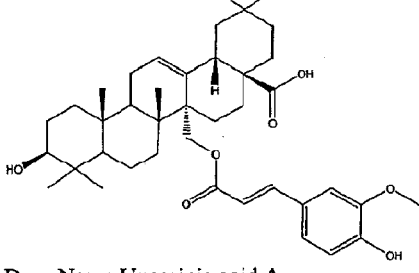
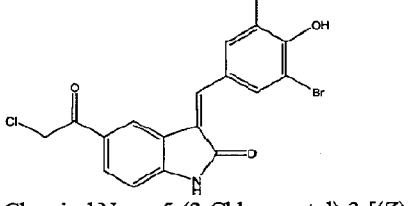
 Chemical Name 3-[3-Methoxy-4-(1-pyrrolidinylmethyl)benzyl]-2-[6-[2-(1-pyrrolidinyl)ethoxy]-3-pyridinyl]benzothiophen-6-ol	 Drug Name AR-H040922, H-409/22 Chemical Name Nalpa-(2,2-Diphenylacetyl)-N1-[1(R)-(4-hydroxyphenyl)ethyl]-D-argininamide	 Drug Name Kutkoside Chemical Name (1aS,2S,2aR,6S,6aS,6bS)-2-Hydroxy-6b-(4-hydroxy-3-methoxybenzoyloxymethyl)-2,2a,6,6a-tetrahydrooxireno[4,5]cyclopenta[1,2-c]pyran-6-yl beta-D-glucopyranoside
 Drug Name DB-67, NSC-708298 Chemical Name (20S)-7-(tert-Butyldimethylsilyl)-10-hydroxycamptothecin; 11-(tert-Butyldimethylsilyl)-4(S)-ethyl-4,9-dihydroxy-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14-dione	 Drug Name Fisetin Chemical Name 3,3',4',7-Tetrahydroxyflavone; 2-(3,4-Dihydroxyphenyl)-3,7-dihydroxy-4H-1-benzopyran-4-one	 Drug Name 8-OH-DPAT Chemical Name 7-(Di-N-propylamino)-5,6,7,8-tetrahydro-1-naphthalenol; 8-Hydroxy-2-(di-N-propylamino)tetralin
 Drug Name Epinephrine, Adrenaline, Twinject, EpiPen Chemical Name (-)-4-[1(R)-Hydroxy-2-(methylamino)ethyl]-1,2-benzenediol	 Drug Name Uncarinic acid A Chemical Name 3beta-Hydroxy-27-[3-(4-hydroxy-3-methoxyphenyl)-2(E)-propenoyloxy]olean-12-en-28-oic acid	 Chemical Name 5-(2-Chloroacetyl)-3-[(Z)-3,5-dibromo-4-hydroxybenzylidene]-2,3-dihydro-1H-indol-2-one

FIGURE 1 cont.

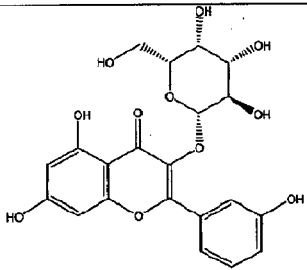
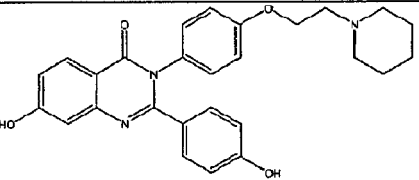
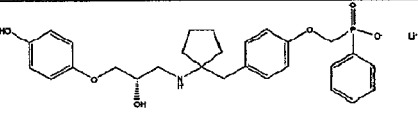
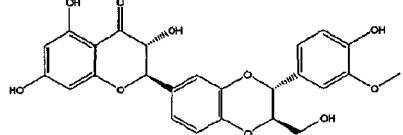
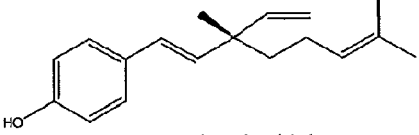
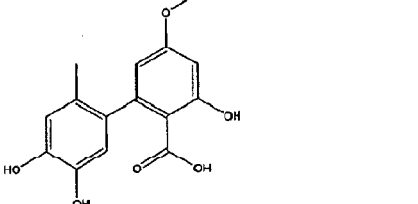
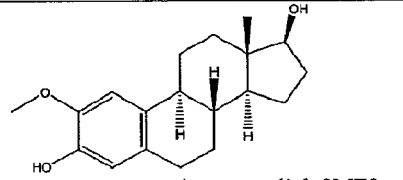
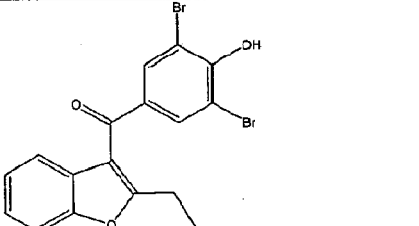
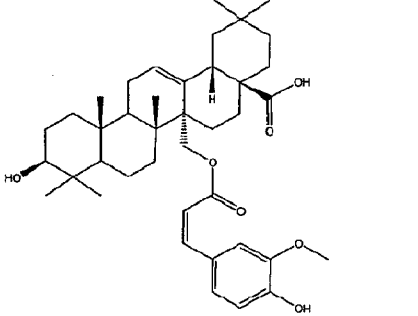
 Drug Name Hyperoside, Quercetin-3-O-beta-D-galactopyranoside, Quercetin 3-galactoside, Hyperin Chemical Name 3,3',4',5,7-Pentahydroxyflavone 3-O-beta-D-galactopyranoside; 2-(3,4-dihydroxyphenyl)-5,7-Dihydroxy-4-oxo-4H-1-benzopyran-3-yl beta-D-galactopyranoside	 Chemical Name 7-Hydroxy-2-(4-hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenyl]-4(3H)-quinazolinone	 Drug Name SB-251023 Chemical Name 4-[4-[2(S)-Hydroxy-3-[3-(4-hydroxyphenoxy)propylamino]cyclopentyl methyl]phenoxy methyl](phenyl)phosphonic acid lithium salt
 Drug Name Silibinin, Silymarin I, Silybin Chemical Name (+)-(2R,3R)-3,5,7-Trihydroxy-2-[2(R)-(hydroxymethyl)-3(R)-(4-hydroxy-3-methoxyphenyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2,3-dihydro-4H-1-benzopyran-4-one	 Drug Name Drupanol, Bakuchiol Chemical Name (+)-4-[3(S),7-Dimethyl-3-vinylocta-1(E),6-dienyl]phenol	 Drug Name Alutenusin, Alutenusin Chemical Name 2',4',5'-Trihydroxy-5-methoxy-2'-methylbiphenyl-2-carboxylic acid
 Drug Name 2-Methoxyestradiol, 2ME2, NSC-659853, 2-ME, Panzem NCD, PulmoLAR, Panzem Chemical Name 2-Methoxyestra-1,3,5(10)-triene-3,17beta-diol	 Drug Name Benzbromarone, Benzbromaron, MJ-10061, L-2214, Narcaricin, Desuric Chemical Name 1-(3,5-Dibromo-4-hydroxyphenyl)-1-(2-ethyl-1-benzofuran-3-yl)methanone	 Drug Name Uncarinic acid B Chemical Name 3beta-Hydroxy-27-[3-(4-hydroxy-3-methoxyphenyl)-2(Z)-propenyloxy]olean-12-en-28-oic acid

FIGURE 1 cont.

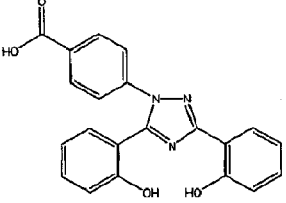
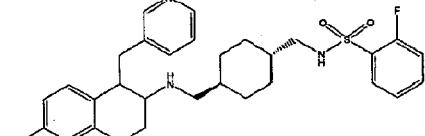
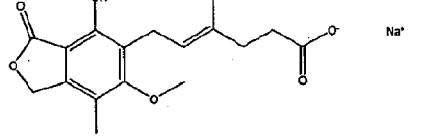
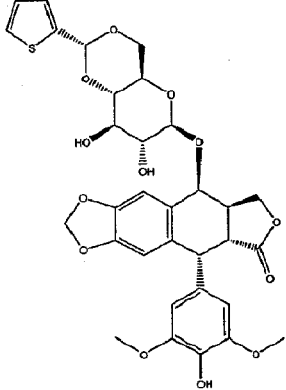
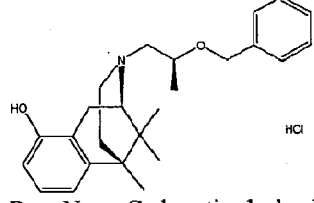
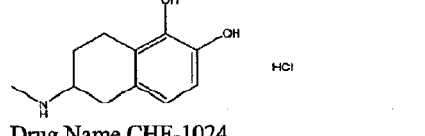
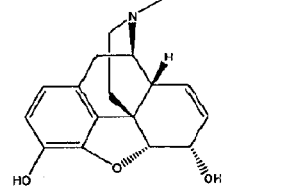
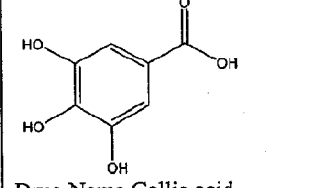
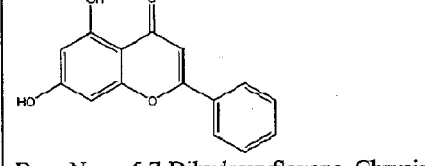
 Drug Name Deferasirox, ICL-670A, CGP-72670, ICL-670, Exjade Chemical Name 4-[3,5-Bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]benzoic acid	 Chemical Name trans-2-Fluoro-N-[trans-4-[6-hydroxy-1-(3-pyridinylmethyl)-1,2,3,4-tetrahydronaphthalen-2-ylaminomethyl]cyclohexylmethyl]benzenesulfonamide	 Drug Name Mycophenolate sodium, Mycophenolic acid sodium salt, ERL-080, ERL-080A, Myfortic Chemical Name 6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-5-isobenzofuranyl)-4-methyl-4(E)-hexenoic acid monosodium salt
 Drug Name Teniposide, VM-26, Vumon Chemical Name [5R-[5alpha,5abeta,8aalpha,9beta(R*)]]-9-[4,6-O-(2-Thienylmethylene)-beta-D-glucopyranosyloxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one; 4'-Demethylepipodophyllotoxin 9-[4,6-O-(2-Thienylmethylene)-beta-D-glucopyranoside]	 Drug Name Crobenetine hydrochloride, BIII-890-CL Chemical Name (2R,6S)-3-[2(S)-Benzyloxypropyl]-6,11,11-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-10-ol hydrochloride	 Drug Name CHF-1024 Chemical Name (±)-6-(Methylamino)-5,6,7,8-tetrahydronaphthalene-1,2-diol hydrochloride
 Drug Name Morphine hydrochloride, MH-15E, TAK-453-SR, MH-200, AN-982, Anpec, Opso Chemical Name 7,8-Didehydro-4,5alpha-epoxy-17-methylmorphinan-3,6alpha-diol hydrochloride	 Drug Name Gallic acid Chemical Name 3,4,5-Trihydroxybenzoic acid	 Drug Name 5,7-Dihydroxyflavone, Chrysin, NSC-407436 Chemical Name 5,7-Dihydroxy-2-phenyl-4H-1-benzopyran-4-one

FIGURE 1 cont.

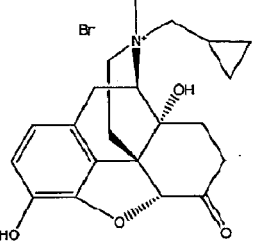
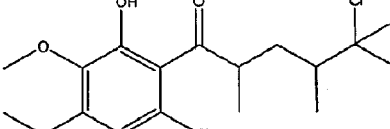
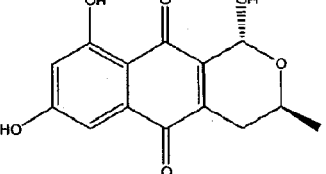
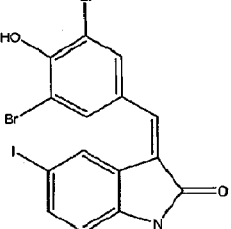
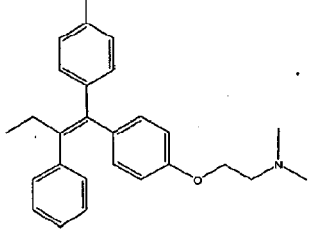
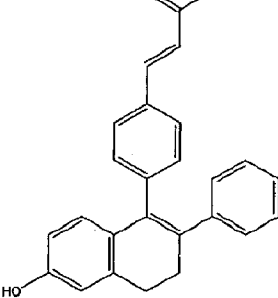
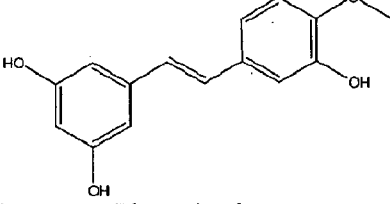
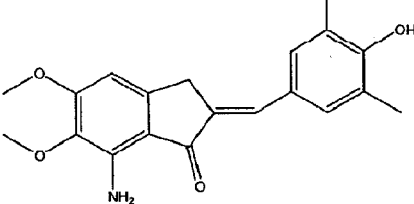
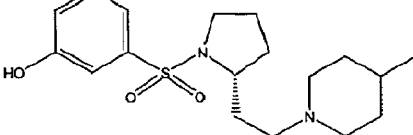
 Drug Name Methylnaltrexone bromide, MNTX-302, MNTX, MRZ-2663BR Chemical Name 17-(Cyclopropylmethyl)- 4,5alpha-epoxy-3,14-dihydroxy-17- methyl-6-oxomorphinanum bromide; N-Methylnaltrexone bromide	 Drug Name WF-16675 A2 Chemical Name 5-Chloro-1-(2,6- dihydroxy-3,4-dimethoxyphenyl)-2,4,5- trimethylhexan-1-one	 Drug Name (-)-Thysanone Chemical Name (1R,3S)-1,7,9-Trihydroxy- 3-methyl-3,4-dihydro-1H-naphtho[2,3- c]pyran-5,10-dione
 Drug Name GW-5074 Chemical Name 3-(3,5-Dibromo-4- hydroxybenzylidene)-5-iodo-2,3-dihydro- 1H-indol-2-one	 Drug Name (Z)-4-Hydroxytamoxifen, cis-4- Hydroxytamoxifen, 4-OHT, TamoGel Chemical Name 1-[4-(2- Dimethylaminoethoxy)phenyl]-1-(4- hydroxyphenyl)-2-phenylbut-1(Z)-ene; 4-[1-[4-[2-(Dimethylamino)ethoxy]phenyl]- 2-phenyl-1(Z)-butenyl]phenol	 Chemical Name 3-[4-(6-Hydroxy-2-phenyl- 3,4-dihydronaphthalen-1-yl)phenyl]-2- propenoic acid
 Drug Name Rhapontigenin Chemical Name 3,3',5-Trihydroxy-4'- methoxy-trans-stilbene	 Drug Name Indanocine, NSC-698666 Chemical Name 7-Amino-2-[(E)-(4- hydroxy-3,5-dimethylbenzylidene)-5,6- dimethoxyindan-1-one	 Drug Name SB-269970-A Chemical Name 3-[2(R)-[2-(4- Methylpiperidin-1-yl)ethyl]pyrrolidin-1- ylsulfonyl]phenol

FIGURE 1 cont.

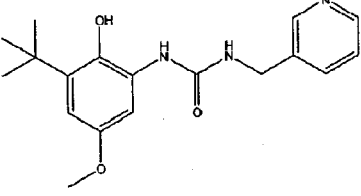
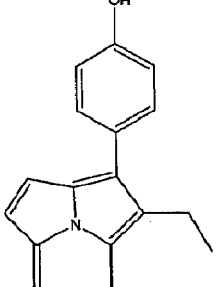
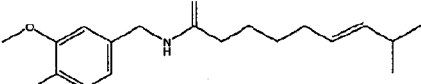
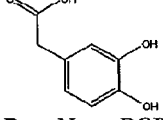
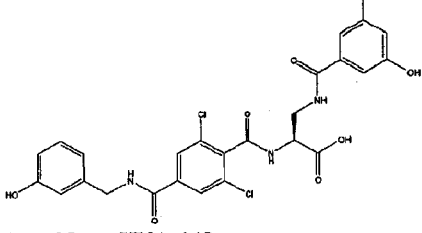
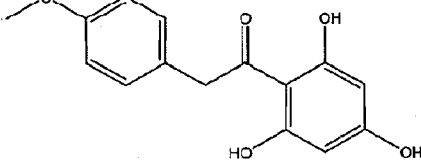
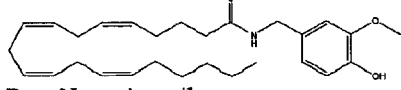
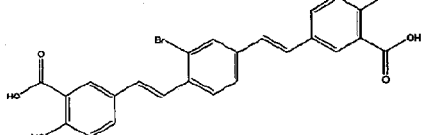
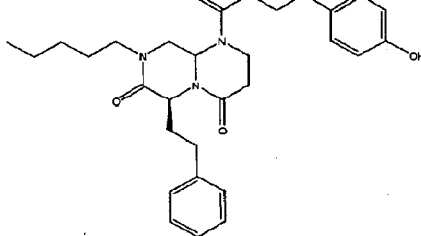
 Drug Name T-0162 Chemical Name N-[3-(tert-Butyl)-2-hydroxy-5-methoxyphenyl]-N'-(3-pyridylmethyl)urea hydrochloride	 Drug Name NNC-45-0095 Chemical Name 4-(1-Ethylpyrrolo[2,1,5-cd]indolizin-2-yl)phenol; 1-Ethyl-2-(4-hydroxyphenyl)pyrrolo[2,1,5-cd]indolizine	 Drug Name Capsaicin, TQ-1018, MR3H3, NGX-4010, Transacin, Zostrix HP, Zostrix, Axsain Chemical Name N-(4-Hydroxy-3-methoxybenzyl)-8-methyl-6(E)-nonenamide
 Drug Name DOPAC Chemical Name 2-(3,4-Dihydroxyphenyl)acetic acid	 Drug Name XVA-143 Chemical Name 2(S)-[2,6-Dichloro-4-[N-(3-hydroxybenzyl)carbamoyl]benzamido]-3-(3,5-dihydroxybenzamido)propionic acid	 Drug Name D-58 Chemical Name 1-(2,4,6-Trihydroxyphenyl)-2-(4-methoxyphenyl)ethan-1-one
 Drug Name Arvanil Chemical Name N-(4-Hydroxy-3-methoxybenzyl)-5(Z),8(Z),11(Z),14(Z)-icosatetraenamide	 Drug Name BSB Chemical Name 5-[(E)-2-[2-Bromo-4-[(E)-2-(3-carboxy-4-hydroxyphenyl)vinyl]phenyl]vinyl]-2-hydroxybenzoic acid	 Drug Name MOL-5210 Chemical Name 4,7-Dioxo-8-pentyl-6(S)-(2-phenylethyl)perhydropyrazino[1,2-a]pyrimidine-1-carboxylic acid 2-(4-hydroxyphenyl)ethyl ester

FIGURE 1 cont.

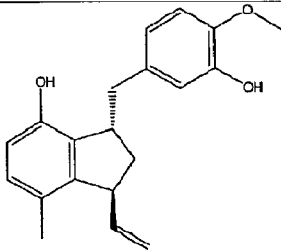
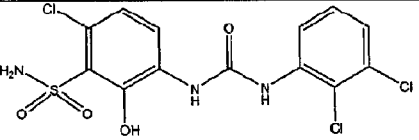
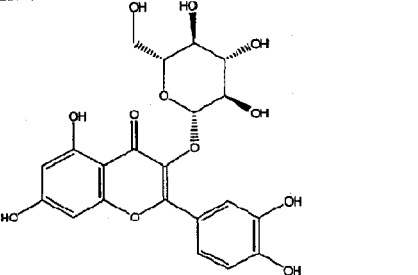
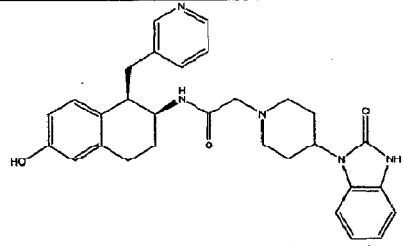
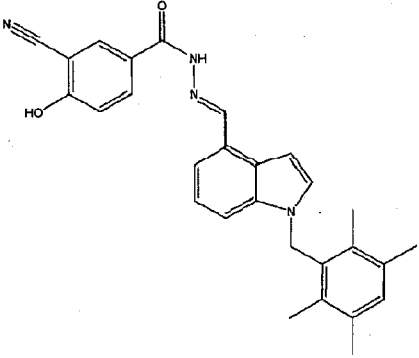
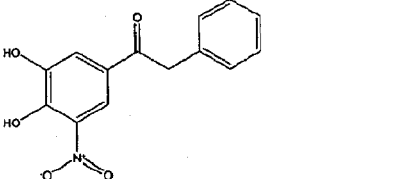
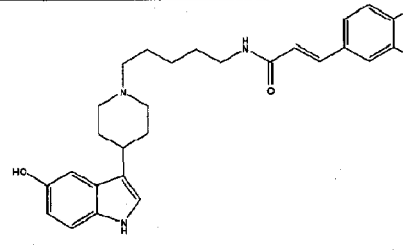
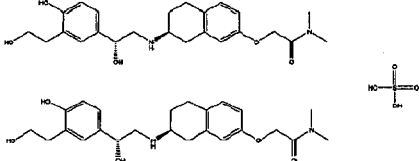
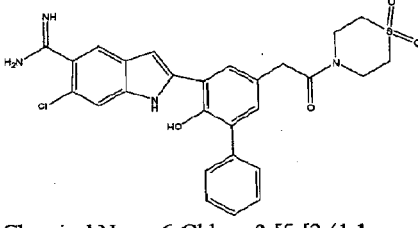
 Drug Name RPR-115781 Chemical Name 3(S)-(3-Hydroxy-4-methoxybenzyl)-7-methyl-1(S)-vinyl-2,3-dihydro-1H-inden-4-ol	 Drug Name 332235, SB-332235 Chemical Name 6-Chloro-3-[3-(2,3-dichlorophenyl)ureido]-2-hydroxybenzenesulfonamide	 Drug Name Quercetin 3-glucoside, Quercetin 3-beta-glucopyranoside, Isoquercitrin Chemical Name 3,3',4',5,7-Pentahydroxyflavone 3-O-beta-D-glucopyranoside; 2-(3,4-dihydroxyphenyl)-5,7-Dihydroxy-4-oxo-4H-1-benzopyran-3-yl beta-D-glucopyranoside
 Chemical Name N-[cis-6-Hydroxy-1-(3-pyridinylmethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-2-[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]acetamide	 Drug Name NNC-25-2504 Chemical Name 3-Cyano-4-hydroxy-N'-[1-(2,3,5,6-tetramethylbenzyl)-1H-indol-4-ylmethylene]benzohydrazide	 Drug Name Nebicapone, BIA-3-202 Chemical Name 1-(3,4-Dihydroxy-5-nitrophenyl)-2-phenyl-1-ethanone
 Chemical Name 3-(3,4-Dichlorophenyl)-N-[5-[4-(5-hydroxy-1H-indol-3-yl)piperidin-1-yl]pentyl]-2(E)-propenamide	 Drug Name Bedoradrine sulfate, MN-221, KUR-1246 Chemical Name (-)-2-[7(S)-[2(R)-Hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethylamino]-5,6,7,8-tetrahydronaphthalen-2-yloxy]-N,N-dimethylacetamide sulfate (2:1)	 Chemical Name 6-Chloro-2-[5-[2-(1,1-dioxothiophenyl)-2-oxoethyl]-2-hydroxybiphenyl-3-yl]-1H-indole-5-carboxamide

FIGURE 1 cont.

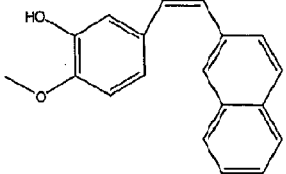
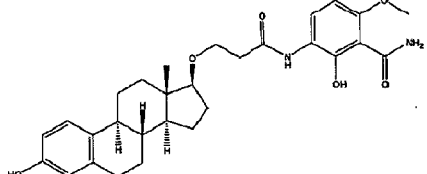
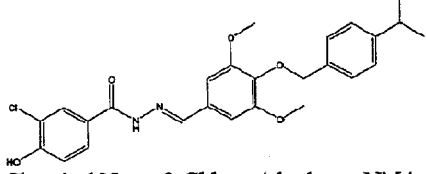
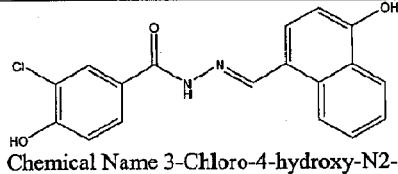
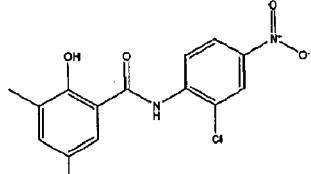
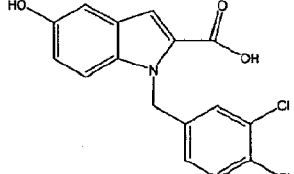
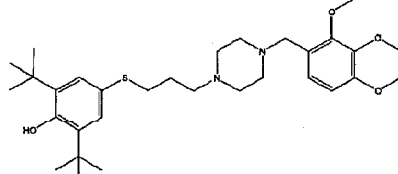
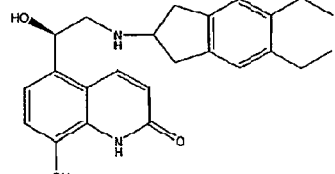
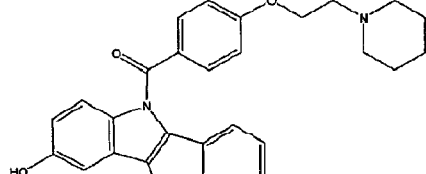
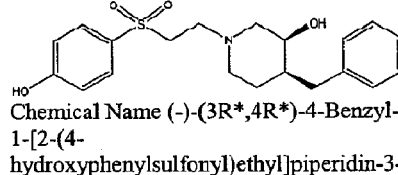
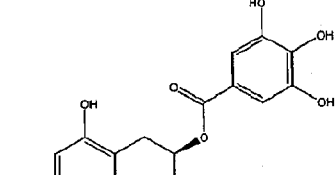
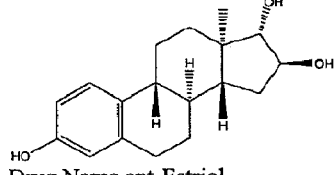
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 Chemical Name 3-Chloro-4-hydroxy-N2-(4-hydroxynaphthalen-1-ylmethylidene)benzohydrazide	 Drug Name YM-138552 Chemical Name 5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxy-3-methylbenzamide	 Drug Name AZD-6942 Chemical Name 1-(3,4-Dichlorobenzyl)-5-hydroxy-1H-indole-2-carboxylic acid
 Drug Name S-15176, S-151276 Chemical Name 2,6-Di-tert-butyl-4-[3-[4-(2,3,4-trimethoxybenzyl)-1-piperazinyl]propylsulfanyl]phenol	 Drug Name Indacaterol, QAB-149 Chemical Name 5-[2-(5,6-Diethyl-2,3-dihydro-1H-inden-2-ylamino)-1(R)-hydroxyethyl]-8-hydroxyquinolin-2(1H)-one	 Chemical Name 1-[5-Hydroxy-2-(4-hydroxyphenyl)-3-methyl-1H-indol-1-yl]-1-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone
 Chemical Name (-)-(3R*,4R*)-4-Benzyl-1-[2-(4-hydroxyphenylsulfonyl)ethyl]piperidin-3-ol	 Drug Name (-)-Epicatechin-3-gallate, ECG Chemical Name 3,4,5-Trihydroxybenzoic acid 5,7-dihydroxy-2(R)-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3(S)-yl ester	 Drug Name ent-Estriol Chemical Name ent-Estra-1,3,5(10)-triene-3,16beta,17alpha-triol

FIGURE 1 cont.

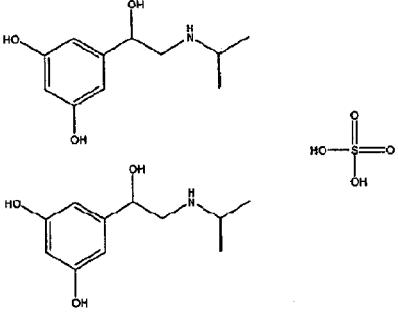
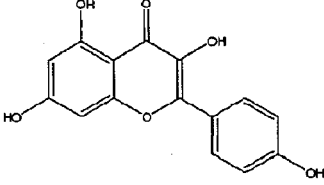
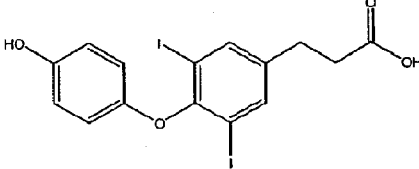
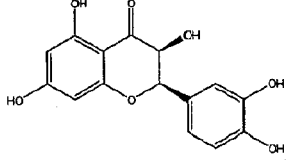
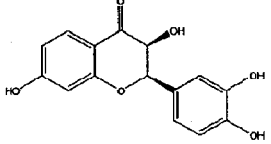
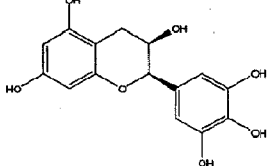
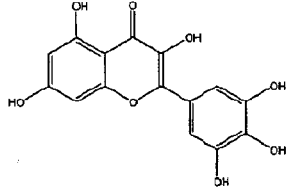
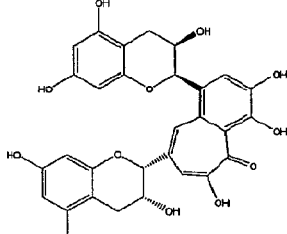
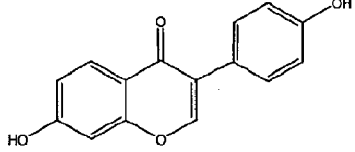
 Drug Name Metaproterenol sulfate, Orciprenaline sulphate, Th-152, Alupent, Metaprel Chemical Name 5-[1-Hydroxy-2-(isopropylamino)ethyl]benzene-1,3-diol sulfate (2:1)	 Drug Name Kaempferol Chemical Name 3,4',5,7-Tetrahydroxyflavone; 3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one	 Drug Name DITPA Chemical Name 3-[4-(4-Hydroxyphenoxy)-3,5-diiodophenyl]propionic acid; 3,5-Diiodothyropropionic acid
 Drug Name Taxifolin, Taxifoliol, Dihydroquercetin, Diquertin, Distylin Chemical Name (+)-2(R)-(3,4-Dihydroxyphenyl)-3(R),5,7-trihydroxy-2,3-dihydro-4H-1-benzopyran-4-one	 Drug Name Fustin Chemical Name 3(S),3',4',7-Tetrahydroxy-7-methoxyflavanone; 2(R)-(3,4-Dihydroxyphenyl)-3(S),7-dihydroxy-3,4-dihydro-2H-1-benzopyran-4-one	 Drug Name (-)-Epigallocatechin, EGC Chemical Name 2(R)-cis-2-(3,4,5-Trihydroxyphenyl)-2,3-dihydro-4H-1-benzopyran-3,5,7-triol
 Drug Name Myricetin, Myricetin, NSC-407290 Chemical Name 3,3',4',5,5',7-Hexahydroxyflavone; 3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-1-benzopyran-4-one	 Drug Name Theaflavin, TF-1 Chemical Name 3(S),5,7-Trihydroxy-2(R)-[3,4,6-trihydroxy-5-oxo-8-[3(S),5,7-trihydroxy-3,4-dihydro-2H-1-benzopyran-2(R)-yl]-5H-benzo[a]cyclohept-1-yl]-3,4-dihydro-2H-1-benzopyran	 Drug Name Daidzein Chemical Name 4',7-Dihydroxyisoflavanone; 7-Hydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one

FIGURE 1 cont.

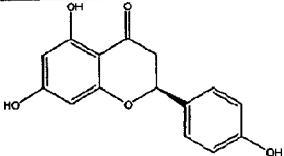
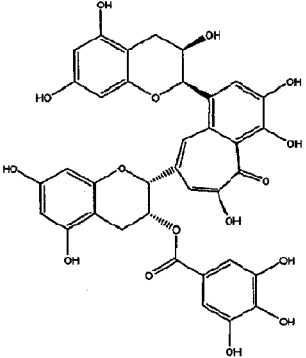
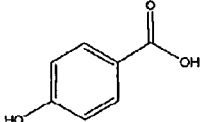
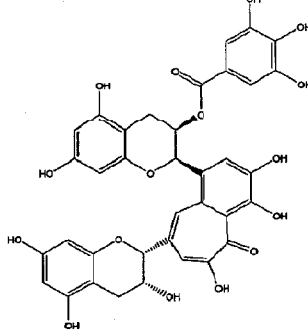
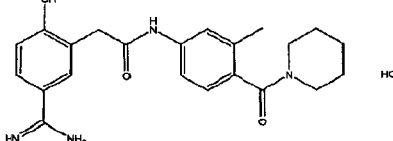
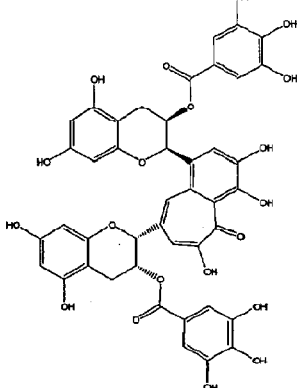
 Drug Name Naringenin Chemical Name (-)-5,7-Dihydroxy-2(S)-(4-hydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-4-one	 Drug Name Theaflavin-3'-gallate, TF-2b Chemical Name 3,4,5-Trihydroxybenzoic acid 5,7-dihydroxy-2(R)-[3,4,6-trihydroxy-5-oxo-1-[3(S),5,7-trihydroxy-3,4-dihydro-2H-1-benzopyran-2(R)-yl]-5H-benzo[a]cyclohepten-8-yl]-3,4-dihydro-2H-1-benzopyran-3(S)-yl ester	 Drug Name 4-HBA Chemical Name 4-Hydroxybenzoic acid
 Drug Name Theaflavin-3-gallate, TF-2a Chemical Name 3,4,5-Trihydroxybenzoic acid 5,7-dihydroxy-2(R)-[3,4,6-trihydroxy-5-oxo-8-[3(S),5,7-trihydroxy-3,4-dihydro-2H-1-benzopyran-2(R)-yl]-5H-benzo[a]cyclohepten-1-yl]-3,4-dihydro-2H-1-benzopyran-3(S)-yl ester	 Chemical Name 2-(5-Amidino-2-hydroxyphenyl)-N-[3-methyl-4-(piperidin-1-ylcarbonyl)phenyl]acetamide hydrochloride	 Drug Name Theaflavin-3,3'-digallate, TF-3 Chemical Name 3,4,5-Trihydroxybenzoic acid 2(R)-[1-[5,7-dihydroxy-4-oxo-3(S)-(3,4,5-trihydroxybenzoyloxy)-3,4-dihydro-2H-1-benzopyran-2(R)-yl]-3,4,6-trihydroxy-5-oxo-5H-benzo[a]cyclohepten-8-yl]-5,7-dihydroxy-4-oxo-3,4-dihydro-2H-1-benzopyran-3(S)-yl ester

FIGURE 1 cont.

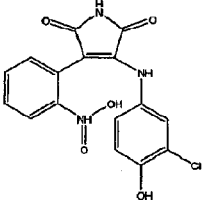
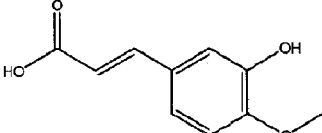
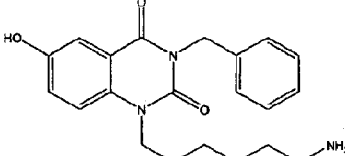
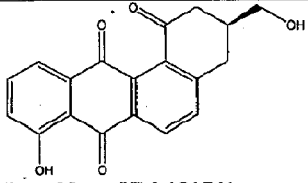
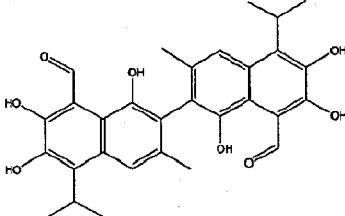
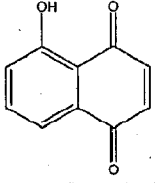
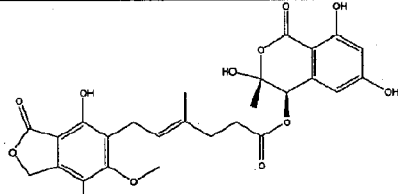
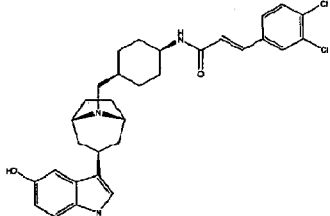
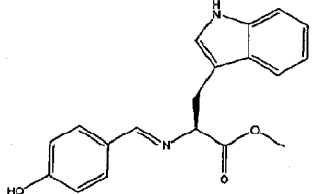
 Drug Name SB-415286 Chemical Name 3-(3-Chloro-4-hydroxyphenylamino)-4-(2-nitrophenyl)-1H-pyrrole-2,5-dione	 Drug Name Isoferulic acid Chemical Name 3-(3-Hydroxy-4-methoxyphenyl)-2-propenoic acid	 Drug Name UK-156974 Chemical Name 1-(6-Aminohexyl)-3-benzyl-6-hydroxyquinazoline-2,4(1H,3H)-dione
 Drug Name YM-181741 Chemical Name 8-Hydroxy-3(S)-(hydroxymethyl)-1,2,3,4,7,12-hexahydrobenzo[a]anthracene-1,7,12-trione	 Drug Name (R)-Gossypol, (-)-Gossypol, AT-101, NSC-726190, BL-193 Chemical Name (-)-(R)-1,1',6,6',7,7'-Hexahydroxy-5,5'-diisopropyl-3,3'-dimethyl-2,2'-binaphthalene-8,8'-dicarboxaldehyde; (-)-(R)-2,2'-Bis(8-formyl-5-isopropyl-1,6,7-trihydroxy-3-methylnaphthalene)	 Drug Name Juglone Chemical Name 5-Hydroxy-1,4-naphthoquinone
 Drug Name F-13459 Chemical Name 6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4(E)-hexenoic acid 3,6,8-trihydroxy-3(R)-methyl-1-oxo-3,4-dihydro-1H-2-benzopyran-4(R)-yl ester	 Drug Name SB-380732 Chemical Name cis-3-(3,4-Dichlorophenyl)-N-[4-[exo-3-(5-hydroxy-1H-indol-3-yl)-8-azabicyclo[3.2.1]oct-8-ylmethyl]cyclohexyl]-2-propenamide	 Chemical Name N-(4-Hydroxybenzylidene)-L-tryptophan methyl ester

FIGURE 1 cont.

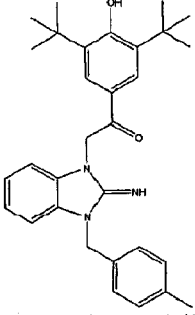
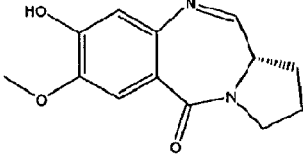
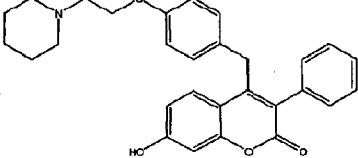
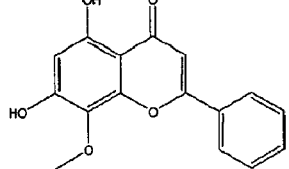
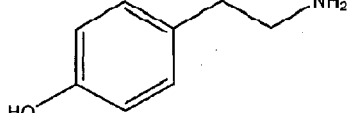
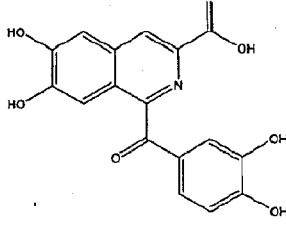
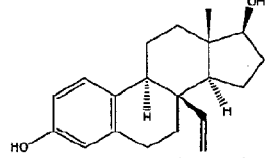
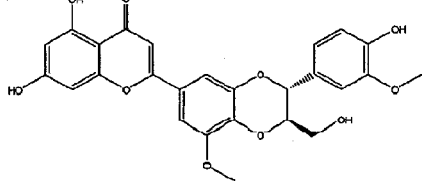
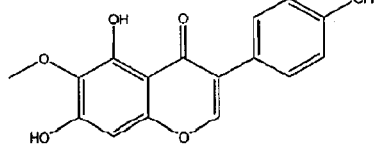
 Chemical Name 1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-[2-imino-3-(4-methylbenzyl)-2,3-dihydro-1H-benzimidazol-1-yl]ethanone	 Drug Name DC-81 Chemical Name (11aS)-8-Hydroxy-7-methoxy-2,3,5,11a-tetrahydro-1H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one	 Drug Name SP-500263 Chemical Name 7-Hydroxy-3-phenyl-4-[4-[2-(1-piperidinyl)ethoxy]benzyl]-2H-1-benzopyran-2-one hydrochloride
 Drug Name Wogonin Chemical Name 5,7-Dihydroxy-8-methoxy-2-phenyl-4H-1-benzopyran-4-one	 Drug Name Tyramine hydrochloride, Mydrial, Uteramin Chemical Name 4-(2-Aminoethyl)phenol hydrochloride	 Drug Name NBI-31772 Chemical Name 1-(3,4-Dihydroxybenzoyl)-6,7-dihydroxyisoquinoline-3-carboxylic acid
 Chemical Name 8beta-Vinylestra-1,3,5(10)-triene-3,17beta-diol	 Drug Name 5'-Methoxyhydrnocarpin D Chemical Name (±)-trans-5,7-Dihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-8-methoxy-2,3-dihydro-1,4-benzodioxin-6-yl]-4H-1-benzopyran-4-one	 Drug Name Tectorigenin Chemical Name 4',5,7-Trihydroxy-6-methoxyisoflavone; 5,7-Dihydroxy-3-(4-hydroxyphenyl)-6-methoxy-4H-1-benzopyran-4-one

FIGURE 1 cont.

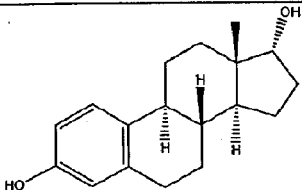
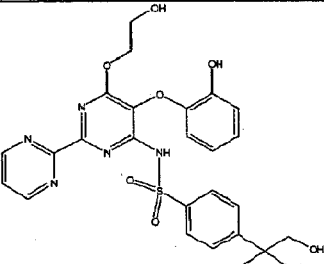
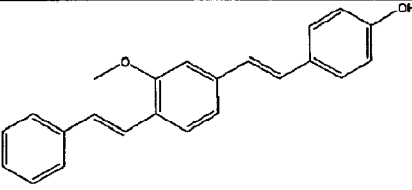
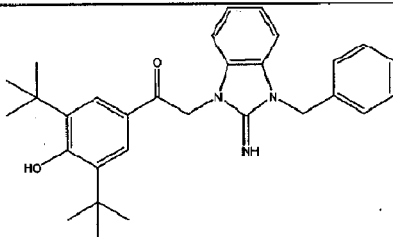
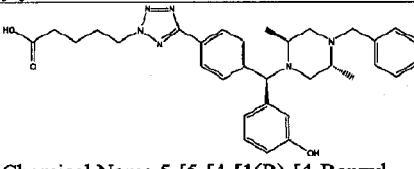
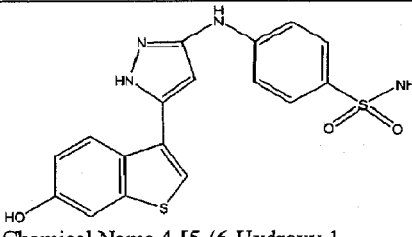
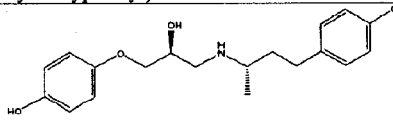
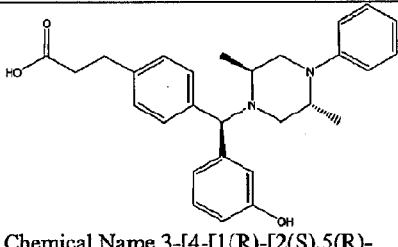
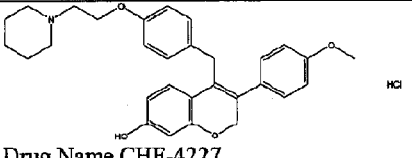
 Drug Name 17-alpha-Estradiol, Alfatradiol, MX-4509, ABP-150, MITO-4509 Chemical Name Estra-1,3,5(10)-triene-3,17alpha-diol	 Drug Name Ro-64-1056 Chemical Name 4-(2-Hydroxy-1,1-dimethylethyl)-N-[6-(2-hydroxyethoxy)-5-(2-hydroxyphenoxy)-2,2'-bipyrimidin-4-yl]benzenesulfonamide	 Drug Name Methoxy-XO4 Chemical Name 4-[2-[3-Methoxy-4-(2-phenylvinyl)phenyl]vinyl]phenol
 Drug Name Sch-328725 Chemical Name 2-(3-Benzyl-2-imino-2,3-dihydro-1H-benzimidazol-1-yl)-1-(3,5-di-tert-butyl-4-hydroxyphenyl)ethanone	 Chemical Name 5-[5-[4-[1(R)-[4-Benzyl-2(S),5(R)-dimethylpiperazin-1-yl]-1-(3-hydroxyphenyl)methyl]phenyl]-2H-tetrazol-2-yl]pentanoic acid	 Chemical Name 4-[5-(6-Hydroxy-1-benzothien-3-yl)-1H-pyrazol-3-ylamino]benzenesulfonamide
 Chemical Name 4-[2(S)-Hydroxy-3-[3-(4-methoxyphenyl)-1(S)-methylpropylamino]propoxy]phenol	 Chemical Name 3-[4-[1(R)-[2(S),5(R)-Dimethyl-4-phenylpiperazin-1-yl]-1-(3-hydroxyphenyl)methyl]phenyl]propionic acid	 Drug Name CHF-4227 Chemical Name 3-(4-Methoxyphenyl)-4-[4-[2-(1-piperidinyl)ethoxy]benzyl]-2H-1-benzopyran-7-ol hydrochloride

FIGURE 1 cont.

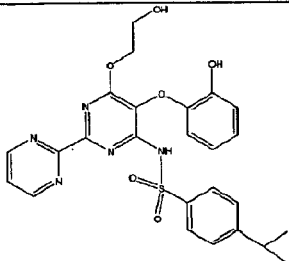
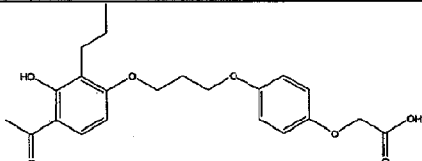
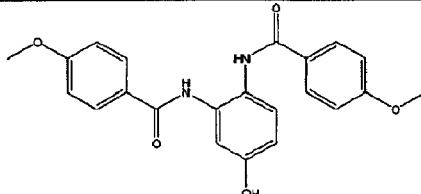
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FIGURE 2

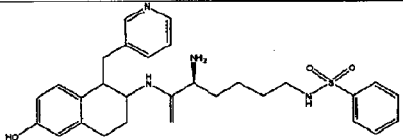
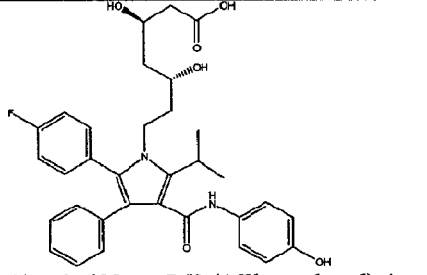
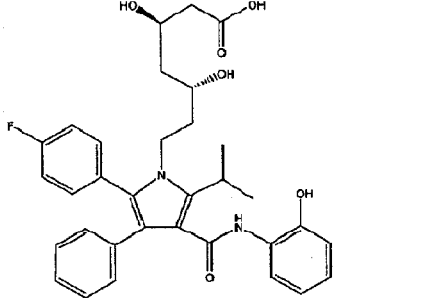
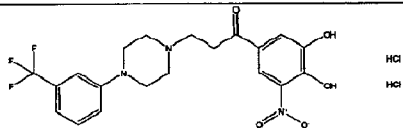
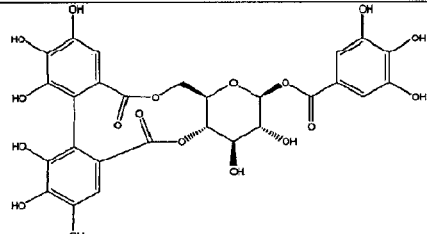
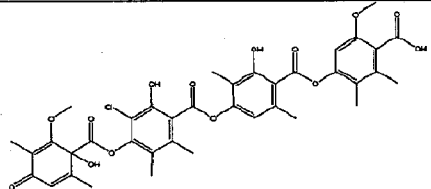
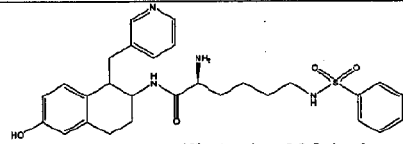
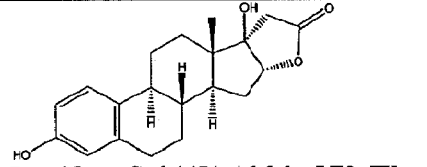
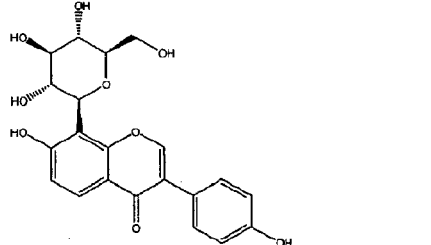
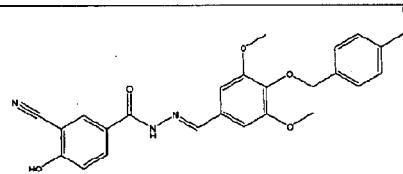
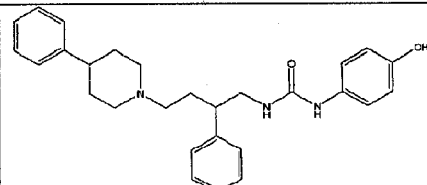
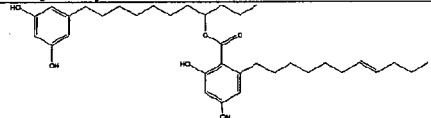
 Chemical Name N-[5(S)-Amino-6-[6-hydroxy-1-(pyridin-3-ylmethyl)-1,2,3,4-tetrahydronaphthalen-2-ylamino]hept-6-enyl]benzenesulfonamide	 Chemical Name 7-[2-(4-Fluorophenyl)-4-[N-(4-hydroxyphenyl)carbamoyl]-5-isopropyl-3-phenyl-1H-pyrrol-1-yl]-3(R),5(R)-dihydroxyheptanoic acid	 Chemical Name 7-[2-(4-Fluorophenyl)-4-[N-(2-hydroxyphenyl)carbamoyl]-5-isopropyl-3-phenyl-1H-pyrrol-1-yl]-3(R),5(R)-dihydroxyheptanoic acid
 Drug Name BIA-3-335 Chemical Name 1-(3,4-Dihydroxy-5-nitrophenyl)-3-[4-[3-(trifluoromethyl)phenyl]piperazin-1-yl]propan-1-one dihydrochloride	 Drug Name Strictinin Chemical Name Cyclic 4,6-(4,4',5,5',6,6'-hexahydroxy[1,1'-biphenyl]-2,2'-dicarboxylate)-1-O-(3,4,5-trihydroxybenzoyl)-beta-D-glucopyranoside	 Drug Name CJ-21164 Chemical Name 4-[4-[3-Chloro-2-hydroxy-4-(1-hydroxy-2-methoxy-3,6-dimethyl-4-oxocyclohexa-2,5-dien-1-ylcarbonyloxy)-5,6-dimethylbenzoyloxy]-2-hydroxy-3,6-dimethylbenzoyloxy]-6-methoxy-2,3-dimethylbenzoic acid
 Chemical Name 2(S)-Amino-N-[cis-6-hydroxy-1-(pyridin-3-ylmethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-6-(phenylsulfonamido)hexanamide	 Drug Name Cpd-1471, 16alpha-LE2, ZK-281471 Chemical Name 3,16alpha,17beta-Trihydroxy-19-norpregna-1,3,5(10)-trien-21-oic acid gamma-lactone; 3,17beta-Dihydroxy-19-norpregna-1,3,5(10)-triene-21,16alpha-lactone	 Drug Name Puerarin, NPI-31G Chemical Name 8-(beta-D-Glucopyranosyl)-7-hydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one; 8-(beta-D-Glucopyranosyl)-4',7-dihydroxyisoflavone
 Chemical Name 3-Cyano-4-hydroxy-N'-[4-(4-isopropylbenzyloxy)-3,5-	 Chemical Name N-(4-Hydroxyphenyl)-N'	 Drug Name Integracin C Chemical Name 2,4-Dihydroxy-6-(7-undecenyl)benzoic acid 8-(3,5-

FIGURE 2 cont.

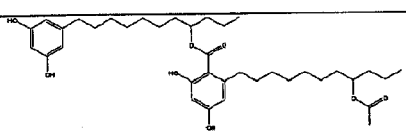
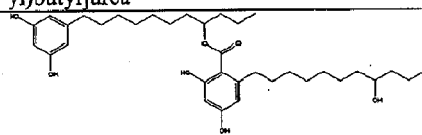
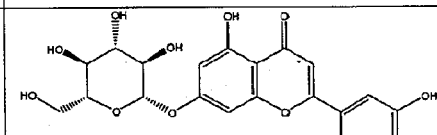
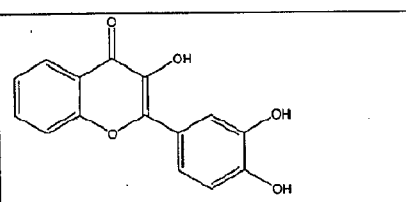
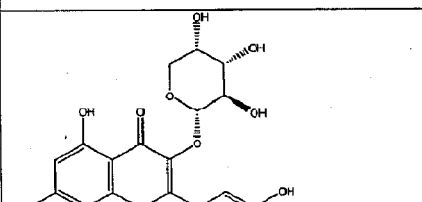
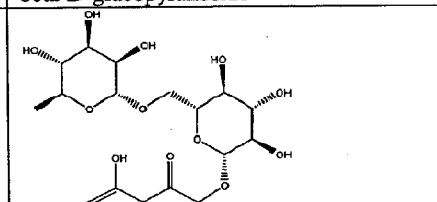
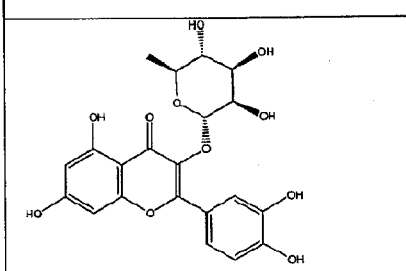
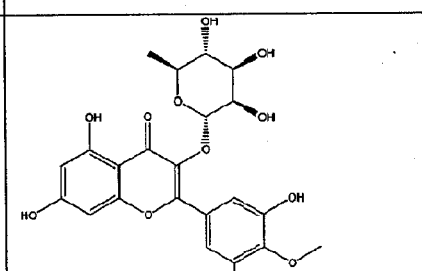
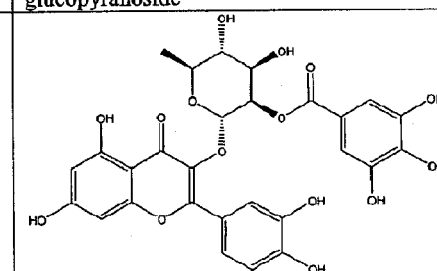
dimethoxybenzylidene]benzohydrazide  Drug Name Integracin A Chemical Name 2-(8-Acetoxyundecyl)-4,6-dihydroxybenzoic acid 8-(3,5-dihydroxyphenyl)-1-propyloctyl ester	[2-phenyl-4-(4-phenylpiperidin-1-yl)butyl]urea  Drug Name Integracin B Chemical Name 2,4-Dihydroxy-6-(8-hydroxyundecyl)benzoic acid 8-(3,5-dihydroxyphenyl)-1-propyloctyl ester	dihydroxyphenyl)-1-propyloctyl ester  Drug Name Cynaroside, Luteolin 7-O-D-glucoside Chemical Name 2-(3,4-Dihydroxyphenyl)-5-hydroxy-4-oxo-4H-1-benzopyran-7-yl beta-D-glucopyranoside
 Drug Name DiOHF Chemical Name 2-(3,4-Dihydroxyphenyl)-3-hydroxy-4H-1-benzopyran-4-one; 3,3',4'-Trihydroxyflavone	 Drug Name Guaijaverin Chemical Name 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl alpha-L-arabinopyranoside	 Drug Name Rutin Chemical Name 1-O-[2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl]-6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranoside; 1-O-[2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl]-6-O-(alpha-L-rhamnopyranosyl)-beta-D-glucopyranoside
 Drug Name Quercitrin Chemical Name 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl 6-deoxy-alpha-L-mannopyranoside; 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl alpha-L-rhamnopyranoside	 Drug Name Mearnitrin Chemical Name 2-(3,5-Dihydroxy-4-methoxyphenyl)-5,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl alpha-L-rhamnopyranoside; 2-(3,5-Dihydroxy-4-methoxyphenyl)-5,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl 6-deoxy-alpha-L-mannopyranoside	 Drug Name Desmanthin-1 Chemical Name 5,7-Dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4H-1-benzopyran-3-yl 6-deoxy-2-O-(3,4,5-trihydroxybenzoyl)-alpha-L-mannopyranoside; 5,7-Dihydroxy-4-oxo-2-(3,4,5-

FIGURE 2 cont.

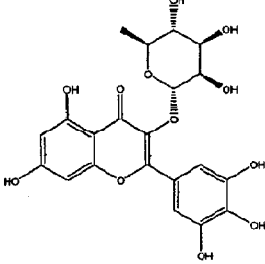
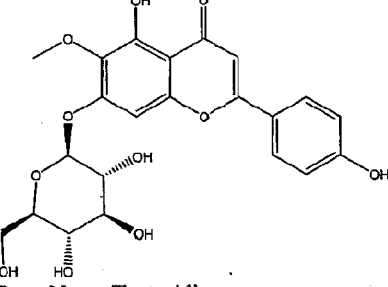
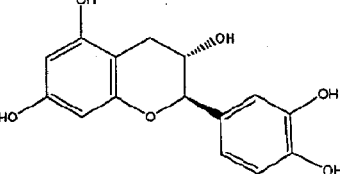
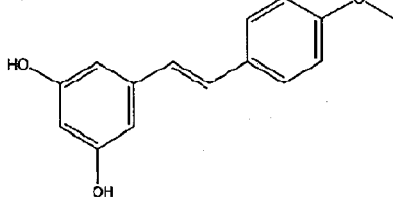
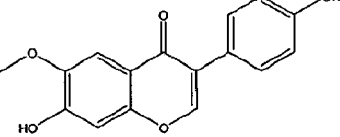
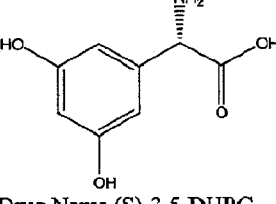
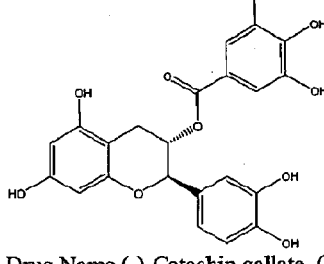
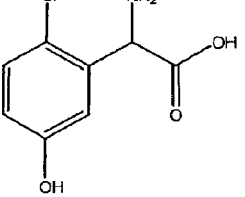
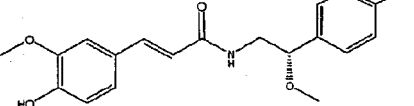
 Drug Name Myricitrin Chemical Name 5,7-Dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4H-1-benzopyran-3-yl 6-deoxy-alpha-L-mannopyranoside; 5,7-Dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4H-1-benzopyran-3-yl alpha-L-rhamnopyranoside	 Drug Name Tectoridin Chemical Name 5-Hydroxy-2-(4-hydroxyphenyl)-6-methoxy-4-oxo-4H-1-benzopyran-7-yl beta-D-glucopyranoside	trihydroxyphenyl)-4H-1-benzopyran-3-yl 2-O-(3,4,5-trihydroxybenzoyl)-alpha-L-rhamnopyranoside  Drug Name Biocatechin, Catechin, Dexcyanidanol, Cyanidanol, (+)-Catechin, NSC-2819 Chemical Name 2(R)-trans-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3,5,7-triol
 Drug Name Deoxyrhapontigenin Chemical Name 3,5-Dihydroxy-4'-methoxy-trans-stilbene	 Drug Name Glycitein Chemical Name 4',7-Dihydroxy-6-methoxyisoflavone; 7-Hydroxy-3-(4-hydroxyphenyl)-6-methoxy-4H-1-benzopyran-4-one	 Drug Name (S)-3,5-DHPG Chemical Name 2(S)-Amino-2-(3,5-dihydroxyphenyl)acetic acid; alpha(S)-Amino-3,5-dihydroxybenzeneacetic acid
 Drug Name (-)-Catechin gallate, (-)-CG Chemical Name 3,4,5-Trihydroxybenzoic acid 2(R)-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-1-benzopyran-3(S)-yl ester	 Drug Name CHPG Chemical Name 2-Amino-2-(2-chloro-5-hydroxyphenyl)acetic acid	 Chemical Name 3-(4-Hydroxy-3-methoxyphenyl)-N-[2(S)-(4-hydroxyphenyl)-2-methoxyethyl]-2-propenamide

FIGURE 2 cont.

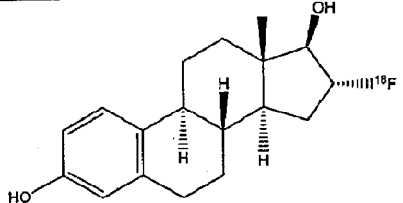
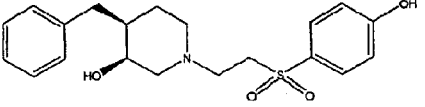
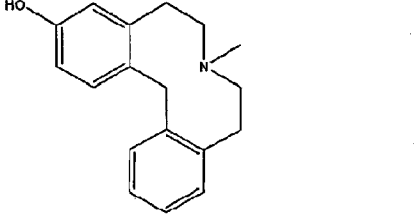
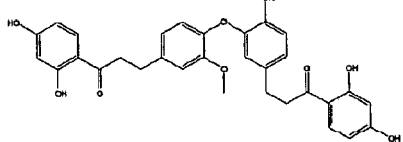
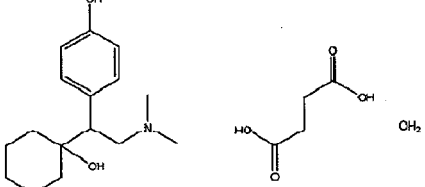
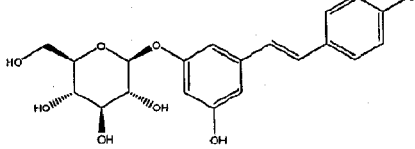
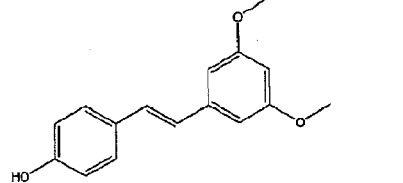
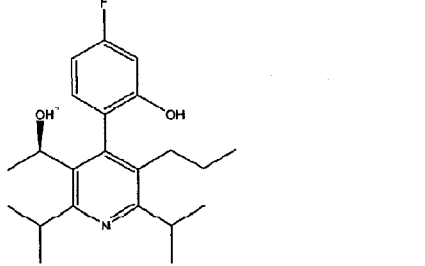
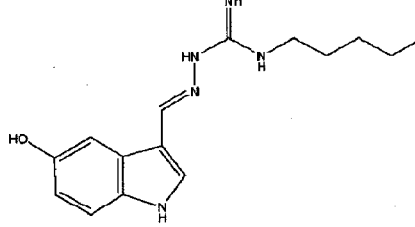
 Chemical Name (16α,17β)-16-[18F]Fluoroestra-1,3,5(10)-triene-3,17-diol	 Drug Name RO-67-8867, R.O-0678867 Chemical Name 4(S)-Benzyl-1-[2-(4-hydroxyphenylsulfonyl)ethyl]piperidin-3(S)-ol	 Drug Name LE-404 Chemical Name 7-Methyl-5,6,7,8,9,14-hexahydrodibenzo[d,g]azecin-3-ol
 Drug Name Verbenachalcone Chemical Name 1-(2,4-Dihydroxyphenyl)-3-[4-[5-[3-(2,4-dihydroxyphenyl)-3-oxopropyl]-2-hydroxyphenoxy]-3-methoxyphenyl]propan-1-one	 Drug Name Desvenlafaxine succinate, O-Desmethylvenlafaxine, DVS-233, WY-45233 (free base) Chemical Name 4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenol succinate hydrate	 Drug Name Piceid Chemical Name trans-1-[3-Hydroxy-5-[2-(4-hydroxyphenyl)vinyl]phenyl]-beta-D-glucopyranoside
 Drug Name Pterostilbene Chemical Name 4-[(E)-2-(3,5-Dimethoxyphenyl)vinyl]phenol	 Chemical Name 5-Fluoro-2-[3-[1(R)-hydroxyethyl]-2,6-diisopropyl-5-propylpyridin-4-yl]phenol	 Chemical Name 2-(5-Hydroxy-1H-indol-3-yl)methylene]-N-pentylhydrazinecarboxamide

FIGURE 2 cont.

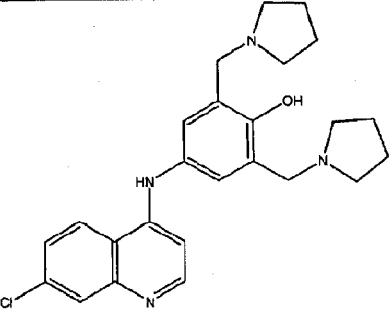
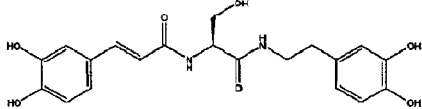
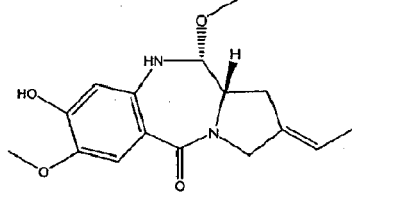
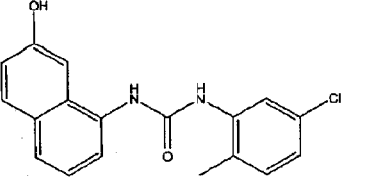
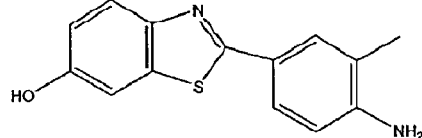
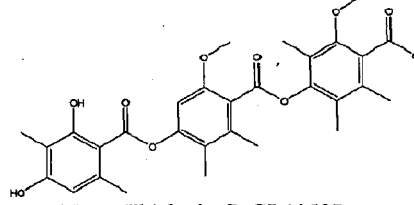
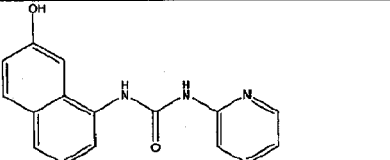
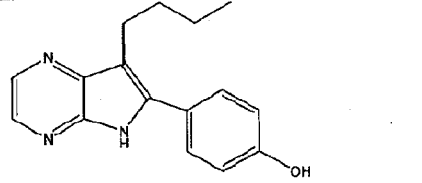
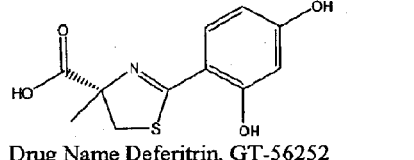
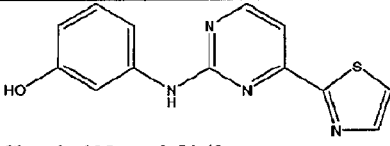
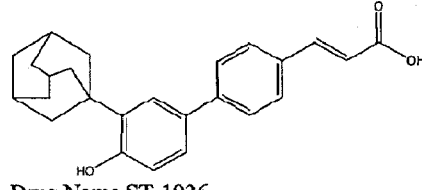
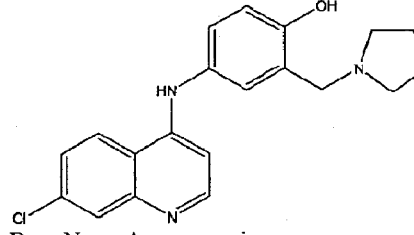
 Drug Name Bispyroquine, M-6407 Chemical Name 4-(7-Chloroquinolin-4-ylamino)-2,6-bis(pyrrolidin-1-ylmethyl)phenol	 Chemical Name N1-[2-(3,4-Dihydroxyphenyl)ethyl]-N2-[3-(3,4-dihydroxyphenyl)-2-propenoyl]-L-serinamide	 Drug Name Tomaymycin Chemical Name (2E,11R,11aS)-2-Ethylidene-8-hydroxy-7,11-dimethoxy-2,3,5,10,11,11a-hexahydro-1H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one
 Chemical Name N-(5-Chloro-2-methylphenyl)-N'-(7-hydroxynaphthalen-1-yl)urea	 Chemical Name 2-(4-Amino-3-methylphenyl)benzothiazol-6-ol	 Drug Name Thielavin G, CJ-19587 Chemical Name 4-[4-(2,4-Dihydroxy-3,6-dimethylbenzoyloxy)-6-methoxy-2,3-dimethylbenzoyloxy]-2-methoxy-3,5,6-trimethylbenzoic acid
 Chemical Name N-(7-Hydroxynaphthalen-1-yl)-N'-(2-pyridyl)urea	 Drug Name Aloisine A, RP-107 Chemical Name 4-(7-Butyl-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenol	 Drug Name Deferitritin, GT-56252 Chemical Name (+)-2-(2,4-Dihydroxyphenyl)-4-methyl-4,5-dihydrothiazole-4(S)-carboxylic acid
 Chemical Name 3-[4-(2-Thiazolyl)pyrimidin-2-ylamino]phenol	 Drug Name ST-1926 Chemical Name 3-[3'-(1-Adamantyl)-4'-hydroxybiphenyl-4-yl]-2(E)-propenoic acid	 Drug Name Amopyroquine Chemical Name 4-(7-Chloroquinolin-4-ylamino)-2-(pyrrolidin-1-ylmethyl)phenol

FIGURE 2 cont.

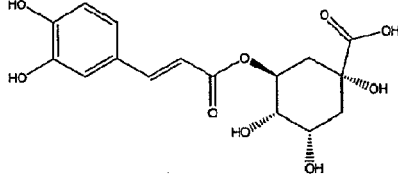
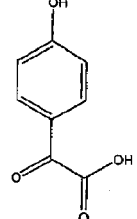
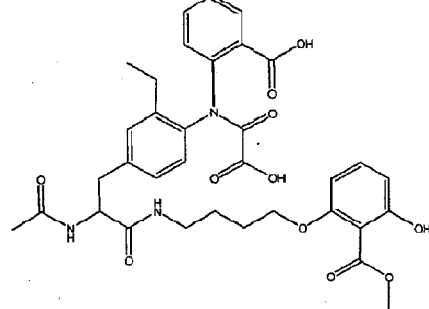
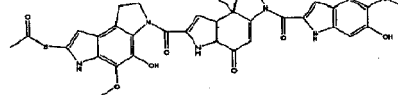
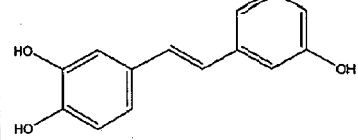
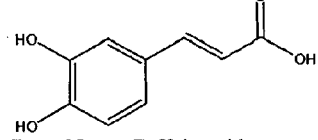
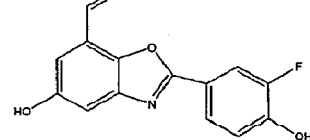
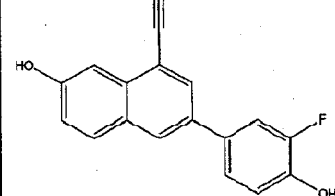
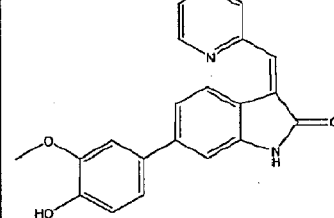
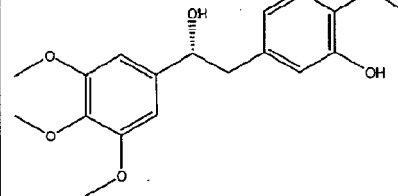
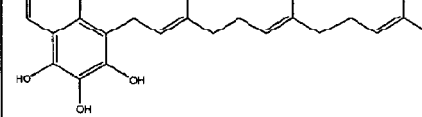
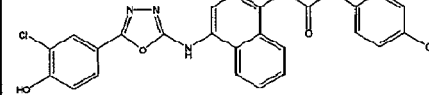
 Drug Name Chlorogenic acid Chemical Name (1R,3S,4S,5S)-3-[3-(3,4-Dihydroxyphenyl)-2-propenoxy]-1,4,5-trihydroxycyclohexanecarboxylic acid	 Drug Name HPG Chemical Name 2-(4-Hydroxyphenyl)-2-oxoacetic acid; 4-Hydroxyphenylglyoxylic acid	 Chemical Name 2-[N-[4-[2-Acetamido-2-[N-[4-[3-hydroxy-2-(methoxycarbonyl)phenoxy]butyl]carbamoyl]ethyl]-2-ethylphenyl]-N-(2-hydroxyoxalyl)amino]benzoic acid
 Drug Name Yatakemycin Chemical Name Thioacetic acid S-[5-hydroxy-6-[6-(6-hydroxy-5-methoxy-1H-indol-2-ylcarbonyl)-8-oxo-1,4,4a,5,6,8-hexahydrocyclopropa[c]pyrrolo[3,2-e]indol-2-ylcarbonyl]-4-methoxy-3,6,7,8-tetrahydropyrrolo[3,2-e]indol-2-yl] ester	 Chemical Name 3,3',4-Trihydroxystilbene; 4-[2-(3-Hydroxyphenyl)vinyl]benzene-1,2-diol	 Drug Name Caffeic acid Chemical Name 3-(3,4-Dihydroxyphenyl)-2-propenoic acid
 Drug Name Prinaberel, ERB-041 Chemical Name 2-(3-Fluoro-4-hydroxyphenyl)-7-vinylbenzoxazol-5-ol	 Drug Name ERB-196, WAY-202196 Chemical Name 3-(3-Fluoro-4-hydroxyphenyl)-7-hydroxynaphthalene-1-carbonitrile	 Chemical Name 6-(4-Hydroxy-3-methoxyphenyl)-3(E)-(pyridin-2-ylmethylene)-2,3-dihydro-1H-indol-2-one
 Drug Name Combretastatin, NSC-348103 Chemical Name 5-[2(R)-Hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl]-2-methoxyphenol	 Chemical Name 2,3,4-Trihydroxy-6-methyl-5-(3,7,11-trimethyldodeca-2,6,10-trienyl)benzaldehyde	 Drug Name GW-4123X Chemical Name N-[4-[5-(3-Chloro-4-hydroxyphenyl)-1,3,4-oxadiazol-2-ylamino]naphthalen-1-yl]-2-(4-chlorophenyl)acetamide

FIGURE 2 cont.

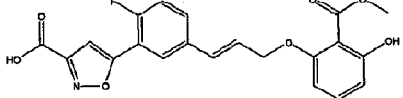
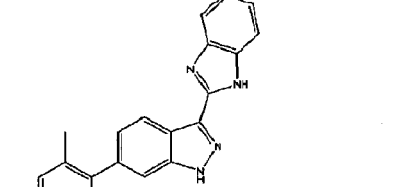
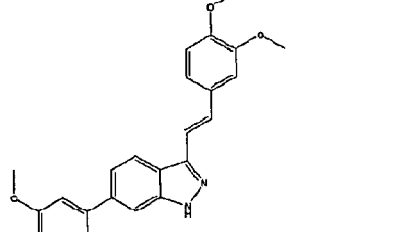
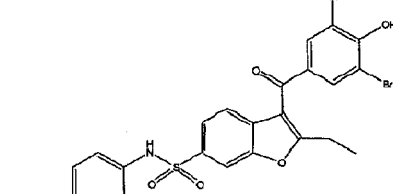
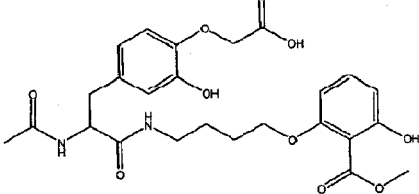
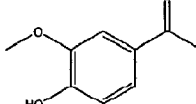
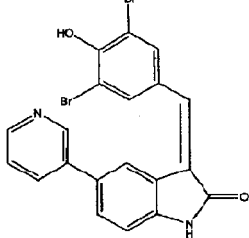
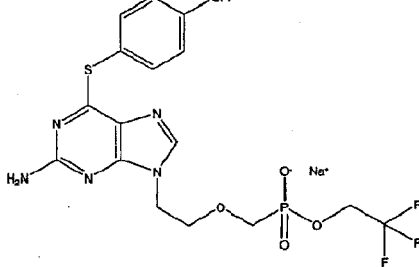
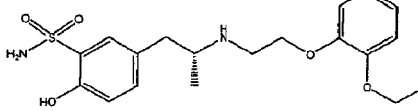
 Chemical Name 5-[2-Fluoro-5-[3-[3-hydroxy-2-(methoxycarbonyl)phenoxy]-1-propenyl]phenyl]isoxazole-3-carboxylic acid	 Chemical Name 4-[3-(1H-Benzimidazol-2-yl)-1H-indazol-6-yl]-3-methylphenol	 Chemical Name 4-[3-[2-(3,4-Dimethoxyphenyl)vinyl]-1H-indazol-6-yl]-2-methoxyphenol
 Chemical Name 3-(3,5-Dibromo-4-hydroxybenzoyl)-2-ethyl-N-(4-sulfamoylphenyl)-1-benzofuran-6-sulfonamide	 Chemical Name N2-Acetyl-O-(carboxymethyl)-3-hydroxy-N1-[4-[3-hydroxy-2-(methoxycarbonyl)phenoxy]butyl]-DL-tyrosinamide	 Drug Name Acetovanillone, Apocynin Chemical Name 1-(4-Hydroxy-3-methoxyphenyl)ethanone
 Chemical Name 3-(3,5-Dibromo-4-hydroxybenzylidene)-5-(3-pyridyl)-2,3-dihydro-1H-indol-2-one	 Drug Name 602075 Chemical Name 2-[2-Amino-6-(4-hydroxyphenylsulfanyl)-9H-purin-9-yl]ethoxymethylphosphonic acid 2,2,2-trifluoroethyl ester sodium salt	 Drug Name RBx-9001 Chemical Name 5-[2(R)-[2-(2-Ethoxyphenoxy)ethylamino]propyl]-2-hydroxybenzenesulfonamide

FIGURE 2 cont.

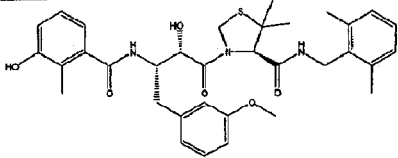
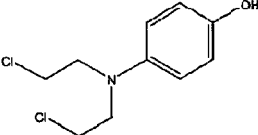
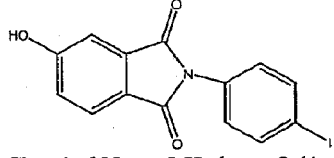
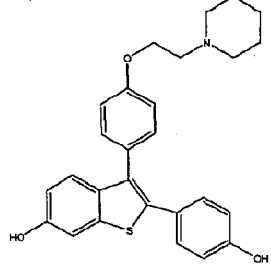
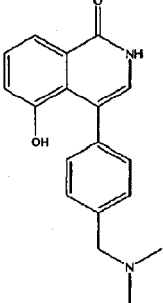
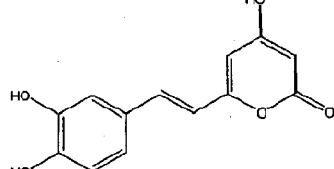
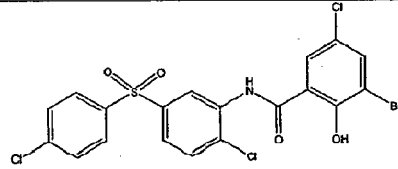
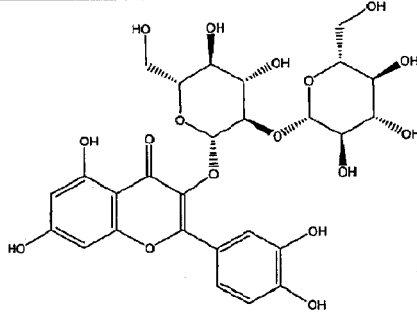
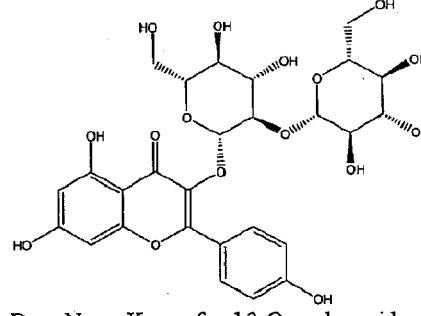
 Drug Name SM-322377 Chemical Name N-(2,6-Dimethylbenzyl)-3-[2(S)-hydroxy-3(S)-(3-hydroxy-2-methylbenzamido)-4-(3-methoxyphenyl)butyryl]-5,5-dimethylthiazolidine-4(R)-carboxamide	 Chemical Name 4-[Bis(2-chloroethyl)amino]phenol	 Chemical Name 5-Hydroxy-2-(4-iodophenyl)-2,3-dihydro-1H-isindole-1,3-dione
 Chemical Name 2-(4-Hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenyl]-1-benzothiophene-6-ol	 Drug Name KCL-010440, KCL-440 Chemical Name 4-[4-(Dimethylaminomethyl)phenyl]-5-hydroxyisoquinolin-1(2H)-one	 Drug Name Hispidin Chemical Name (E)-6-[2-(3,4-Dihydroxyphenyl)vinyl]-4-hydroxy-2H-pyran-2-one
 Drug Name BH3I-2 Chemical Name 3-Bromo-5-chloro-N-[2-chloro-5-(4-chlorophenylsulfonyl)phenyl]-2-hydroxybenzamide	 Drug Name Quercetin 3-O-sophoroside Chemical Name 1-O-[2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl]-2-O-beta-D-glucopyranosyl-beta-D-glucopyranoside	 Drug Name Kaempferol 3-O-sophoroside Chemical Name 1-O-[5,7-Dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-1-benzopyran-3-yl]-2-O-beta-D-glucopyranosyl-beta-D-glucopyranoside

FIGURE 2 cont.

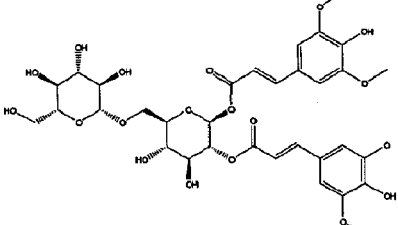
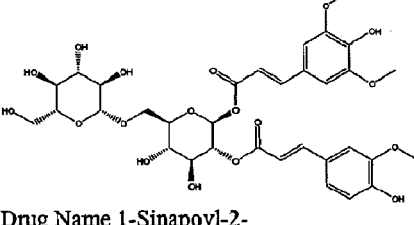
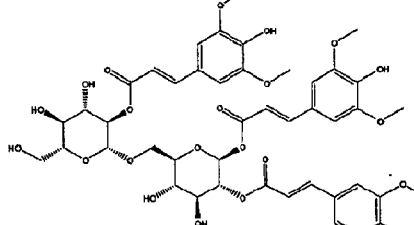
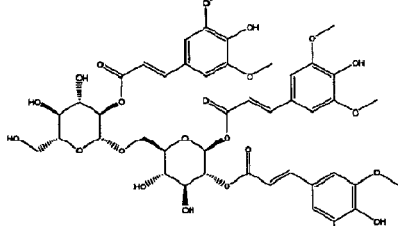
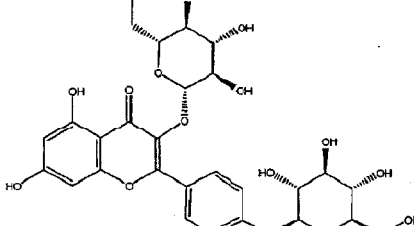
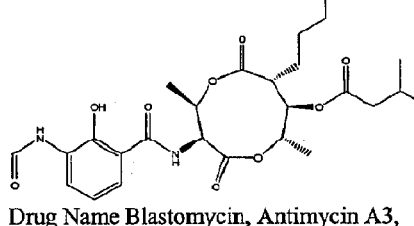
 Drug Name 1,2-Disinapoylgentiobioside Chemical Name 6-O-beta-D-Glucopyranosyl-1,2-bis-O-[3-(4-hydroxy-3,5-dimethoxyphenyl)-2(E)-propenoyl]-beta-D-glucopyranose	 Drug Name 1-Sinapoyl-2-feruloylgentiobioside Chemical Name 6-O-beta-D-Glucopyranosyl-1-O-[3-(4-hydroxy-3,5-dimethoxyphenyl)-2(E)-propenoyl]-2-O-[3-(4-hydroxy-3-methoxyphenyl)-2(E)-propenoyl]-beta-D-glucopyranose	 Drug Name 1,2'-Disinapoyl-2-feruloylgentiobiose Chemical Name 1,2'-Disinapoyl-2-feruloylgentiobiose; 1-O-[3-(4-Hydroxy-3,5-dimethoxyphenyl)-2(E)-propenoyl]-6-O-[2-O-[3-(4-hydroxy-3,5-dimethoxyphenyl)-2(E)-propenoyl]-beta-D-glucopyranosyl]-2-O-[3-(4-hydroxy-3-methoxyphenyl)-2(E)-propenoyl]-beta-D-glucopyranose
 Drug Name 1,2,2'-Trisinapoylgentiobiose Chemical Name 1,2-Bis-O-[3-(4-hydroxy-3,5-dimethoxyphenyl)-2(E)-propenoyl]-6-O-[2-O-[3-(4-hydroxy-3,5-dimethoxyphenyl)-2(E)-propenoyl]-beta-D-glucopyranosyl]-beta-D-glucopyranose	 Drug Name Quercetin 3,4'-di-O-beta-D-glucopyranoside Chemical Name 1-O-[4-[3-(beta-D-Glucopyranosyloxy)-5,7-dihydroxy-4-oxo-4H-1-benzopyran-2-yl]-2-hydroxyphenyl]-beta-D-glucopyranoside; Quercetin 3,4'-di-O-beta-D-glucopyranoside	 Drug Name Blastomycin, Antimycin A3, Blastmycin, NSC-58239 Chemical Name 3-Methylbutyric acid (2R,3S,6S,7R,8R)-8-butyl-3-[3-(formylamino)-2-hydroxybenzamido]-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester

FIGURE 2 cont.

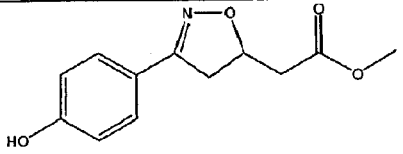
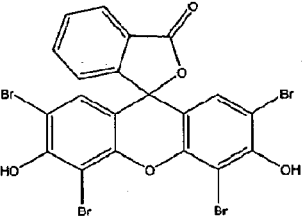
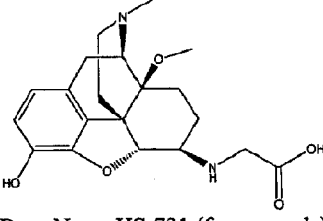
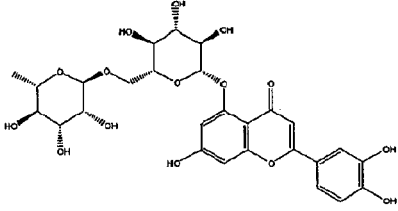
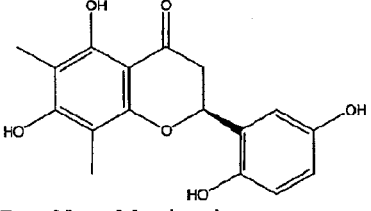
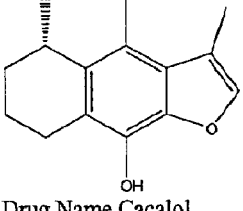
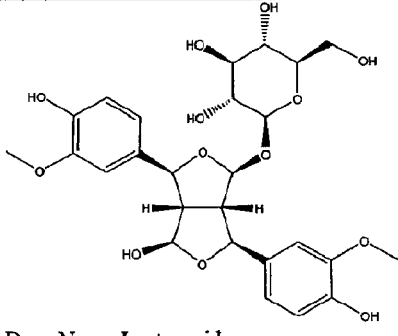
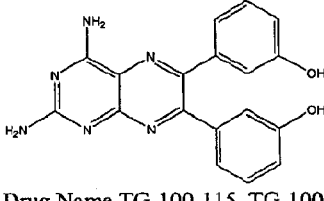
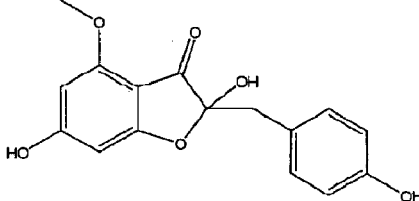
 Drug Name ISO-1 Chemical Name 2-[3-(4-Hydroxyphenyl)-4,5-dihydroisoxazol-5-yl]acetic acid methyl ester	 Drug Name Eosin Y, 2',4',5',7'-Tetrabromofluorescein, NSC-244436 Chemical Name 2',4',5',7'-Tetrabromo-3',6'-dihydroxyspiro[isobenzofuran-1(3H),9'-[9H]xanthen]-3-one;	 Drug Name HS-731 (former code), AS-006 Chemical Name N-(3-Hydroxy-14beta-methoxy-17-methyl-4,5alpha-epoxymorphinan-6beta-yl)glycine;
 Drug Name Luteolin-5-O-beta-rutinoside Chemical Name 6-O-(6-Deoxy-alpha-L-mannopyranosyl)-1-O-[2-(3,4-dihydroxyphenyl)-7-hydroxy-4-oxo-4H-1-benzopyran-5-yl]-beta-D-glucopyranoside	 Drug Name Myricacetin Chemical Name 2(S)-(2,5-Dihydroxyphenyl)-5,7-dihydroxy-6,8-dimethyl-3,4-dihydro-2H-1-benzopyran-4-one	 Drug Name Cacalol Chemical Name 3,4,5(S)-Trimethyl-5,6,7,8-tetrahydronaphtho[2,3-b]furan-9-ol
 Drug Name Lactucaside Chemical Name 1-O-[(1S,3S,3aS,4R,6S,6aS)-4-Hydroxy-3,6-bis(4-hydroxy-3-methoxyphenyl)perhydrofuro[3,4-c]furan-1-yl]-beta-D-glucopyranoside	 Drug Name TG-100-115, TG-100115 Chemical Name 3-[2,4-Diamino-6-(3-hydroxyphenyl)pteridin-7-yl]phenol;	 Drug Name Marsupsin Chemical Name (-)-2,6-Dihydroxy-2-(4-hydroxybenzyl)-4-methoxy-1-benzofuran-3(2H)-one

FIGURE 2 cont.

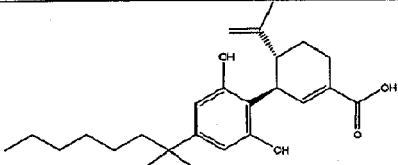
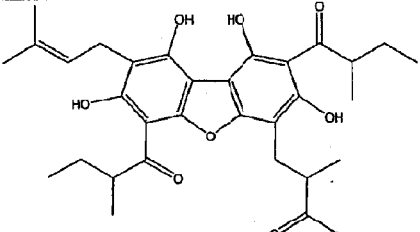
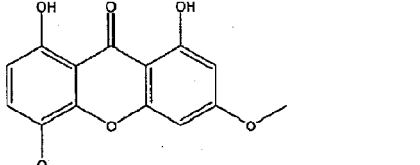
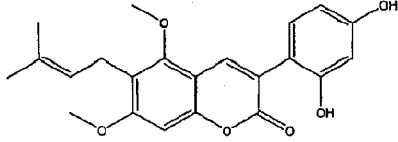
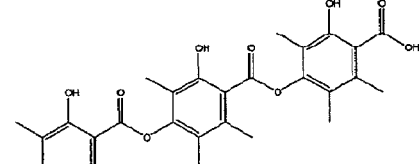
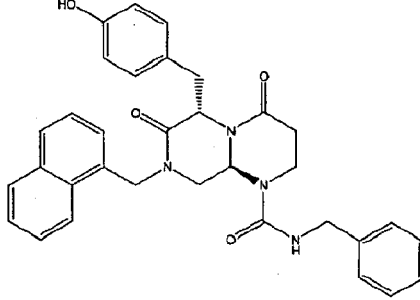
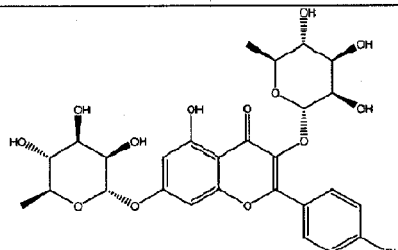
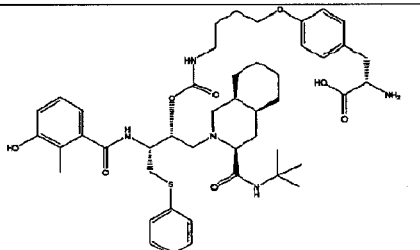
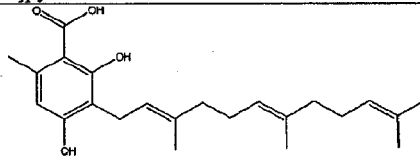
 Drug Name Hebrew University-320, CBD-DMH-7-oic acid, HU-320 Chemical Name 3(R)-[4-(1,1-Dimethylheptyl)-2,6-dihydroxyphenyl]-4(R)-isopropenyl-1-cyclohexene-1-carboxylic acid	 Drug Name Achyrofuran Chemical Name 2-Methyl-1-[1,3,7,9-tetrahydroxy-6-(2-methylbutyryl)-8-(3-methyl-2-butenyl)-4-(2-methyl-3-oxobutyl)dibenzo[b,d]furan-2-yl]butan-1-one	 Drug Name Swerchirin Chemical Name 1,8-Dihydroxy-3,5-dimethoxy-9H-xanthen-9-one
 Drug Name Glycyrin Chemical Name 3-(2,4-Dihydroxyphenyl)-5,7-dimethoxy-6-(3-methyl-2-butenyl)-2H-1-benzopyran-2-one	 Drug Name Thielavin A Chemical Name 4-[4-(2,4-Dihydroxy-3,6-dimethylbenzoyloxy)-2-hydroxy-3,5,6-trimethylbenzoyloxy]-2-hydroxy-3,5,6-trimethylbenzoic acid	 Drug Name ICG-001 Chemical Name (6S,9aS)-N-Benzyl-6-(4-hydroxybenzyl)-8-(naphthalen-1-ylmethyl)-4,7-dioxoperhydropyrazino[1,2-a]pyrimidine-1-carboxamide
 Drug Name Kaempferitrin Chemical Name 3,7-Bis(6-deoxy-alpha-L-mannopyranosyloxy)-5-hydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one	 Chemical Name O-[4-[1(R)-[(3S,4aS,8aS)-3-(N-tert-Butylcarbamoyl)perhydroisoquinolin-2-ylmethyl]-2(R)-(3-hydroxy-2-methylbenzamido)-3-(phenylsulfanyl)propyloxycarbonylamino]butyl]-L-tyrosine	 Drug Name Grifolic acid, Illicolinic acid B Chemical Name 2,4-Dihydroxy-6-methyl-3-[3,7,11-trimethyl-2(E),6(E),10-dodecatricenyl]benzoic acid

FIGURE 2 cont.

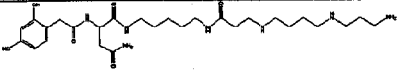
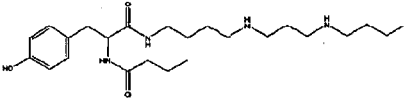
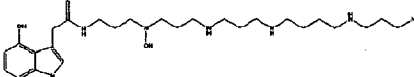
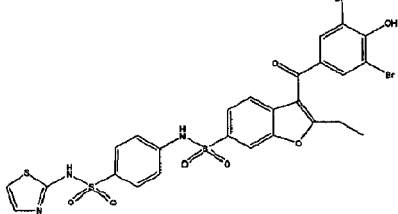
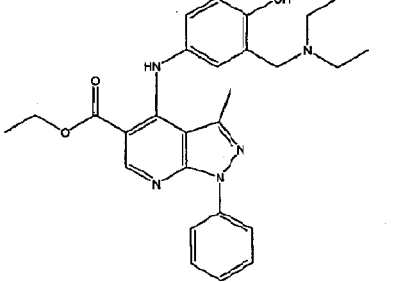
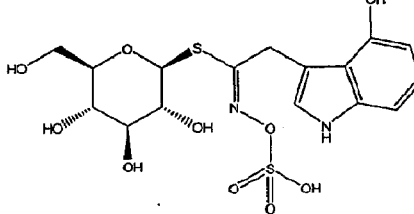
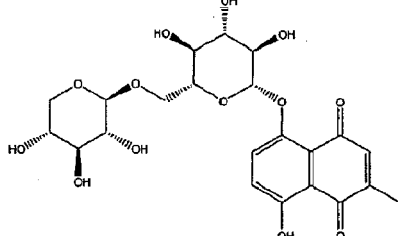
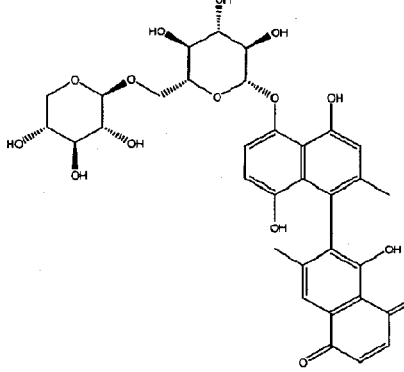
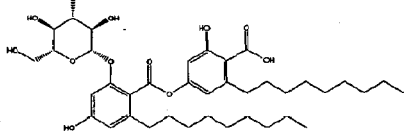
 Drug Name Joro spider toxin, JSTX-3, ALX-630-077 Chemical Name N1-[5-[N-[4-(3-Aminopropylamino)butyl]-beta-alanylaminopentyl]-N2-[2-(2,4-dihydroxyphenyl)acetyl]aspartamide	 Chemical Name N-[4-[3-(3-Aminopropylamino)propylamino]butyl]-N-butyryltyrosinamide	 Drug Name Agel-505 Chemical Name N-(20-Amino-4-hydroxy-4,8,12,17-tetraazaicos-1-yl)-2-(4-hydroxy-1H-indol-3-yl)acetamide
 Chemical Name 3-(3,5-Dibromo-4-hydroxybenzoyl)-2-ethyl-N-[4-[N-(2-thiazolyl)sulfamoyl]phenyl]-1-benzofuran-6-sulfonamide	 Chemical Name 4-[3-(Diethylaminomethyl)-4-hydroxyphenylamino]-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester	 Drug Name 4-Hydroxyglucobrassicin Chemical Name 1-S-[2-(4-Hydroxy-1H-indol-3-yl)-N-(sulfoxy)ethanimidoyl]-1-thio-beta-D-glucopyranose
 Drug Name Diospyroside B Chemical Name 1-O-(4-Hydroxy-6-methyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl)-6-O-beta-D-xylopyranosyl-beta-D-glucopyranoside	 Drug Name Diospyroside C Chemical Name 1-O-[1',4,8-Trihydroxy-2,3'-dimethyl-5',8'-dioxo-5',8'-dihydro-1,2'-binaphthalen-5-yl]-6-O-beta-D-xylopyranosyl-beta-D-glucopyranoside	 Drug Name Exophillic acid Chemical Name 4-[2-(beta-D-Glucopyranosyloxy)-4-hydroxy-6-nonylbenzoyloxy]-2-hydroxy-6-nonylbenzoic acid

FIGURE 2 cont.

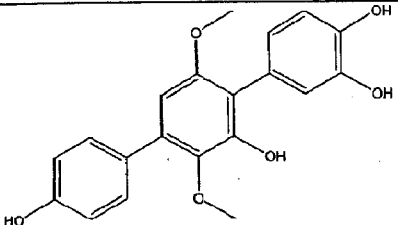
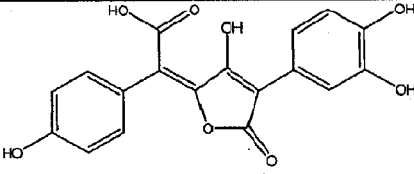
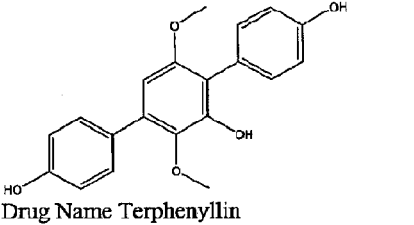
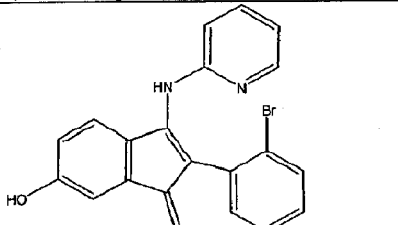
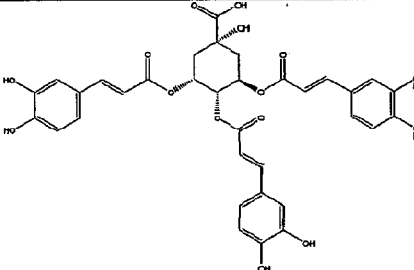
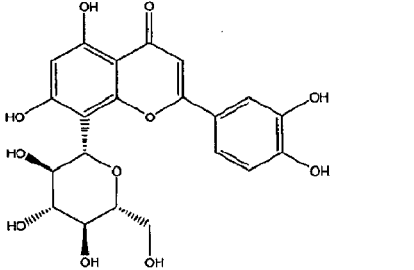
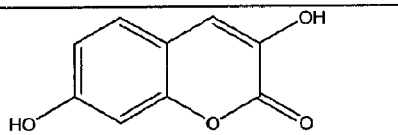
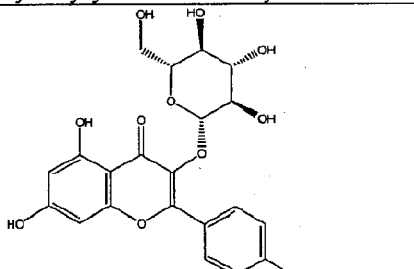
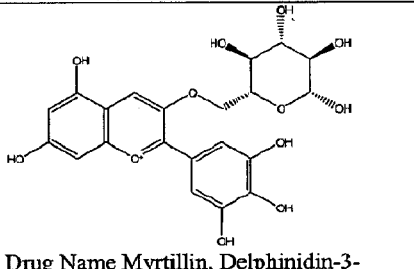
 Drug Name Hydroxyterphenyllin Chemical Name 3',6'-Dimethoxy-1,1':4',1''-terphenyl-2',3,4,4''-tetrol	 Drug Name Xerocomic acid Chemical Name 2-[4-(3,4-Dihydroxyphenyl)-3-hydroxy-5-oxofuran-2(5H)-ylidene]-2-(4-hydroxyphenyl)acetic acid	 Drug Name Terphenyllin Chemical Name 3',6'-Dimethoxy-1,1':4',1''-terphenyl-2',4,4''-triol
 Chemical Name 2-(2-Bromophenyl)-6-hydroxy-3-(pyridin-2-ylamino)-1H-inden-1-one	 Drug Name 3,4,5-tricafeoylquinic acid, 3,4,5-tri-CQA Chemical Name 3(R),4,5(R)-Tris[3-(3,4-dihydroxyphenyl)-2(E)-propenoxy]-1-hydroxycyclohexanecarboxylic acid	 Drug Name Luteolin 8-C-beta-D-glucopyranoside, Lutexin, Orientin Chemical Name 2-(3,4-Dihydroxyphenyl)-8-(beta-D-glucopyranosyl)-5,7-dihydroxy-4H-1-benzopyran-4-one
 Drug Name 3-Hydroxyumbelliferone, 3,7-Dihydroxycoumarin Chemical Name 3,7-Dihydroxy-2H-1-benzopyran-2-one	 Drug Name Astragalin, Kaempferol 3-glucoside, Kaempferol 3-O-beta-D-glucopyranoside Chemical Name 5,7-Dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-1-benzopyran-3-yl beta-D-glucopyranoside	 Drug Name Myrtillin, Delphinidin-3-glucoside Chemical Name 1-O-[5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)benzopyrilium-3-yl]-beta-D-glucopyranoside chloride

FIGURE 2 cont.

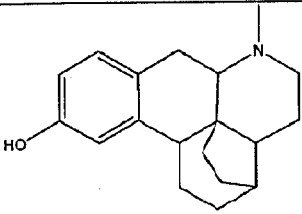
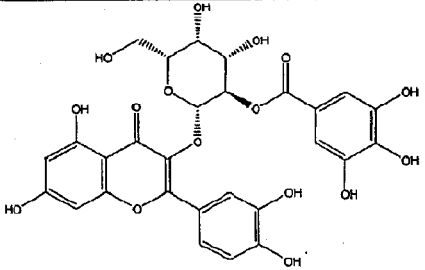
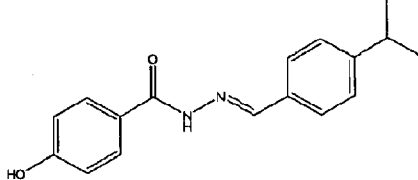
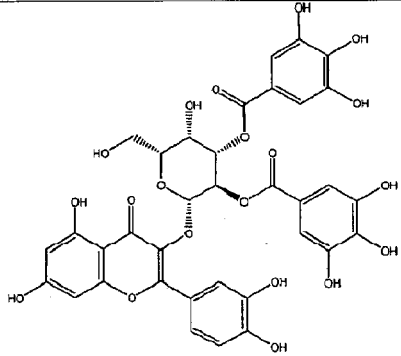
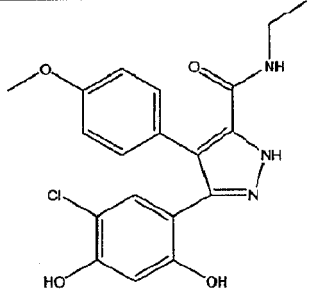
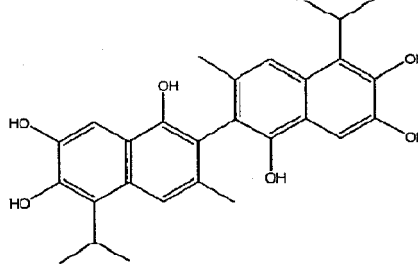
 Drug Name N-Methyl-HHA phenol Chemical Name 6-methyl-1,2,3,3a,4,5,6,6a,7,11b-decahydro-3,11c-ethanodibenzo[de,g]quinolin-10-ol	 Drug Name Quercetin 3-O-(2'-galloyl)-beta-D-galactopyranoside Chemical Name 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl 2-O-(3,4,5-trihydroxybenzoyl)-beta-D-galactopyranoside	 Drug Name GSK-4716 Chemical Name 4-Hydroxy-N'-(4-Isopropylphenylmethylidene)benzohydrazide
 Drug Name Quercetin 3-O-(2'',3''-digalloyl)-beta-D-galactopyranoside Chemical Name 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl 2,3-bis-O-(3,4,5-trihydroxybenzoyl)-beta-D-galactopyranoside	 Drug Name VER-49009 Chemical Name 3-(5-Chloro-2,4-dihydroxyphenyl)-N-ethyl-4-(4-methoxyphenyl)-1H-pyrazole-5-carboxamide	 Drug Name Apogossypol, NSC-736630 Chemical Name 5,5'-Diisopropyl-3,3'-dimethyl-2,2'-binaphthalene-1,1',6,6',7,7'-hexol

FIGURE 2 cont.

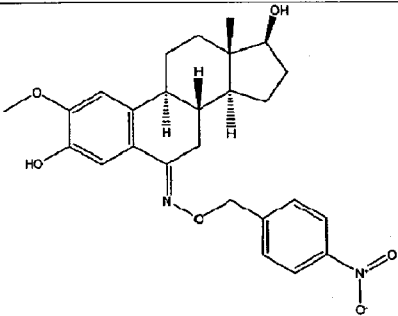
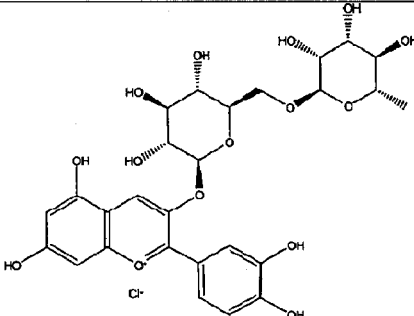
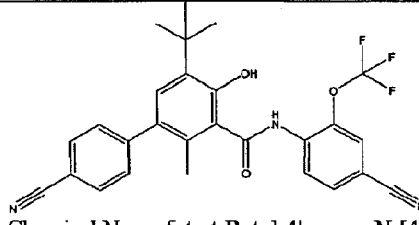
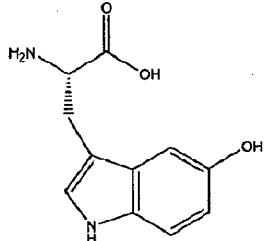
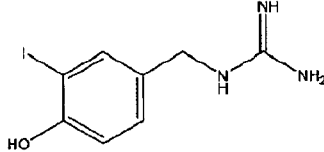
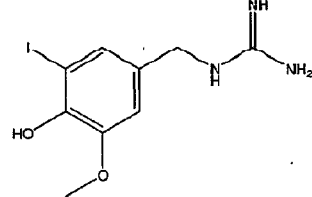
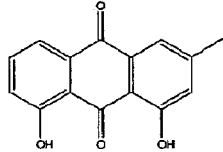
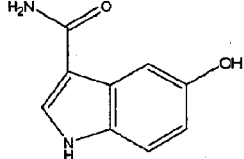
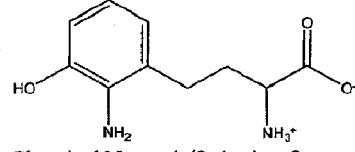
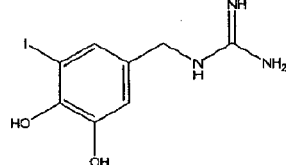
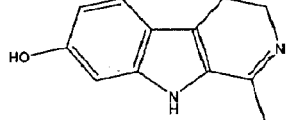
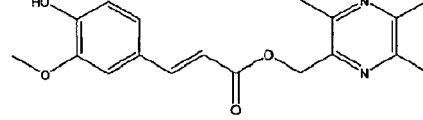
 Drug Name CP-2117 Chemical Name 3,17beta-Dihydroxy-2-methoxyestra-1,3,5(10)-trien-6-one O-(4-nitrobenzyl)oxime	 Drug Name Cyanidin 3-rutinoside, Antirrhinin Chemical Name 1-O-[2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-1-benzopyrylium-3-yl]-6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranoside chloride; 3-[6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranosyloxy]-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-1-benzopyrylium chloride	 Chemical Name 5-tert-Butyl-4'-cyano-N-[4-cyano-2-(trifluoromethoxy)phenyl]-4-hydroxy-2-methylbiphenyl-3-carboxamide
 Chemical Name 5-Hydroxy-L-tryptophan	 Drug Name HIBG Chemical Name N-(4-Hydroxy-3-iodobenzyl)guanidine	 Drug Name HIMBG Chemical Name N-(4-Hydroxy-3-iodo-5-methoxybenzyl)guanidine
 Drug Name Chrysophanol, Chrysophanic acid, NSC-646567, NSC-37132 Chemical Name 1,8-Dihydroxy-3-methylantra-9,10-quinone	 Chemical Name 5-Hydroxy-1H-indole-3-carboxamide	 Chemical Name 4-(2-Amino-3-hydroxyphenyl)-2-ammoniobutanoate
 Drug Name DHIBG Chemical Name N-(3,4-Dihydroxy-5-iodobenzyl)guanidine	 Chemical Name 1-Methyl-4,9-dihydro-3H-beta-carboline-7-ol	 Chemical Name 3-(4-Hydroxy-3-methoxyphenyl)-2-propenoic acid (3,5,6-trimethylpyrazin-2-yl)methyl ester

FIGURE 2 cont.

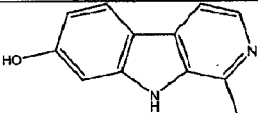
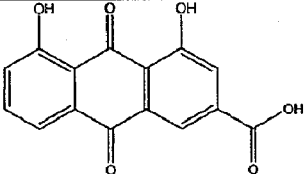
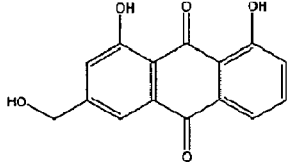
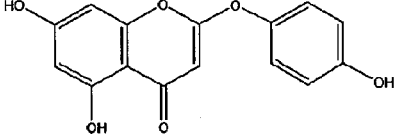
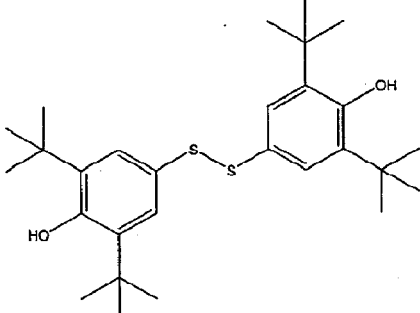
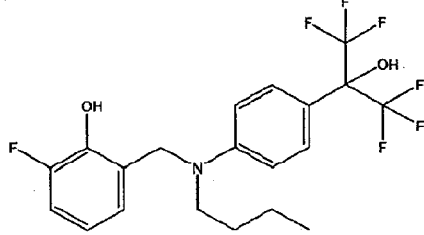
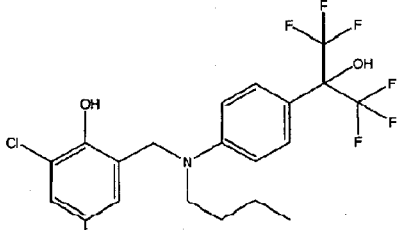
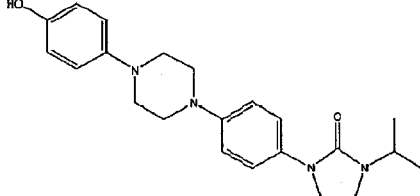
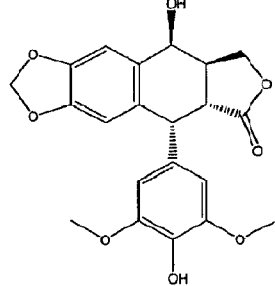
 Chemical Name 1-Methyl-9H-beta-carboline-7-ol	 Drug Name Rhein Chemical Name 4,5-Dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid	 Drug Name aloe-emodin Chemical Name 1,8-Dihydroxy-3-(hydroxymethyl)anthra-9,10-quinone
 Drug Name 6-Desmethoxycapillarisin Chemical Name 5,7-Dihydroxy-2-(4-hydroxyphenoxy)-4H-1-benzopyran-4-one	 Drug Name DTBP Chemical Name 4,4'-Bis(sulfanyl)bis(2,6-di-tert-butylphenol)	 Chemical Name 2-[N-Butyl-N-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]aminomethyl]-6-fluorophenol
 Chemical Name 2-[N-Butyl-N-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]aminomethyl]-4,6-dichlorophenol	 Chemical Name 1-{4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl}-3-isopropyl-2-imidazolidinone	 Chemical Name (5R,5aR,8aR,9S)-9-Hydroxy-5-(4-hydroxy-3,5-dimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(5aH)-one

FIGURE 2 cont.

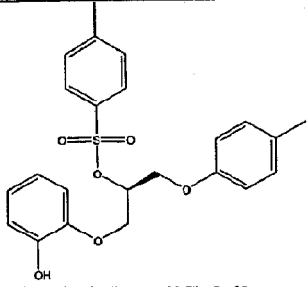
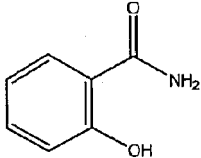
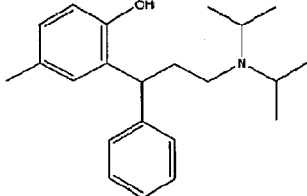
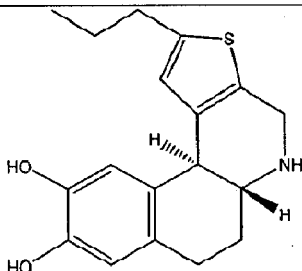
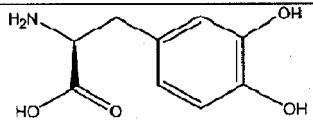
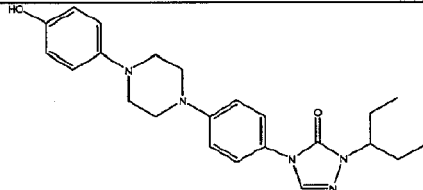
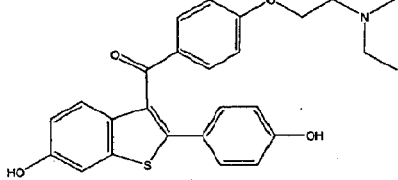
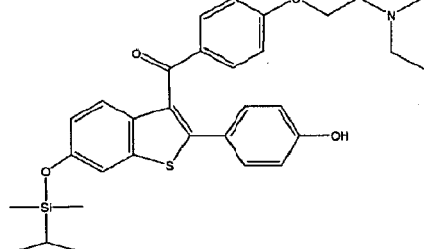
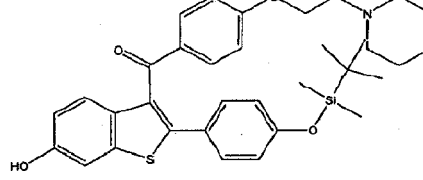
 Chemical Name (1S)-2-(2-hydroxyphenoxy)-1-[(4-methylphenoxy)methyl]ethyl 4-methylbenzenesulfonate	 Chemical Name salicylamide	 Chemical Name 2-[3-(Diisopropylamino)-1-phenylpropyl]-4-methylphenol
 Chemical Name (5aR,11bS)-2-propyl-4,5,5a,6,7,11b-hexahydrobenzo[f]thieno[2,3-c]quinoline-9,10-diol	 Chemical Name Levodopa; (2S)-2-amino-3-(3,4-dihydroxyphenyl)propionic acid; 3-hydroxy-L-tyrosine	 Chemical Name 2-(1-ethylpropyl)-4-[4-(4-hydroxyphenyl)piperazino]phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one
 Chemical Name [6-hydroxy-2-(4-hydroxyphenyl)-1-benzothiophen-3-yl][4-(2-piperidinoethoxy)phenyl]methanone	 Chemical Name [6-[[tert-butyl(dimethyl)silyl]oxy]-2-(4-hydroxyphenyl)-1-benzothiophen-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone	 Chemical Name [2-(4-[[tert-butyl(dimethyl)silyl]oxy]phenyl)-6-hydroxy-1-benzothiophen-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone

FIGURE 2 cont.

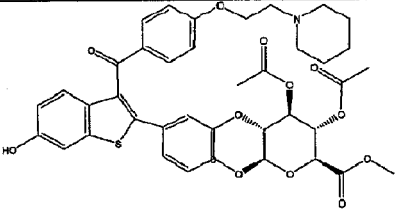
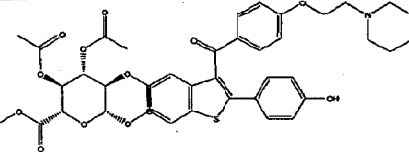
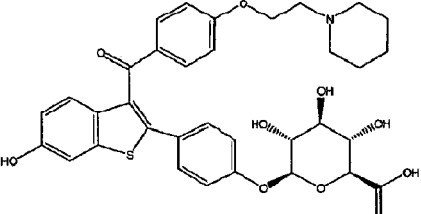
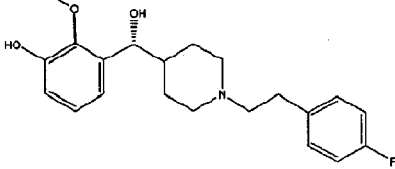
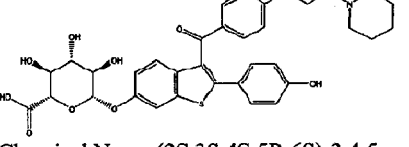
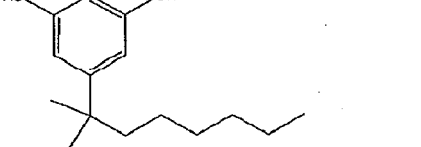
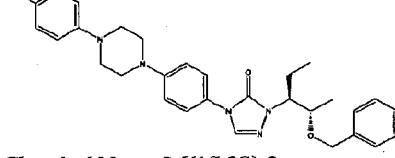
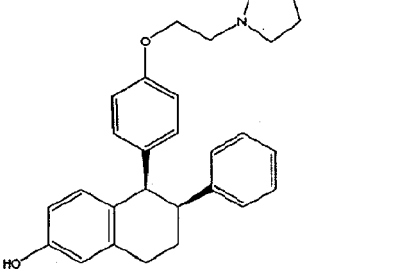
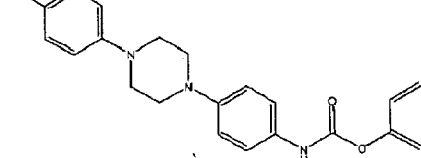
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 Chemical Name 3-[(R)-[1-(4-fluorophenethyl)-4-piperidinyl](hydroxy)methyl]-2-methoxyphenol	 Chemical Name (2S,3S,4S,5R,6S)-3,4,5-trihydroxy-6-[2-(4-hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]-1-benzothiophen-6-yl]oxy]tetrahydro-2H-pyran-2-carboxylic acid	 Chemical Name 5-(1,1-dimethylheptyl)-1,3-benzenediol
 Chemical Name 2-[(1S,2S)-2-(benzyloxy)-1-ethylpropyl]-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one	 Chemical Name (5R,6S)-6-phenyl-5-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-5,6,7,8-tetrahydro-2-naphthalenol	 Chemical Name phenyl N-[4-[4-(4-hydroxyphenyl)piperazinyl]phenyl]carbamate

FIGURE 2 cont.

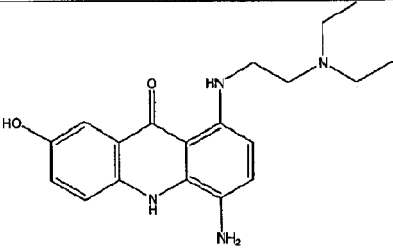
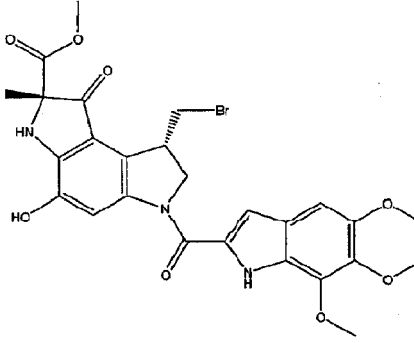
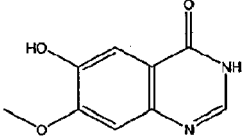
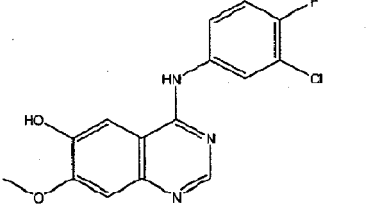
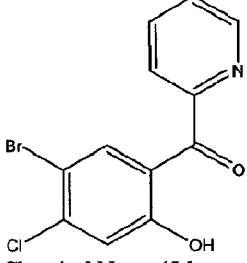
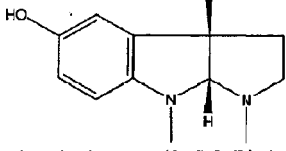
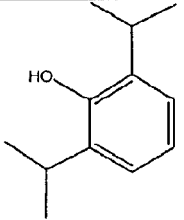
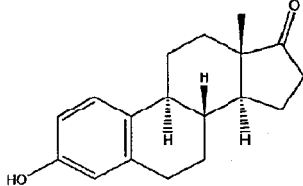
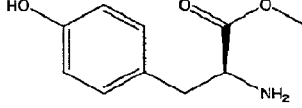
 Chemical Name 4-amino-1-[[2-(diethylamino)ethyl]amino]-7-hydroxy-9(10H)-acridinone		 Chemical Name methyl (2S,8S)-8-(bromomethyl)-4-hydroxy-2-methyl-1-oxo-6-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-1,2,3,6,7,8-hexahydropyrrolo[3,2-e]indole-2-carboxylate
		 Chemical Name 6-hydroxy-7-methoxy-4(3H)-quinazolinone
 Chemical Name 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-quinazolinol	 Chemical Name (5-bromo-4-chloro-2-hydroxyphenyl)(2-pyridinyl)methanone	 Chemical Name (3aS,8aR)-1,3a,8-trimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-5-ol
 Chemical Name 2,6-Diisopropylphenol	 Chemical Name (8R,9S,13S,14S)-3-hydroxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one	 Chemical Name methyl (2S)-2-amino-3-(4-hydroxyphenyl)propanoate

FIGURE 2 cont.

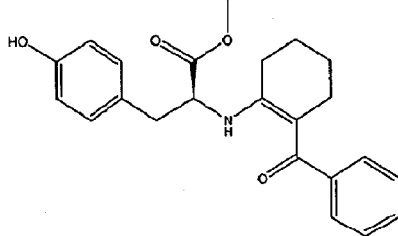
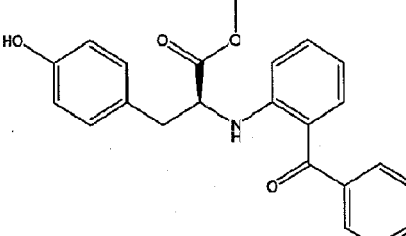
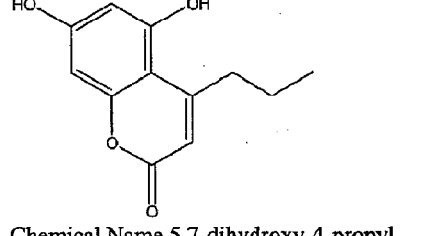
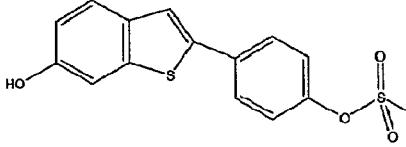
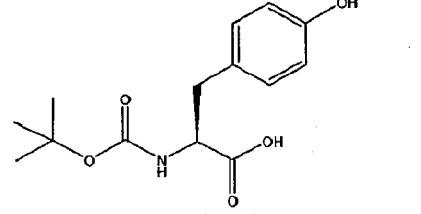
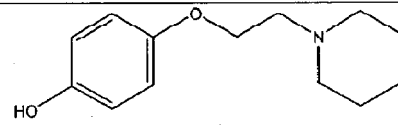
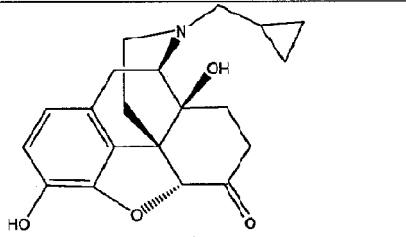
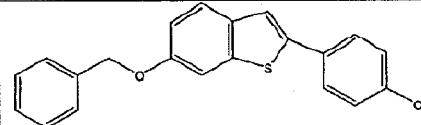
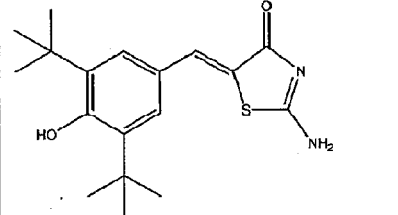
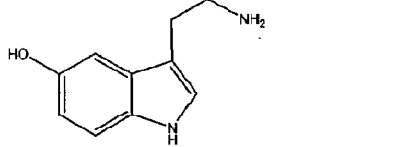
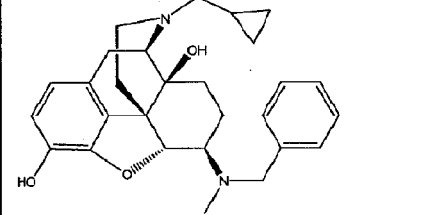
 Chemical Name methyl (2S)-2-[(2-benzoyl-1-cyclohexen-1-yl)amino]-3-(4-hydroxyphenyl)propanoate	 Chemical Name methyl (2S)-2-(2-benzoylanilino)-3-(4-hydroxyphenyl)propanoate	 Chemical Name 5,7-dihydroxy-4-propyl-2H-chromen-2-one
	 Chemical Name 4-(6-hydroxy-1-benzothiophen-2-yl)phenyl methanesulfonate	 Chemical Name (2S)-2-[(tert-butoxycarbonyl)amino]-3-(4-hydroxyphenyl)propionic acid
 Chemical Name 4-[2-(1-piperidinyl)ethoxy]phenol	 Chemical Name Naltrexone; (1S,5R,13R,17S)-4-(cyclopropylmethyl)-10,17-dihydroxy-12-oxa-4-azapentacyclo[9.6.1.0(1,13).0(5,17).0(7,18)]octadeca-7(18),8,10-trien-14-one	 Chemical Name 4-[6-(benzyloxy)-1-benzothiophen-2-yl]phenol
 Chemical Name 2-amino-5-[(Z)-[3,5-di(tert-butyl)-4-methylphenyl]methylidene]-1,3-thiazol-4-one	 Chemical Name 3-(2-Aminoethyl)-1H-indol-5-ol; 5-Hydroxytryptamine; 3-(2-Aminoethyl)-5-hydroxyindole	 Chemical Name (1S,5R,13R,14R,17S)-14-[benzyl(methyl)amino]-4-(cyclopropylmethyl)-12-oxa-4-azapentacyclo[9.6.1.0(1,13).0(5,17).0(7,18)]octadeca-7(18),8,10-triene-10,17-diol

FIGURE 2 cont.

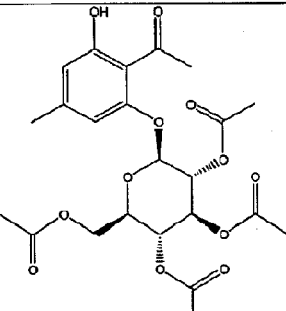
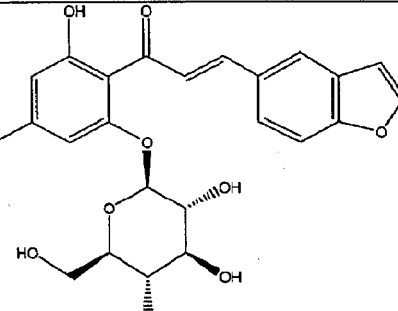
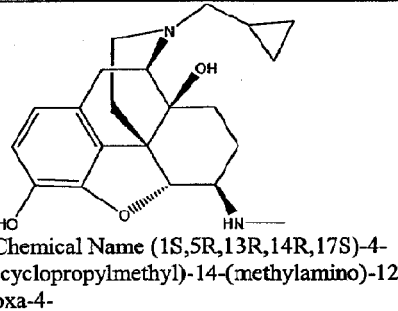
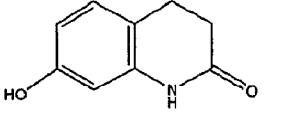
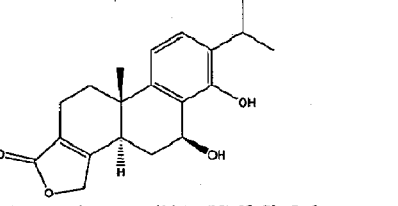
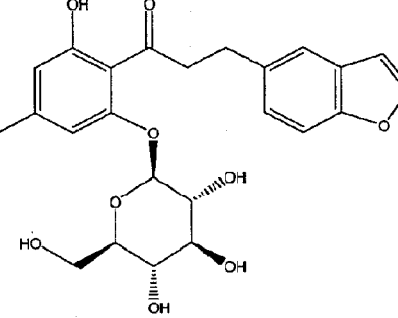
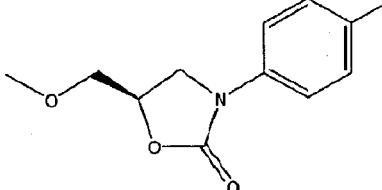
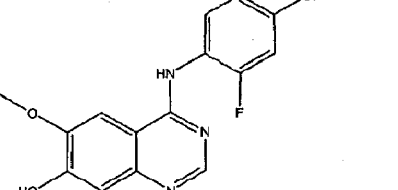
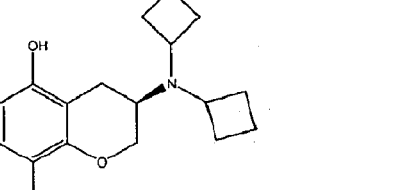
 Chemical Name (2R,3R,4S,5R,6S)-6-(2-acetyl-3-hydroxy-5-methylphenoxy)-4,5-bis(acetoxy)-2-[(acetoxymethyl)tetrahydro-2H-pyran-3-yl]acetate	 Chemical Name (E)-3-(1-benzofuran-5-yl)-1-(2-hydroxy-4-methyl-6-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl]oxy]phenyl)-2-propen-1-one	 Chemical Name (1S,5R,13R,14R,17S)-4-(cyclopropylmethyl)-14-(methylamino)-12-oxa-4-azapentacyclo[9.6.1.0(1,13).0(5,17).0(7,18)]octadeca-7(18),8,10-triene-10,17-diol
 Chemical Name 7-hydroxy-3,4-dihydro-2(1H)-quinolinone	 Chemical Name (3bR,5S,9bS)-5,6-dihydroxy-7-isopropyl-9b-methyl-3b,4,5,9b,10,11-hexahydrophenanthro[1,2-c]furan-1(3H)-one	 Chemical Name 3-(1-benzofuran-5-yl)-1-(2-hydroxy-4-methyl-6-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl]oxy]phenyl)-1-propanone
 Chemical Name (5R)-3-(4-hydroxyphenyl)-5-(methoxymethyl)-1,3-oxazolidin-2-one	 Chemical Name 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-quinazolinol	 Chemical Name (3R)-3-(dicyclobutylamino)-8-fluoro-3,4-dihydro-2H-chromen-5-ol

FIGURE 2 cont.

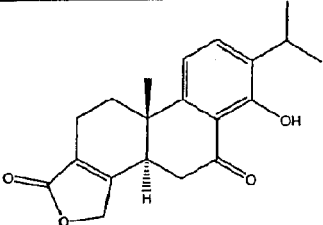
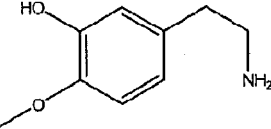
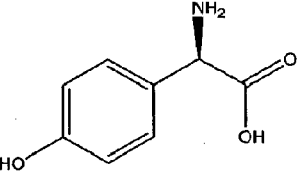
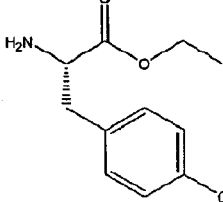
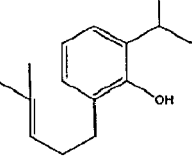
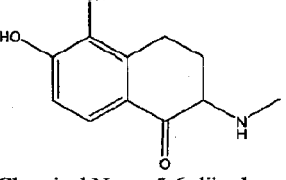
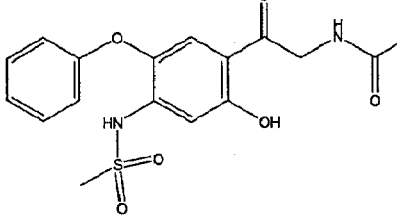
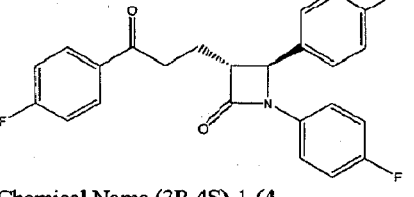
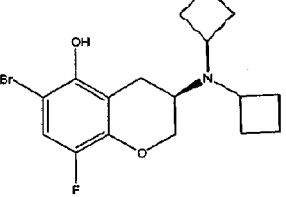
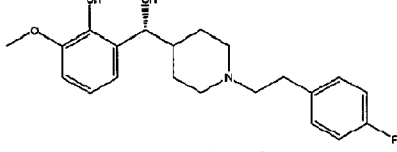
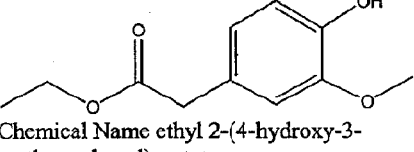
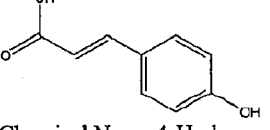
 Chemical Name (3bR,9bS)-6-hydroxy-7-isopropyl-9b-methyl-3,3b,4,9b,10,11-hexahydrophenanthro[1,2-c]furan-1,5-dione	 Chemical Name 5-(2-aminoethyl)-2-methoxyphenol	 Chemical Name D-(-)-p-Hydroxyphenylglycine; (R)-2-amino-2-(4-hydroxyphenyl)acetic acid; (2R)-2-(4-hydroxyphenyl)glycine; (2R)-2-amino-2-(4-hydroxyphenyl)ethanoic acid
 Chemical Name ethyl (2S)-2-amino-3-(4-hydroxyphenyl)propanoate	 Chemical Name 2-isopropyl-6-(4-methyl-3-pentenyl)phenol	 Chemical Name 5,6-dihydroxy-2-(methylamino)-3,4-dihydro-1(2H)-naphthalenone
 Chemical Name N-[4-[2-(formylamino)acetyl]-5-hydroxy-2-phenoxyphenyl]methanesulfonamide	 Chemical Name (3R,4S)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-oxopropyl]-4-(4-hydroxyphenyl)-2-azetidinone	 Chemical Name (3R)-6-bromo-3-(dicyclobutylamino)-8-fluoro-3,4-dihydro-2H-chromen-5-ol
 Chemical Name 2-[(R)-[1-(4-fluorophenethyl)-4-piperidinyl](hydroxy)methyl]-6-methoxyphenol	 Chemical Name ethyl 2-(4-hydroxy-3-methoxyphenyl)acetate	 Chemical Name 4-Hydroxy cinnamic acid; (E)-3-(4-Hydroxyphenyl)-2-propenoic acid

FIGURE 2 cont.

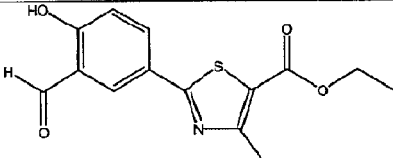
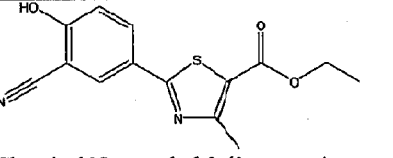
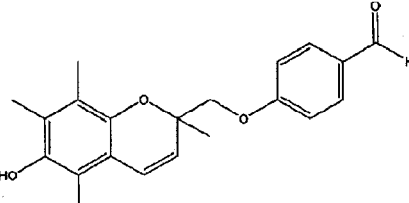
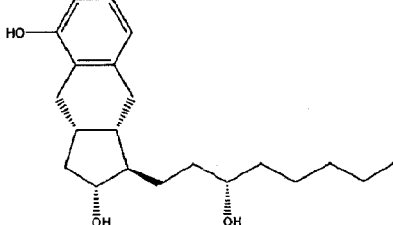
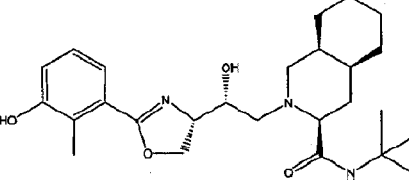
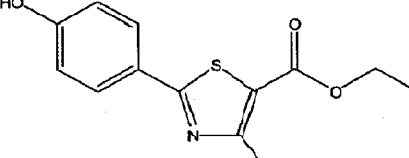
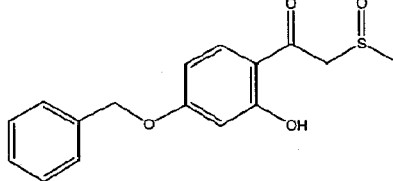
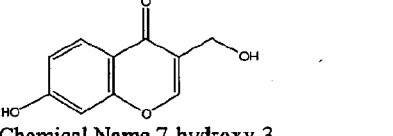
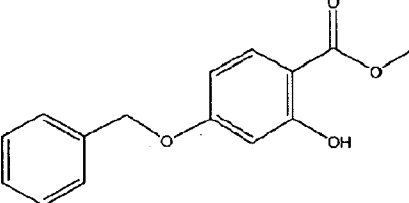
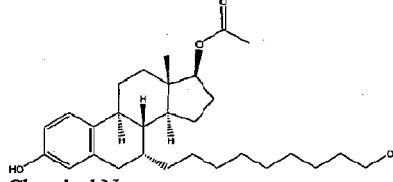
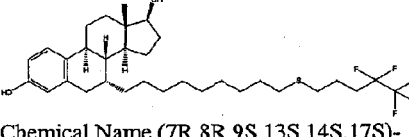
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 Chemical Name (1R,2R,3aS,9aS)-1-[(3S)-3-hydroxyoctyl]-2,3,3a,4,9,9a-hexahydro-1H-cyclopenta[b]naphthalene-2,5-diol	 Chemical Name (3S,4aS,8aS)-N-(tert-butyl)-2-[(2R)-2-hydroxy-2-[(4S)-2-(3-hydroxy-2-methylphenyl)-4,5-dihydro-1,3-oxazol-4-yl]ethyl]decahydro-3-isoquinolinecarboxamide	 Chemical Name ethyl 2-(4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
 Chemical Name 1-[4-(benzyloxy)-2-hydroxyphenyl]-2-(methylsulfinyl)-1-ethanone	 Chemical Name 7-hydroxy-3-(hydroxymethyl)-4H-chromen-4-one	 Chemical Name methyl 4-(benzyloxy)-2-hydroxybenzoate
 Chemical Name (7R,8R,9S,13S,14S,17S)-3-hydroxy-7-(9-hydroxynonyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl acetate	 Chemical Name (7R,8R,9S,13S,14S,17S)-13-methyl-7-[9-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]nonyl]-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol	

FIGURE 2 cont.

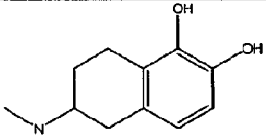
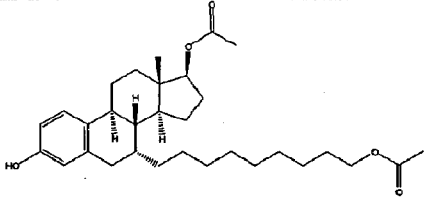
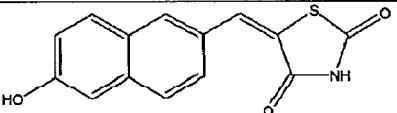
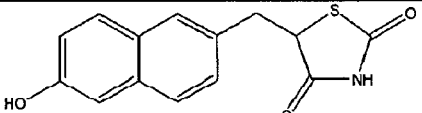
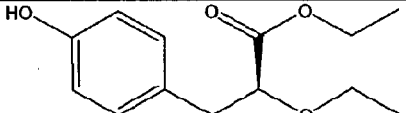
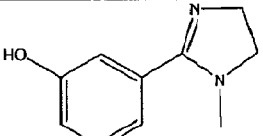
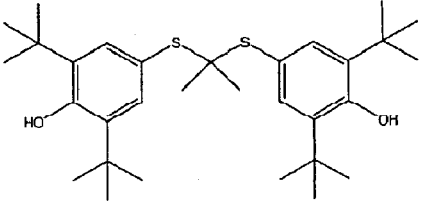
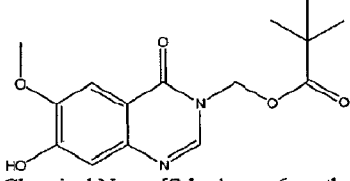
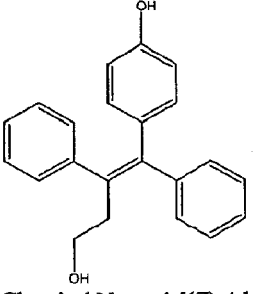
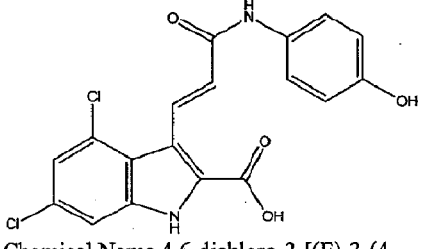
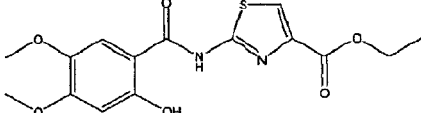
	 Chemical Name 6-(methylamino)-5,6,7,8-tetrahydro-1,2-naphthalenediol	 Chemical Name 9-[(7R,8R,9S,13S,14S,17S)-17-(acetoxy)-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-7-yl]nonyl acetate
 Chemical Name 5-[(E)-(6-hydroxy-2-naphthyl)methylidene]-1,3-thiazolidine-2,4-dione	 Chemical Name 5-[(6-hydroxy-2-naphthyl)methyl]-1,3-thiazolidine-2,4-dione	 Chemical Name ethyl (2S)-2-ethoxy-3-(4-hydroxyphenyl)propanoate
 Chemical Name 3-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)phenol	 Chemical Name 2,6-di(tert-butyl)-4-[(1-[[3,5-di(tert-butyl)-4-hydroxyphenyl]sulfanyl]-1-methylethyl)sulfanyl]phenol	 Chemical Name [7-hydroxy-6-methoxy-4-oxo-3(4H)-quinazolinyl]methyl pivalate
 Chemical Name 4-[(Z)-4-hydroxy-1,2-diphenyl-1-butenyl]phenol	 Chemical Name 4,6-dichloro-3-[(E)-3-(4-hydroxyanilino)-3-oxo-1-propenyl]-1H-indole-2-carboxylic acid	 Chemical Name ethyl 2-[(2-hydroxy-4,5-dimethoxybenzoyl)amino]-1,3-thiazole-4-carboxylate

FIGURE 2 cont.

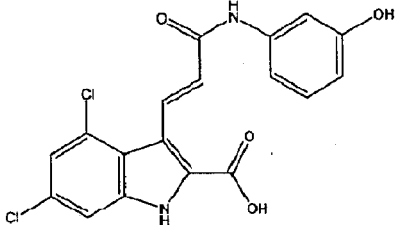
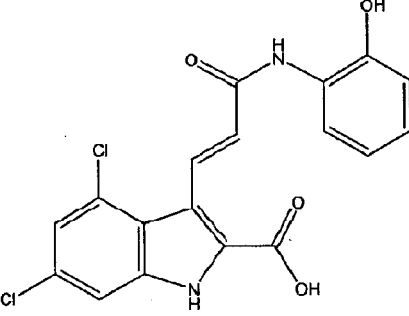
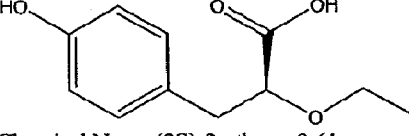
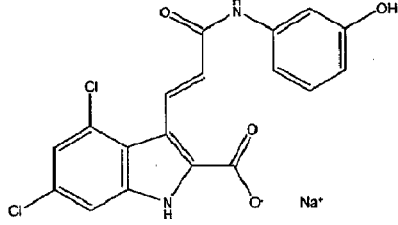
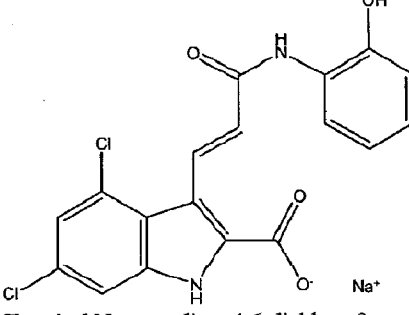
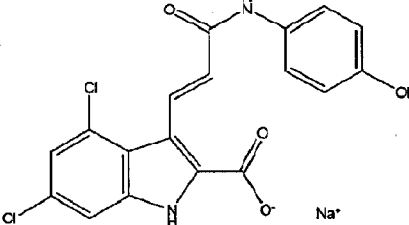
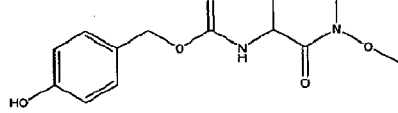
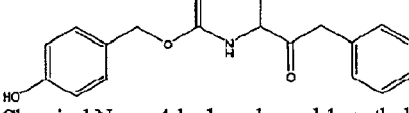
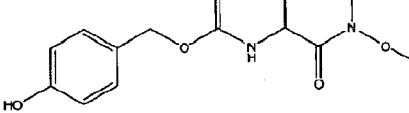
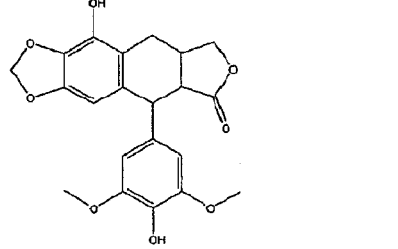
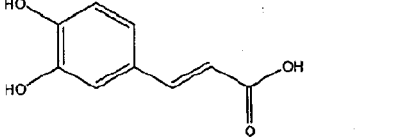
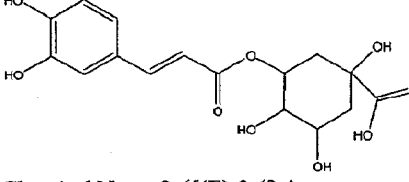
 Chemical Name 4,6-dichloro-3-[(E)-3-(3-hydroxyanilino)-3-oxo-1-propenyl]-1H-indole-2-carboxylic acid	 Chemical Name 4,6-dichloro-3-[(E)-3-(2-hydroxyanilino)-3-oxo-1-propenyl]-1H-indole-2-carboxylic acid	 Chemical Name (2S)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid
 Chemical Name sodium 4,6-dichloro-3-[(E)-3-(3-hydroxyanilino)-3-oxo-1-propenyl]-1H-indole-2-carboxylate	 Chemical Name sodium 4,6-dichloro-3-[(E)-3-(2-hydroxyanilino)-3-oxo-1-propenyl]-1H-indole-2-carboxylate	 Chemical Name sodium 4,6-dichloro-3-[(E)-3-(4-hydroxyanilino)-3-oxo-1-propenyl]-1H-indole-2-carboxylate
 Chemical Name 4-hydroxybenzyl 2-[methoxy(methyl)amino]-1-methyl-2-oxoethylcarbamate	 Chemical Name 4-hydroxybenzyl 1-methyl-2-oxo-3-phenylpropylcarbamate	 Chemical Name 4-hydroxybenzyl 2-[methoxy(methyl)amino]-1-methyl-2-oxoethylcarbamate
 Chemical Name 10-hydroxy-5-(4-hydroxy-3,5-dimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(5aH)-one	 Chemical Name (E)-3-(3,4-dihydroxyphenyl)-2-propenoic acid	 Chemical Name 3-([(E)-3-(3,4-dihydroxyphenyl)-2-propenyl]oxy)-1,4,5-trihydroxycyclohexanecarboxylic acid

FIGURE 2 cont.

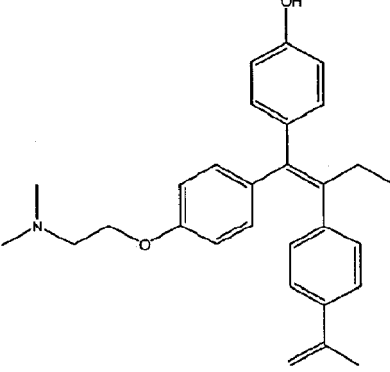
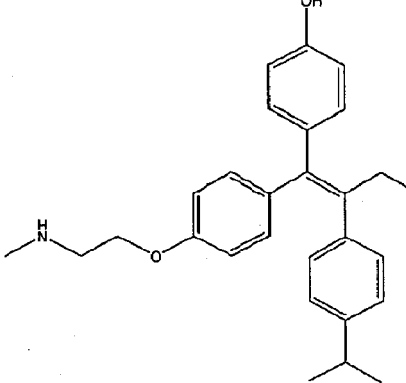
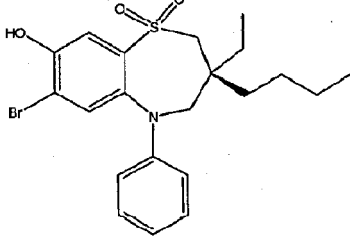
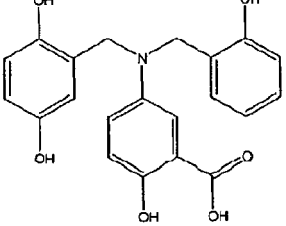
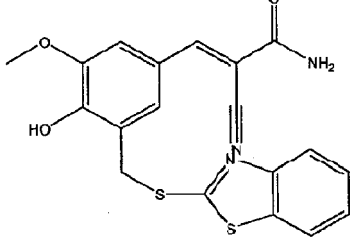
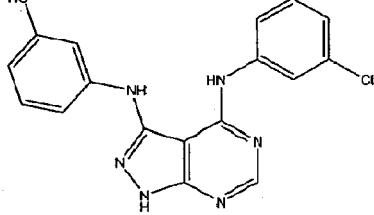
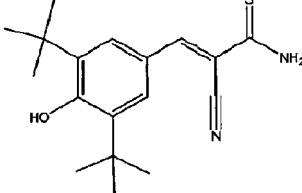
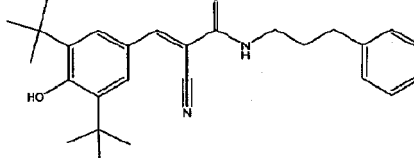
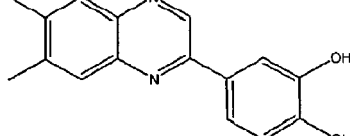
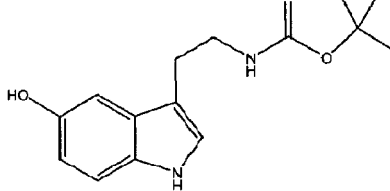
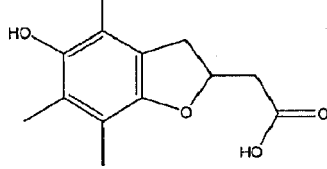
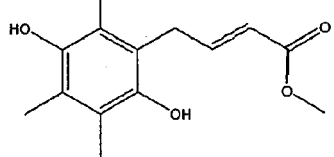
 Chemical Name 4-[(Z)-1-{4-[2-(dimethylamino)ethoxy]phenyl}-2-(4-isopropenylphenyl)-1-butenyl]phenol	 Chemical Name 4-[(Z)-2-(4-isopropylphenyl)-1-{4-[2-(methylamino)ethoxy]phenyl}-1-butenyl]phenol	 Chemical Name (3S)-7-bromo-3-butyl-3-ethyl-8-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1H-1lambda~6~,5-benzothiazepine-1,1-dione
 Chemical Name 5-[(2,5-dihydroxybenzyl)(2-hydroxybenzyl)amino]-2-hydroxybenzoic acid	 Chemical Name (E)-3-{3-[(1,3-benzothiazol-2-ylsulfanyl)methyl]-4-hydroxy-5-methoxyphenyl}-2-cyano-2-propenamide	 Chemical Name 3-{[4-(3-chloroanilino)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]amino}phenol
 Chemical Name (E)-2-cyano-3-[3,5-di(tert-butyl)-4-hydroxyphenyl]-2-propenethioamide	 Chemical Name (E)-2-cyano-3-[3,5-di(tert-butyl)-4-hydroxyphenyl]-N-(3-phenylpropyl)-2-propenamide	 Chemical Name 4-(6,7-dimethyl-2-quinoxaliny)-1,2-benzenediol
 Chemical Name tert-butyl 2-(5-hydroxy-1H-indol-3-yl)ethylcarbamate	 Chemical Name 2-(5-hydroxy-4,6,7-trimethyl-2,3-dihydro-1-benzofuran-2-yl)acetic acid	 Chemical Name methyl (E)-4-(2,5-dihydroxy-3,4,6-trimethylphenyl)-2-butenate

FIGURE 2 cont.

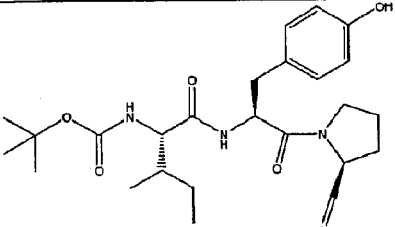
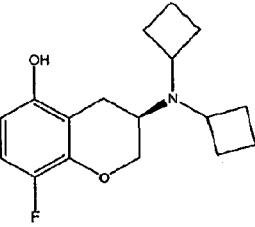
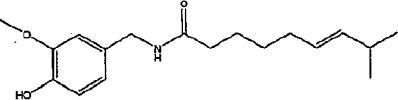
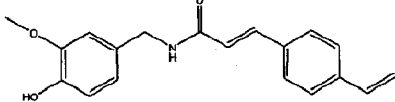
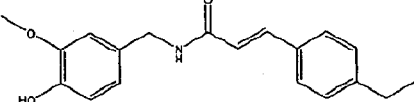
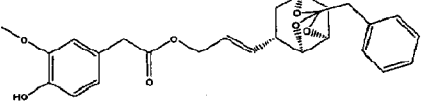
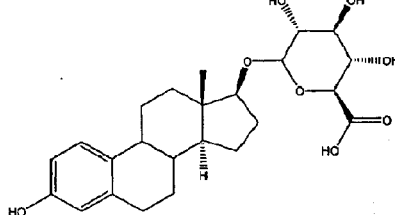
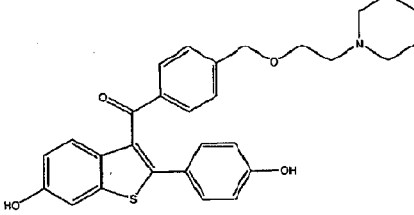
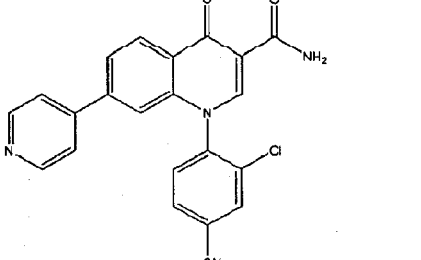
 Chemical Name tert-butyl (1S,2R)-1-([[(1S)-2-[(2S)-2-formylpyrrolidinyl]-1-(4-hydroxybenzyl)-2-oxoethyl]amino]carbonyl)-2-methylbutylcarbamate	 Chemical Name (3R)-3-(dicyclobutylamino)-8-fluoro-3,4-dihydro-2H-chromen-5-ol	 Chemical Name (E)-N-(4-hydroxy-3-methoxybenzyl)-8-methyl-6-nonenamide
 Chemical Name (E)-N-(4-hydroxy-3-methoxybenzyl)-3-(4-vinylphenyl)-2-propenamide	 Chemical Name (E)-3-(4-ethylphenyl)-N-(4-hydroxy-3-methoxybenzyl)-2-propenamide	 Chemical Name (E)-3-[(3R,4S,6S,8S)-1-benzyl-2,9,10-trioxatricyclo[4.3.1.0-3,8-]dec-4-yl]-2-propenyl 2-(4-hydroxy-3-methoxyphenyl)acetate
 Chemical Name (2S,3S,4S,5R)-3,4,5-trihydroxy-6-([[(13S,14S,17S)-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl]oxy]tetrahydro-2H-pyran-2-carboxylic acid	 Chemical Name [6-hydroxy-2-(4-hydroxyphenyl)-1-benzothiophen-3-yl](4-{[2-(1-piperidinyl)ethoxy]methyl}phenyl)methanone	 Chemical Name 1-(2-chloro-4-hydroxyphenyl)-4-oxo-7-(4-pyridinyl)-1,4-dihydro-3-quinolinecarboxamide

FIGURE 3

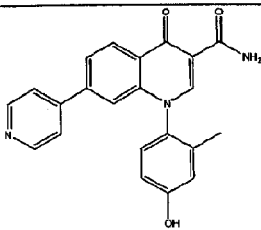
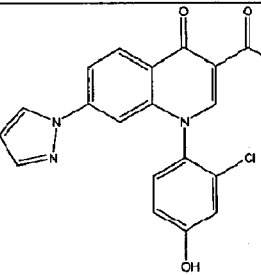
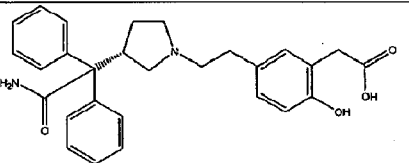
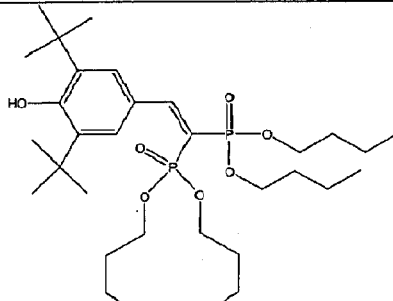
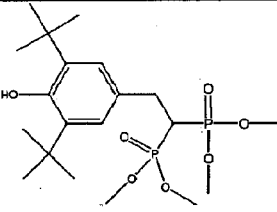
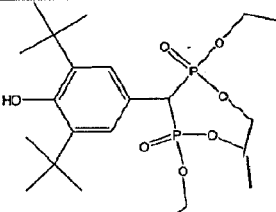
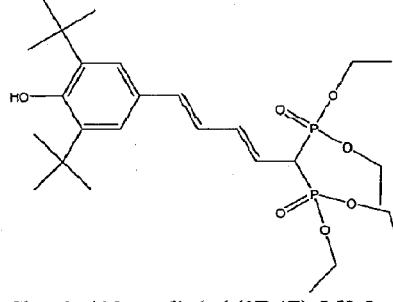
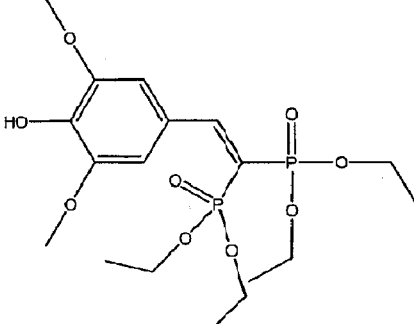
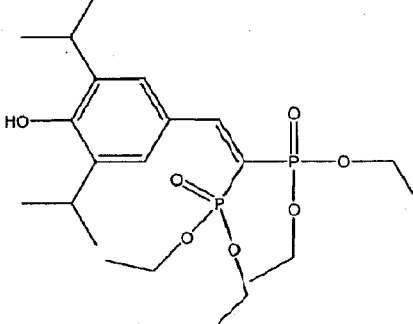
 Chemical Name 1-(4-hydroxy-2-methylphenyl)-4-oxo-7-(4-pyridinyl)-1,4-dihydro-3-quinolinecarboxamide	 Chemical Name 1-(2-chloro-4-hydroxyphenyl)-4-oxo-7-(1H-pyrazol-1-yl)-1,4-dihydro-3-quinolinecarboxamide	 Chemical Name 2-(5-{2-[(3S)-3-(2-amino-2-oxo-1,1-diphenylethyl)pyrrolidinyl]ethyl}-2-hydroxyphenyl)acetic acid
 Chemical Name dibutyl 1-(dibutoxyphosphoryl)-2-[3,5-di(tert-butyl)-4-hydroxyphenyl]vinylphosphonate	 Chemical Name dimethyl 2-[3,5-di(tert-butyl)-4-hydroxyphenyl]-1-(dimethoxyphosphoryl)ethylphosphonate	 Chemical Name diethyl [3,5-di(tert-butyl)-4-hydroxyphenyl](diethoxyphosphoryl)methylphosphonate
 Chemical Name diethyl (2E,4E)-5-[3,5-di(tert-butyl)-4-hydroxyphenyl]-1-(diethoxyphosphoryl)-2,4-pentadienylphosphonate	 Chemical Name diethyl 1-(diethoxyphosphoryl)-2-(4-hydroxy-3,5-dimethoxyphenyl)vinylphosphonate	 Chemical Name diethyl 1-(diethoxyphosphoryl)-2-(4-hydroxy-3,5-diisopropylphenyl)vinylphosphonate

FIGURE 3 cont.

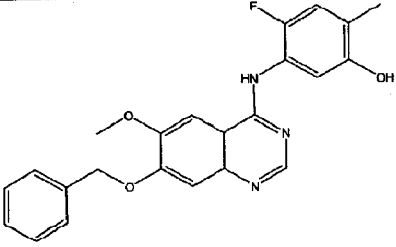
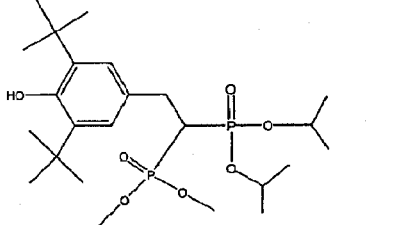
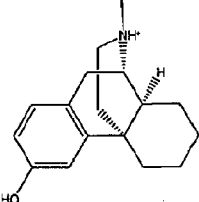
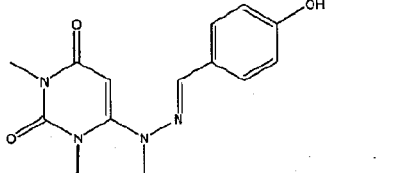
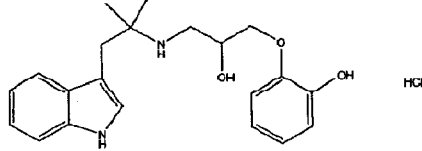
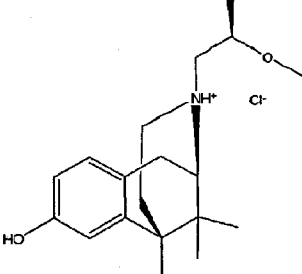
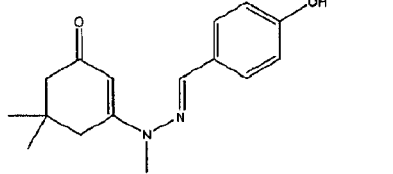
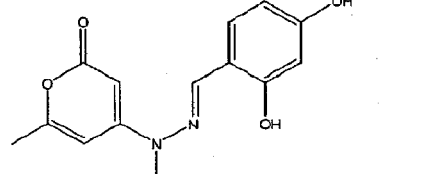
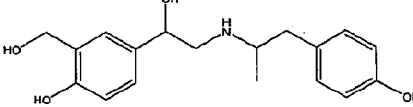
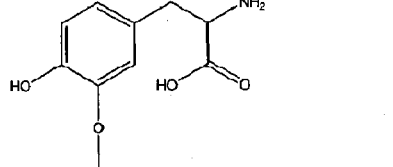
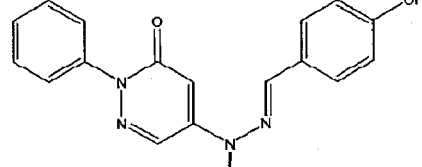
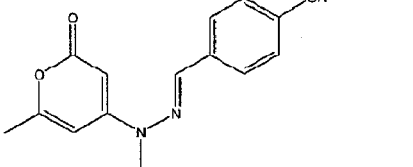
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 Chemical Name 4-hydroxybenzaldehyde N-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinyl)-N-methylhydrazone	 Chemical Name 2-(2-hydroxy-3-[[2-(1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy)phenol hydrochloride	 Chemical Name (1S,9R,10R)-4-hydroxy-10-[(2R)-2-methoxypropyl]-1,13,13-trimethyl-10-azoniatricyclo[7.3.1.0~2,7~]trideca-2,4,6-triene chloride
 Chemical Name 4-hydroxybenzaldehyde N-(5,5-dimethyl-3-oxo-1-cyclohexen-1-yl)-N-methylhydrazone	 Chemical Name 2,4-dihydroxybenzaldehyde N-methyl-N-(6-methyl-2-oxo-2H-pyran-4-yl)hydrazone	 Chemical Name 4-(1-hydroxy-2-[[2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl)-2-(hydroxymethyl)phenol
 Chemical Name 4-hydroxy-3-methoxyphenylalanine	 Chemical Name 4-hydroxybenzaldehyde N-methyl-N-(6-oxo-1-phenyl-1,6-dihydro-4-pyridazinyl)hydrazone	 Chemical Name 4-hydroxybenzaldehyde N-methyl-N-(6-methyl-2-oxo-2H-pyran-4-yl)hydrazone

FIGURE 3 cont.

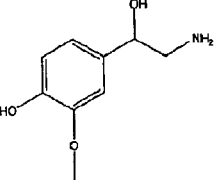
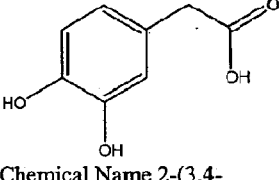
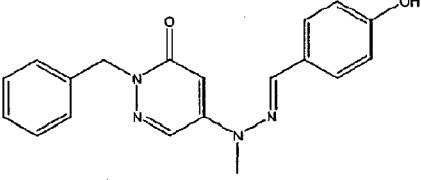
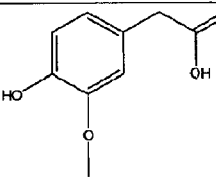
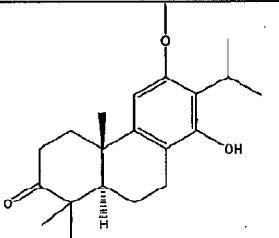
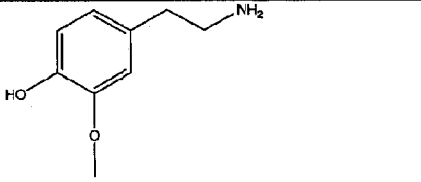
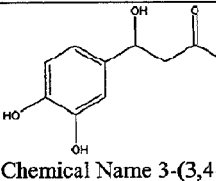
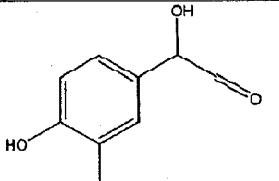
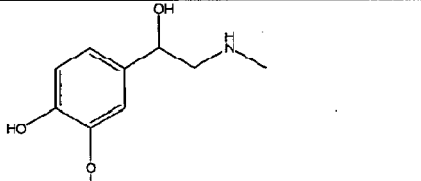
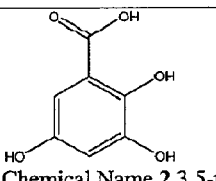
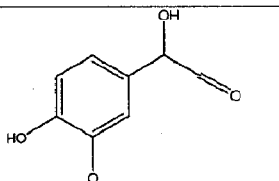
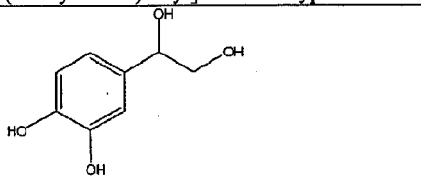
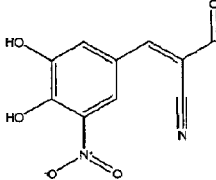
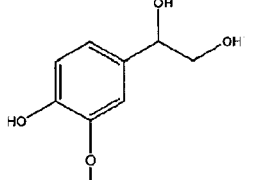
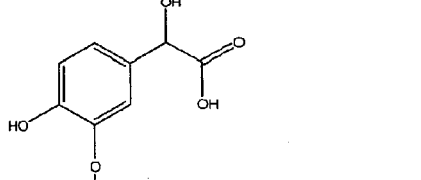
 Chemical Name 4-(2-amino-1-hydroxyethyl)-2-methoxyphenol	 Chemical Name 2-(3,4-dihydroxyphenyl)acetic acid	 Chemical Name 4-hydroxybenzaldehyde N-(1-benzyl-6-oxo-1,6-dihydro-4-pyridazinyl)-N-methylhydrazone
 Chemical Name 2-(4-hydroxy-3-methoxyphenyl)acetic acid	 Chemical Name (4aS,10aR)-8-hydroxy-7-isopropyl-6-methoxy-1,1,4a-trimethyl-3,4,4a,9,10,10a-hexahydro-2(1H)-phenanthrenone	 Chemical Name 4-(2-aminoethyl)-2-methoxyphenol
 Chemical Name 3-(3,4-dihydroxyphenyl)-3-hydroxypropanoic acid	 Chemical Name 2-(3,4-dihydroxyphenyl)-2-hydroxyacetaldehyde	 Chemical Name 4-[1-hydroxy-2-(methylamino)ethyl]-2-methoxyphenol
 Chemical Name 2,3,5-trihydroxybenzoic acid	 Chemical Name 2-hydroxy-2-(4-hydroxy-3-methoxyphenyl)acetaldehyde	 Chemical Name 4-(1,2-dihydroxyethyl)-1,2-benzenediol
 Chemical Name (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-2-propenoic acid	 Chemical Name 1-(4-hydroxy-3-methoxyphenyl)-1,2-ethanediol	 Chemical Name 2-hydroxy-2-(4-hydroxy-3-methoxyphenyl)acetic acid

FIGURE 3 cont.

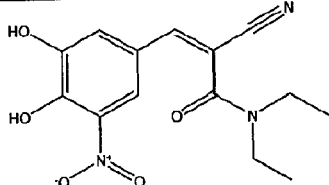
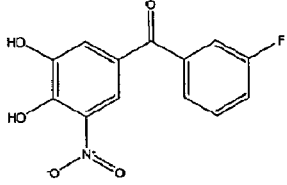
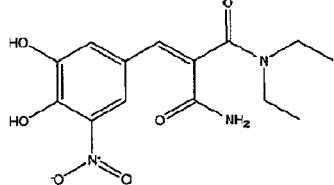
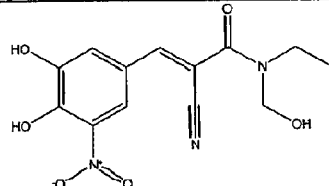
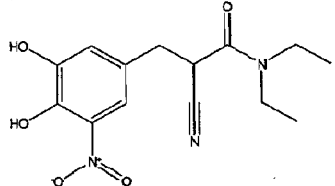
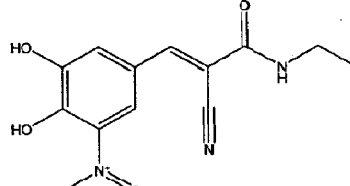
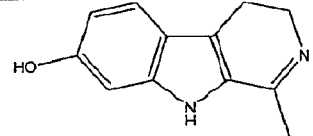
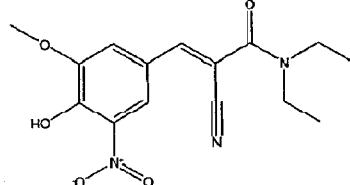
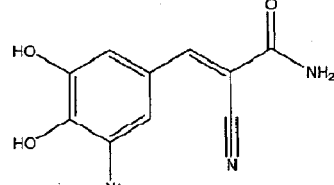
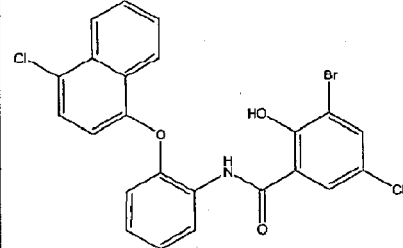
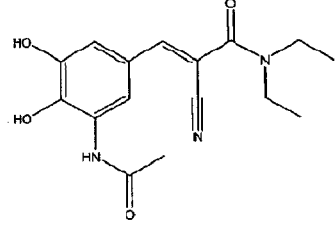
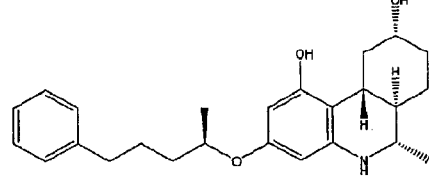
 Chemical Name (Z)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide	 Chemical Name (3,4-dihydroxy-5-nitrophenyl)(3-fluorophenyl)methanone	 Chemical Name 2-[(E)-(3,4-dihydroxy-5-nitrophenyl)methylidene]-N,N-diethylmalonamide
 Chemical Name (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N-ethyl-N-(hydroxymethyl)-2-propenamide	 Chemical Name 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylpropanamide	 Chemical Name (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N-ethyl-2-propenamide
 Chemical Name 1-methyl-4,9-dihydro-3H-beta-carboline-7-ol	 Chemical Name (E)-2-cyano-N,N-diethyl-3-(4-hydroxy-3-methoxy-5-nitrophenyl)-2-propenamide	 Chemical Name (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-2-propenamide
 Chemical Name 3-bromo-5-chloro-N-{2-[(4-chloro-1-naphthyl)oxy]phenyl}-2-hydroxybenzamide	 Chemical Name (E)-3-[3-(acetylamino)-4,5-dihydroxyphenyl]-2-cyano-N,N-diethyl-2-propenamide	 Chemical Name (6S,6aR,9R,10aR)-6-methyl-3-([(1R)-1-methyl-4-phenylbutyl]oxy)-5,6,6a,7,8,9,10,10a-octahydro-1,9-phenanthridinediol

FIGURE 3 cont.

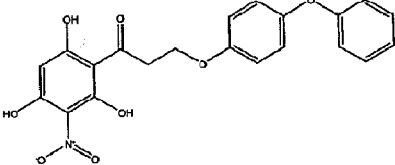
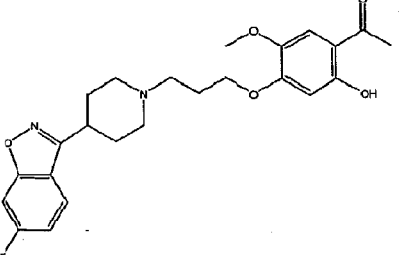
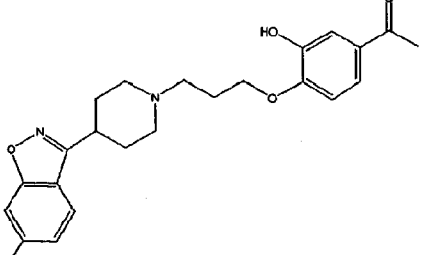
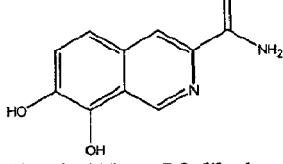
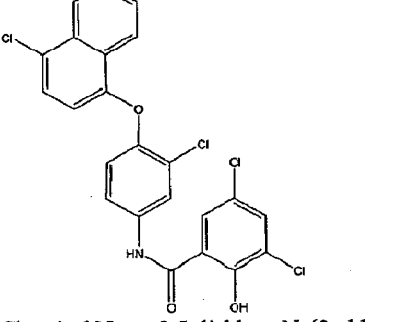
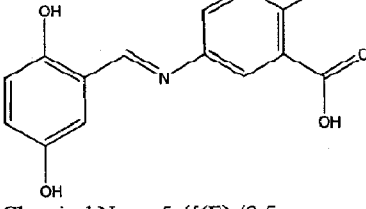
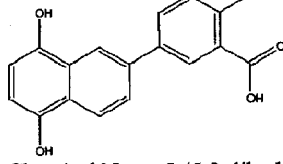
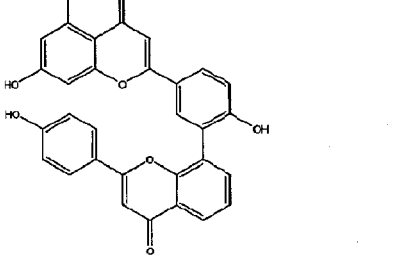
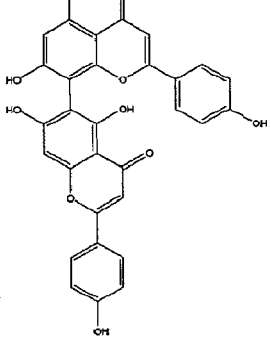
 Chemical Name 3-(4-phenoxyphenoxy)-1-(2,4,6-trihydroxy-3-nitrophenyl)-1-propanone	 Chemical Name 1-(4-{3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy}-2-hydroxy-5-methoxyphenyl)-1-ethanone	 Chemical Name 1-(4-{3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy}-3-hydroxyphenyl)-1-ethanone
 Chemical Name 7,8-dihydroxy-3-isoquinolinecarboxamide	 Chemical Name 3,5-dichloro-N-{3-chloro-4-[(4-chloro-1-naphthyl)oxy]phenyl}-2-hydroxybenzamide	 Chemical Name 5-[(E)-(2,5-dihydroxyphenyl)methylidene]amino}-2-hydroxybenzoic acid
 Chemical Name 5-(5,8-dihydroxy-2-naphthyl)-2-hydroxybenzoic acid	 Chemical Name 5,7-dihydroxy-2-{4-hydroxy-3-[2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]phenyl}-4H-chromen-4-one	

FIGURE 3 cont.

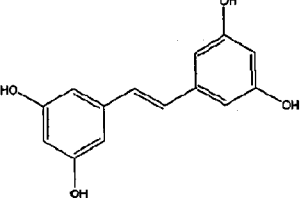
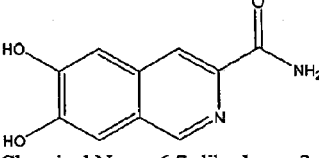
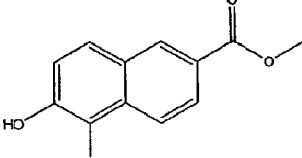
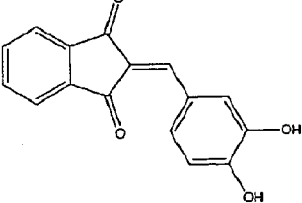
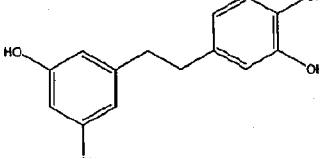
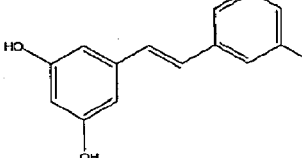
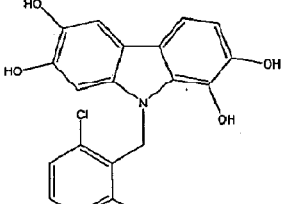
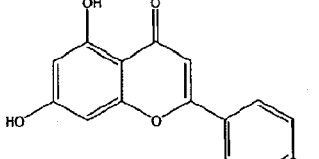
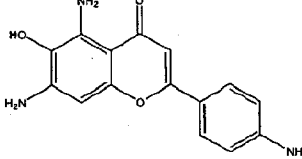
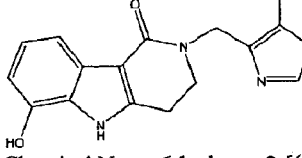
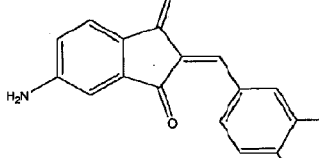
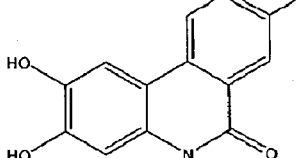
 Chemical Name 5-[(E)-2-(3,5-dihydroxyphenyl)ethenyl]-1,3-benzenediol	 Chemical Name 6,7-dihydroxy-3-isoquinolinecarboxamide	 Chemical Name methyl 5,6-dihydroxy-2-naphthoate
 Chemical Name 2-(3,4-dihydroxybenzylidene)-1H-indene-1,3(2H)-dione	 Chemical Name 4-(3,5-dihydroxyphenethyl)-1,2-benzenediol	 Chemical Name 5-[(E)-2-(3-hydroxyphenyl)ethenyl]-1,3-benzenediol
 Chemical Name 9-(2,6-dichlorobenzyl)-9H-carbazole-1,2,6,7-tetrol	 Chemical Name 2-(4-aminophenyl)-5,7-dihydroxy-4H-chromen-4-one	 Chemical Name 5,7-diamino-2-(4-aminophenyl)-6-hydroxy-4H-chromen-4-one
 Chemical Name 6-hydroxy-2-[(5-methyl-1H-imidazol-4-yl)methyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one	 Chemical Name 5-amino-2-[(E)-(3,4-dihydroxyphenyl)methylidene]-1H-indene-1,3(2H)-dione	 Chemical Name 2,3,8-trihydroxy-6(5H)-phenanthridinone

FIGURE 3 cont.

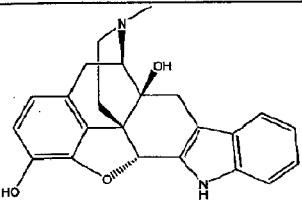
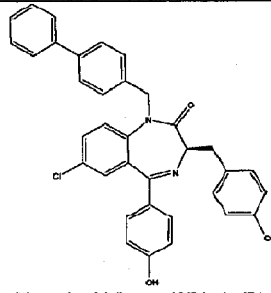
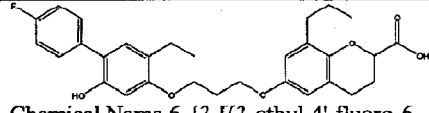
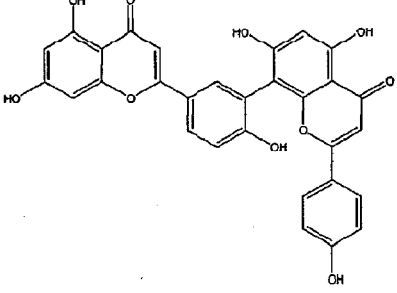
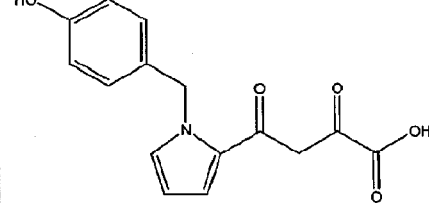
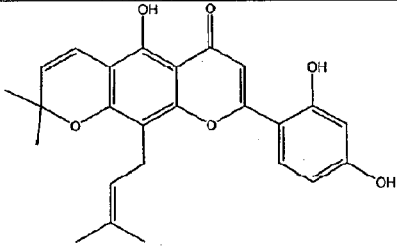
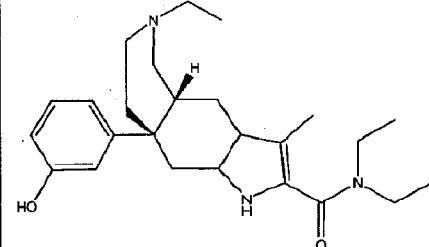
 Chemical Name (1S,2S,13R,21R)-22-methyl-14-oxa-11,22-diazaheptacyclo[13.9.1.0~1,13~.0~2,21~.0~4,12~.0~5,10~.0~19,25~]pentacos-4(12),5,7,9,15(25),16,18-heptaene-2,16-diol	 Chemical Name (3R)-1-([1,1'-biphenyl]-4-ylmethyl)-7-chloro-3-(4-hydroxybenzyl)-5-(4-hydroxyphenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one	 Chemical Name 6-{3-[(3-ethyl-4'-fluoro-6-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy}-8-propyl-2-chromanecarboxylic acid
 Chemical Name 7-hydroxy-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one	 Chemical Name 4-{1-[(4-hydroxyphenyl)methyl]-1H-pyrrol-2-yl}-2,4-dioxobutanoic acid	
 Chemical Name 8-(2,4-dihydroxyphenyl)-5-hydroxy-2,2-dimethyl-10-(3-methyl-2-butenyl)-2H,6H-pyrano[3,2-g]chromen-6-one	 Chemical Name (3R)-8-hydroxy-3-[(Z)-6-pentadecenyl]-3,4-dihydro-1H-2-benzopyran-1-one	 Chemical Name (4aR,8aS)-N,N,6-triethyl-8a-(3-hydroxyphenyl)-3-methyl-3a,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-pyrrolo[2,3-g]isoquinoline-2-carboxamide

FIGURE 3 cont.

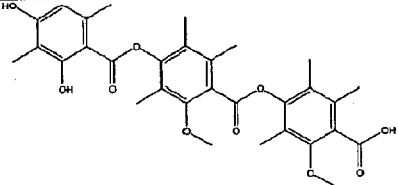
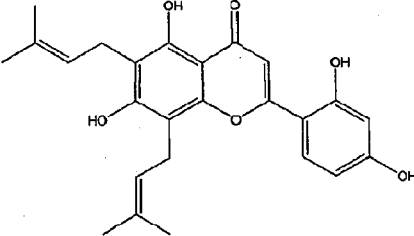
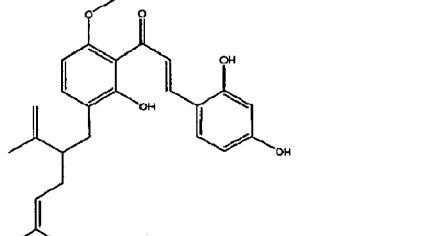
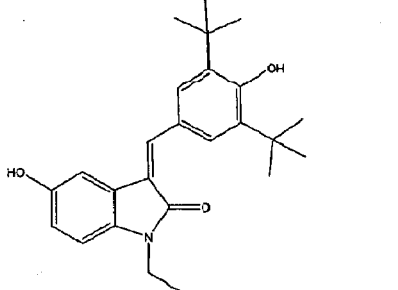
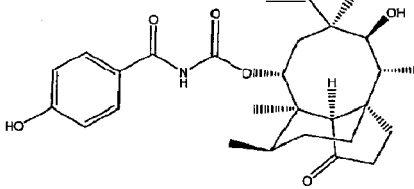
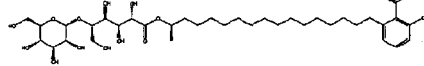
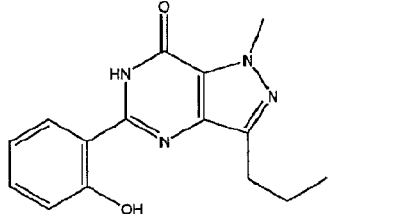
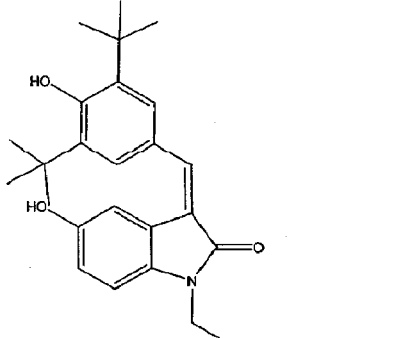
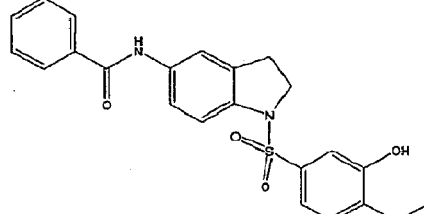
 Chemical Name 4-({4-[(2,4-dihydroxy-3,6-dimethylbenzoyl)oxy]-2-methoxy-3,5,6-trimethylbenzoyl}oxy)-2-methoxy-3,5,6-trimethylbenzoic acid	 Chemical Name 2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-6,8-bis(3-methyl-2-butenyl)-4H-chromen-4-one	 Chemical Name (E)-3-(2,4-dihydroxyphenyl)-1-[2-hydroxy-3-(2-isopropenyl-5-methyl-4-hexenyl)-6-methoxyphenyl]-2-propen-1-one
 Chemical Name 3-((Z)-[3,5-di(tert-butyl)-4-hydroxyphenyl]methylidene)-1-ethyl-5-hydroxy-1H-indol-2-one	 Chemical Name (1S,2R,3S,4S,6R,7R,8R,14R)-3-hydroxy-2,4,7,14-tetramethyl-9-oxo-4-vinyltricyclo[5.4.3.0~1,8~]tetradec-6-yl 4-hydroxybenzoylcarbamate	 Chemical Name 2-hydroxy-6-((16R)-16-(((2S,3S,4S,5R)-2,3,4,6-tetrahydroxy-5-(((2S,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)hexanoyl)oxy)heptadecyl)benzoic acid
 Chemical Name 5-(2-hydroxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one	 Chemical Name 3-((E)-[3,5-di(tert-butyl)-4-hydroxyphenyl]methylidene)-1-ethyl-5-hydroxy-1,3-dihydro-2H-indol-2-one	 Chemical Name N-(1-([3-hydroxy-4-(methyloxy)phenyl]sulfonyl)-2,3-dihydro-1H-indol-5-yl)benzamide

FIGURE 3 cont.

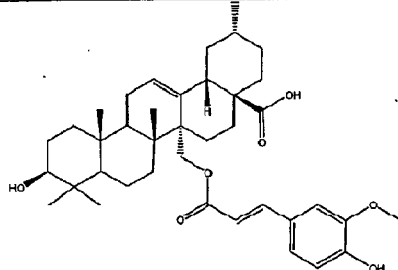
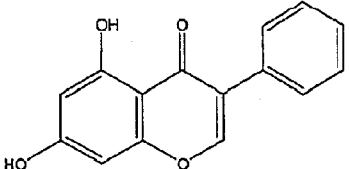
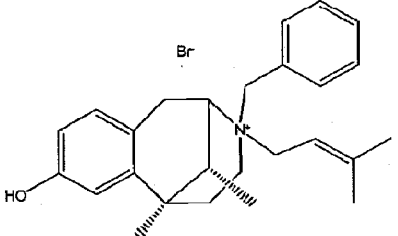
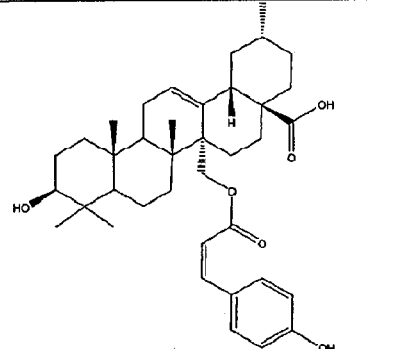
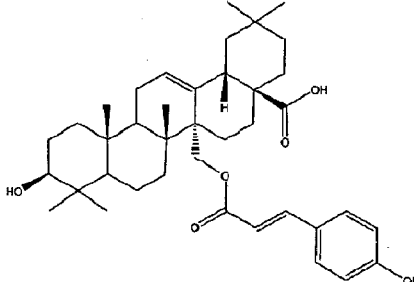
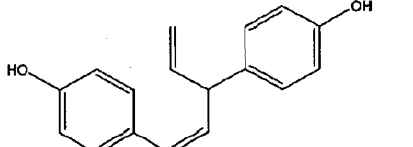
 Chemical Name (2R,6aR,6bR,10S,12aR,14bS)-10-hydroxy-6a-({[(E)-3-(4-hydroxy-3-methoxyphenyl)-2-propenoyl]oxy}methyl)-2,6b,9,9,12a-pentamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydro-4a(2H)-picenecarboxylic acid	 Chemical Name 5,7-dihydroxy-3-phenyl-4H-chromen-4-one	 Chemical Name (6R,11R)-3-benzyl-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocinium bromide
 Chemical Name (2R,6aR,6bR,10S,12aR,14bS)-10-hydroxy-6a-({[(Z)-3-(4-hydroxyphenyl)-2-propenoyl]oxy}methyl)-2,6b,9,9,12a-pentamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydro-4a(2H)-picenecarboxylic acid	 Chemical Name (6aR,6bR,10S,12aR,14bS)-10-hydroxy-6a-({[(E)-3-(4-hydroxyphenyl)-2-propenoyl]oxy}methyl)-2,2,6b,9,9,12a-hexamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydro-4a(2H)-picenecarboxylic acid	 Chemical Name 4-[(Z)-3-(4-hydroxyphenyl)-1-vinyl-2-propenyl]phenol

FIGURE 3 cont.

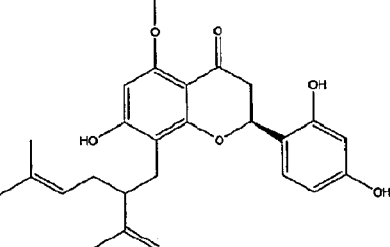
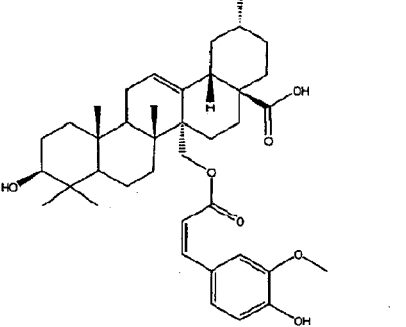
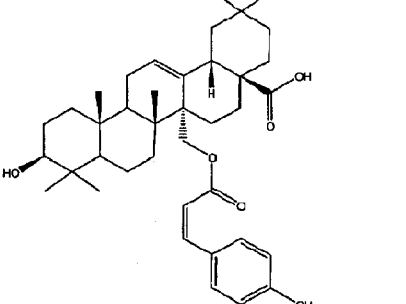
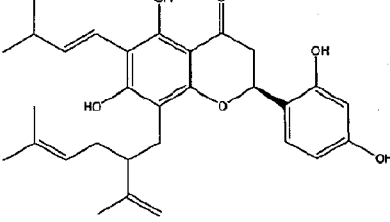
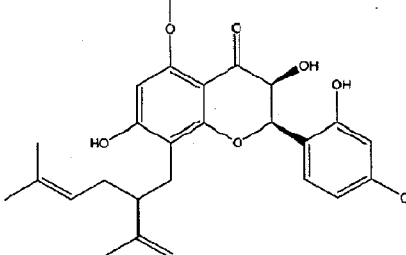
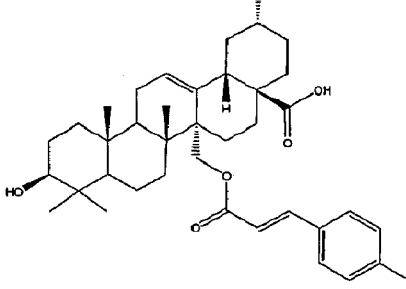
 Chemical Name (2S)-2-(2,4-dihydroxyphenyl)-7-hydroxy-8-(2-isopropenyl-5-methyl-4-hexenyl)-5-methoxy-2,3-dihydro-4H-chromen-4-one	 Chemical Name (2R,6aR,6bR,10S,12aR,14bS)-10-hydroxy-6a-([[(Z)-3-(4-hydroxy-3-methoxyphenyl)-2-propenoyl]oxy]methyl)-2,2,6b,9,9,12a-pentamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydro-4a(2H)-picenecarboxylic acid	 Chemical Name (6aR,6bR,10S,12aR,14bS)-10-hydroxy-6a-([[(Z)-3-(4-hydroxyphenyl)-2-propenoyl]oxy]methyl)-2,2,6b,9,9,12a-hexamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydro-4a(2H)-picenecarboxylic acid
 Chemical Name (2S)-2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-8-(2-isopropenyl-5-methyl-4-hexenyl)-6-[(E)-3-methyl-1-butenyl]-2,3-dihydro-4H-chromen-4-one	 Chemical Name (2R,3S)-2-(2,4-dihydroxyphenyl)-3,7-dihydroxy-8-(2-isopropenyl-5-methyl-4-hexenyl)-5-methoxy-2,3-dihydro-4H-chromen-4-one	 Chemical Name (2R,6aR,6bR,10S,12aR,14bS)-10-hydroxy-6a-([[(E)-3-(4-hydroxyphenyl)-2-propenoyl]oxy]methyl)-2,2,6b,9,9,12a-pentamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydro-4a(2H)-picenecarboxylic acid

FIGURE 3 cont.

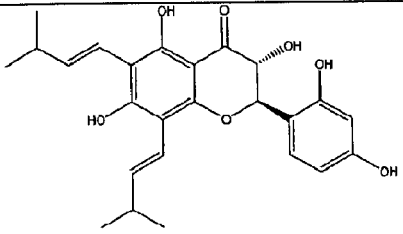
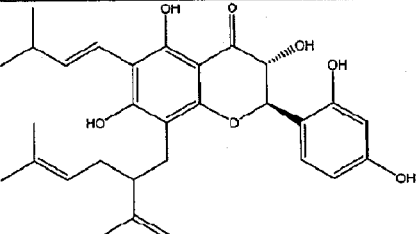
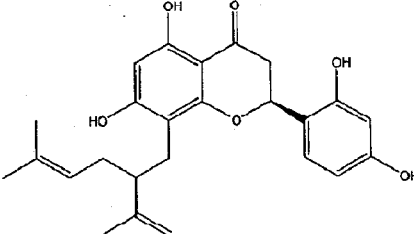
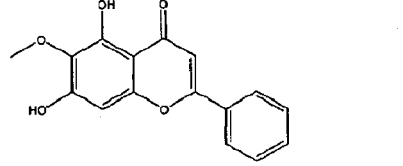
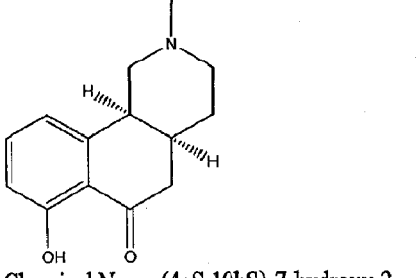
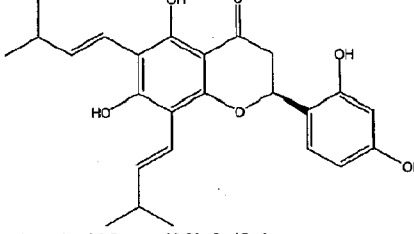
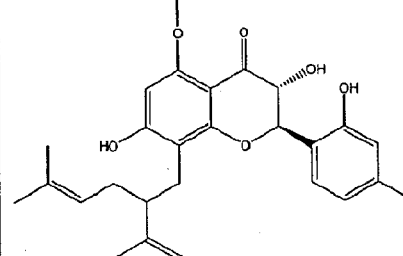
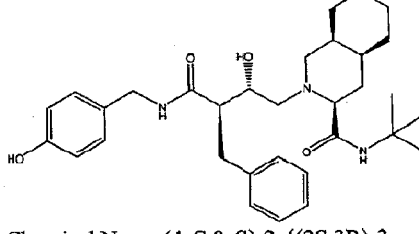
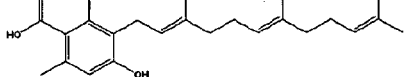
 Chemical Name (2R,3R)-2-(2,4-dihydroxyphenyl)-3,5,7-trihydroxy-6,8-bis[(E)-3-methyl-1-butenyl]-2,3-dihydro-4H-chromen-4-one	 Chemical Name (2R,3R)-2-(2,4-dihydroxyphenyl)-3,5,7-trihydroxy-8-(2-isopropenyl-5-methyl-4-hexenyl)-6-[(E)-3-methyl-1-butenyl]-2,3-dihydro-4H-chromen-4-one	 Chemical Name (2S)-2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-8-(2-isopropenyl-5-methyl-4-hexenyl)-2,3-dihydro-4H-chromen-4-one
 Chemical Name 5,7-dihydroxy-6-methoxy-2-phenyl-4H-chromen-4-one	 Chemical Name (4aS,10bS)-7-hydroxy-2-methyl-1,3,4,4a,5,10b-hexahydrobenzo[h]isoquinolin-6(2H)-one	 Chemical Name (2S)-2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-6,8-bis[(E)-3-methyl-1-butenyl]-2,3-dihydro-4H-chromen-4-one
 Chemical Name (2R,3R)-2-(2,4-dihydroxyphenyl)-3,7-dihydroxy-8-(2-isopropenyl-5-methyl-4-hexenyl)-5-methoxy-2,3-dihydro-4H-chromen-4-one	 Chemical Name (4aS,8aS)-2-((2S,3R)-3-benzyl-2-hydroxy-4-[(4-hydroxybenzyl)amino]-4-oxobutyl)-N-(tert-butyl)decahydro-3-isoquinolinecarboxamide	 Chemical Name 2,4-dihydroxy-6-methyl-3-[(2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyl]benzoic acid

FIGURE 3 cont.

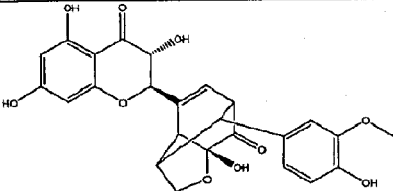
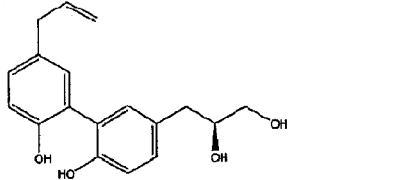
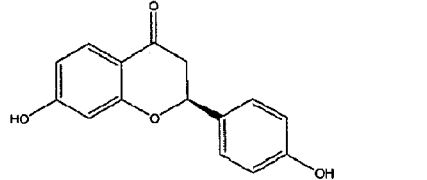
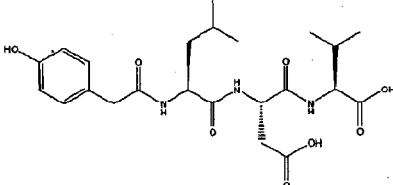
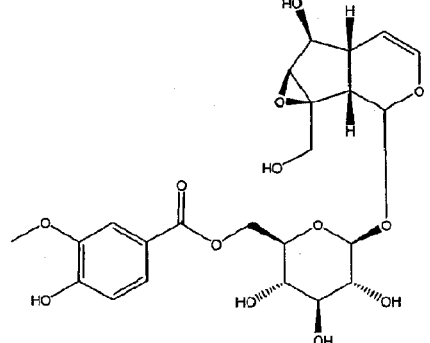
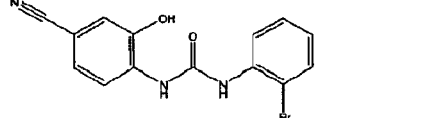
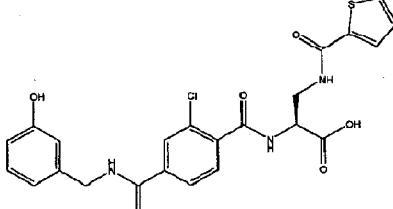
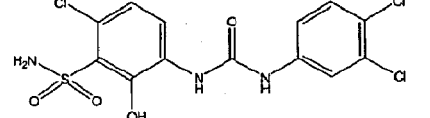
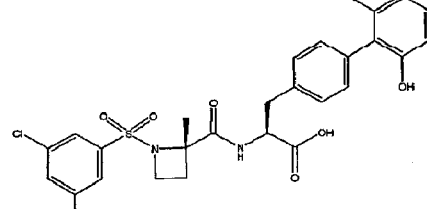
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 EN 502896 No Drug or Chemical Names	 Chemical Name (1aS,1bS,5aR,6S,6aS)-6-hydroxy-1a-(hydroxymethyl)-1a,1b,2,5a,6,6a-hexahydrooxireno[4,5]cyclopenta[1,2-c]pyran-2-yl 6-O-(4-hydroxy-3-methoxybenzoyl)-beta-D-glucopyranoside	 Chemical Name N-(2-bromophenyl)-N'-(4-cyano-2-hydroxyphenyl)urea
 Chemical Name (2S)-2-[(2-chloro-4-[(3-hydroxybenzyl)amino]carbonyl}benzoyl)amino]-3-[(2-thienylcarbonyl)amino]propanoic acid	 Chemical Name 6-chloro-3-({[(3,4-dichlorophenyl)amino]carbonyl}amino)-2-hydroxybenzenesulfonamide	 Chemical Name (2S)-2-[(2S)-1-[(3,5-dichlorophenyl)sulfonyl]-2-methyl-2-azetidinyl]carbonyl]amino]-3-(2'-hydroxy-6'-methyl-1,1'-biphenyl-4-yl)propanoic acid

FIGURE 3 cont.

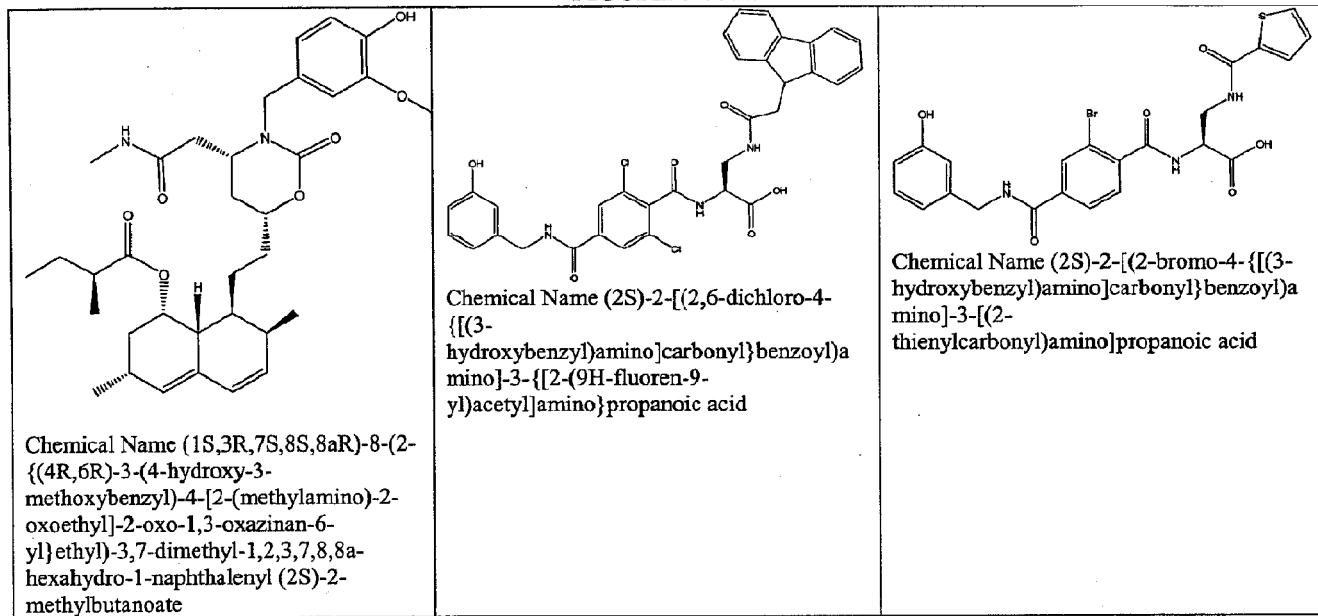


FIGURE 4

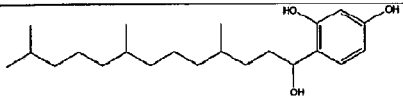
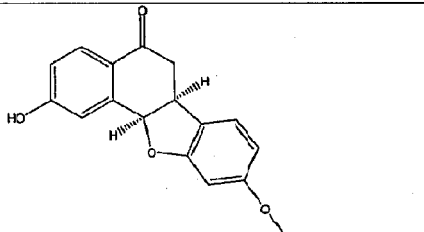
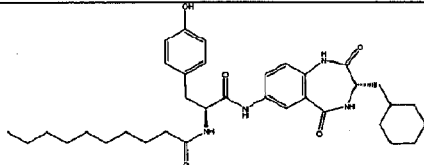
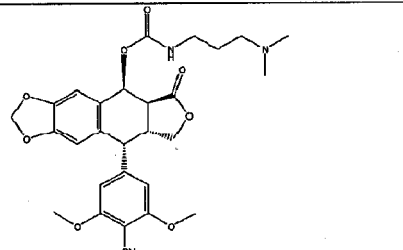
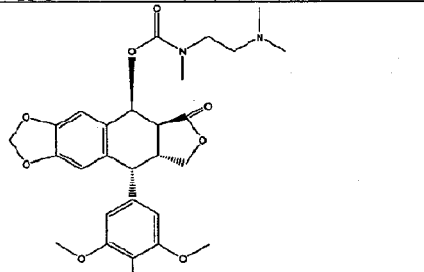
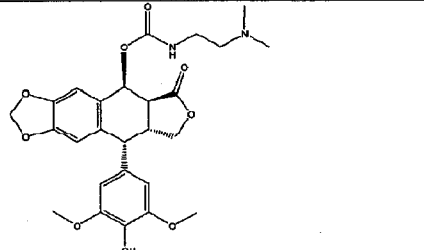
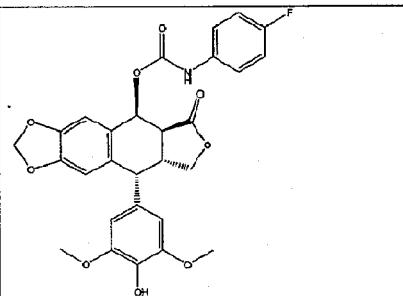
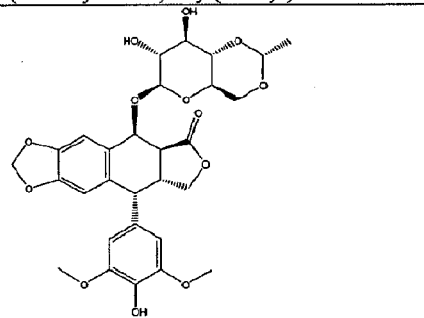
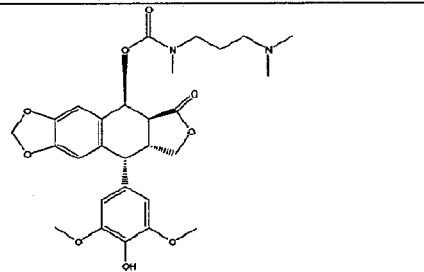
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 Chemical Name (5S,5aS,8aR,9R)-9-(4-hydroxy-3,5-dimethoxyphenyl)-6-oxo-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl 3-(dimethylamino)propylcarbamate	 Chemical Name (5S,5aS,8aR,9R)-9-(4-hydroxy-3,5-dimethoxyphenyl)-6-oxo-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl 2-(dimethylamino)ethyl(methyl)carbamate	 Chemical Name (5S,5aS,8aR,9R)-9-(4-hydroxy-3,5-dimethoxyphenyl)-6-oxo-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl 2-(dimethylamino)ethylcarbamate
 Chemical Name (5S,5aS,8aR,9R)-9-(4-hydroxy-3,5-dimethoxyphenyl)-6-oxo-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl 4-fluorophenylcarbamate	 Chemical Name (5S,5aS,8aR,9R)-5-[[[(2R,4aR,6R,7R,8R,8aS)-7,8-dihydroxy-2-methylhexahydropyran[3,2-d][1,3]dioxin-6-yl]oxy]-9-(4-hydroxy-3,5-dimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(5aH)-one	 Chemical Name (5S,5aS,8aR,9R)-9-(4-hydroxy-3,5-dimethoxyphenyl)-6-oxo-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl 3-(dimethylamino)propyl(methyl)carbamate

FIGURE 4 cont.

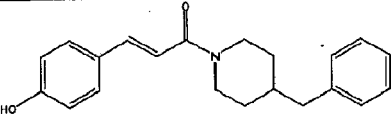
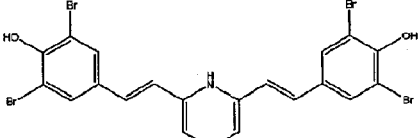
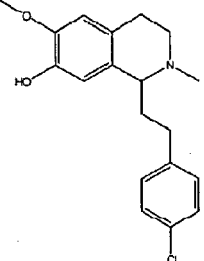
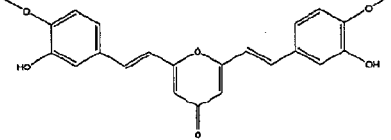
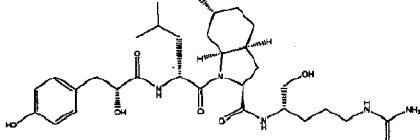
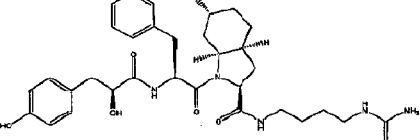
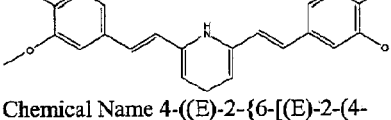
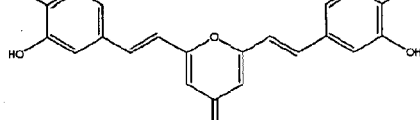
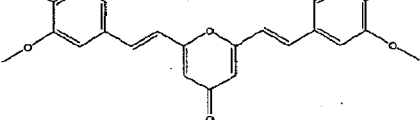
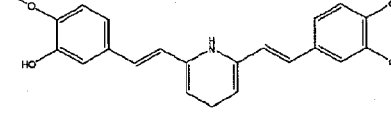
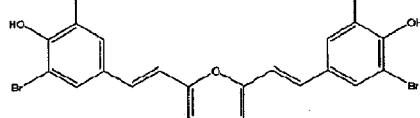
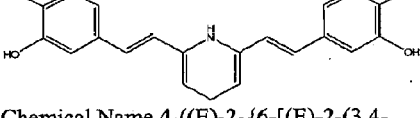
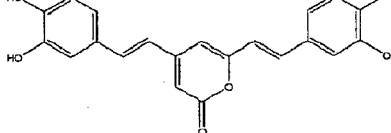
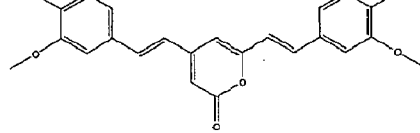
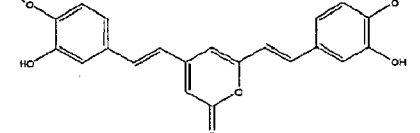
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 Chemical Name 2,6-bis[(E)-2-(3-hydroxy-4-methoxyphenyl)ethenyl]-4H-pyran-4-one	 Chemical Name (2S,3aS,6R,7aS)-N-[(1S)-4-{{[amino(imino)methyl]amino}-1-(hydroxymethyl)butyl}-6-hydroxy-1-((2R)-2-[[[(2R)-2-hydroxy-3-(4-hydroxyphenyl)propanoyl]amino}-4-methylpentanoyl]octahydro-1H-indole-2-carboxamide	 Chemical Name (2S,3aS,6R,7aS)-N-(4-{{[amino(imino)methyl]amino}butyl}-6-hydroxy-1-((2S)-2-[[[(2S)-2-hydroxy-3-(4-hydroxyphenyl)propanoyl]amino]-3-phenylpropanoyl]octahydro-1H-indole-2-carboxamide
 Chemical Name 4-((E)-2-{6-[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-1,4-dihydro-2-pyridinyl}ethenyl)-2-methoxyphenol	 Chemical Name 2,6-bis[(E)-2-(3,4-dihydroxyphenyl)ethenyl]-4H-pyran-4-one	 Chemical Name 2,6-bis[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-4H-pyran-4-one
 Chemical Name 5-((E)-2-{6-[(E)-2-(3-hydroxy-4-methoxyphenyl)ethenyl]-1,4-dihydro-2-pyridinyl}ethenyl)-2-methoxyphenol	 Chemical Name 2,6-bis[(E)-2-(3,5-dibromo-4-hydroxyphenyl)ethenyl]-4H-pyran-4-one	 Chemical Name 4-((E)-2-{6-[(E)-2-(3,4-dihydroxyphenyl)ethenyl]-1,4-dihydro-2-pyridinyl}ethenyl)-1,2-benzenediol
 Chemical Name 4,6-bis[(E)-2-(3,4-dihydroxyphenyl)ethenyl]-2H-pyran-2-one	 Chemical Name 4,6-bis[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-2H-pyran-2-one	 Chemical Name 4,6-bis[(E)-2-(3-hydroxy-4-methoxyphenyl)ethenyl]-2H-pyran-2-one

FIGURE 4 cont.

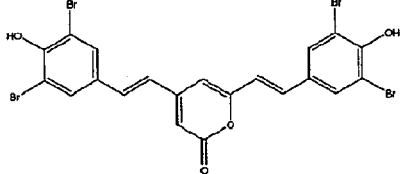
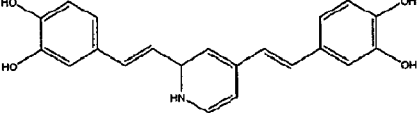
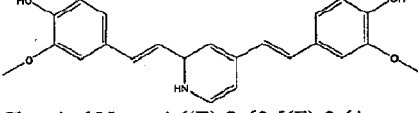
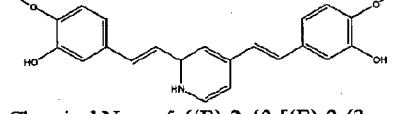
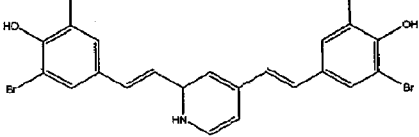
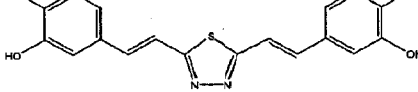
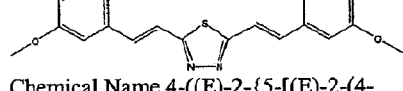
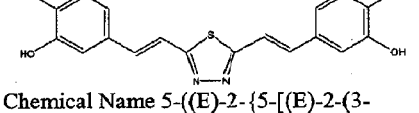
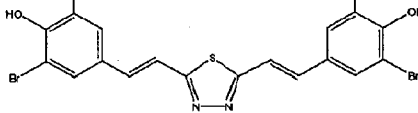
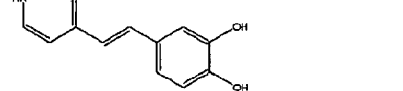
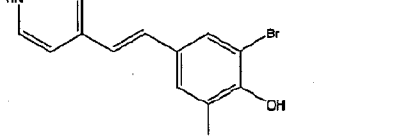
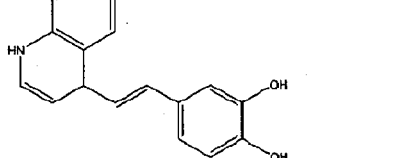
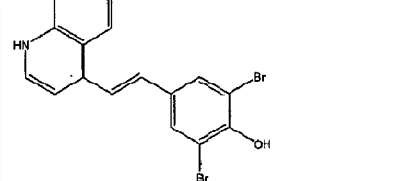
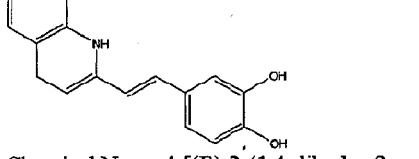
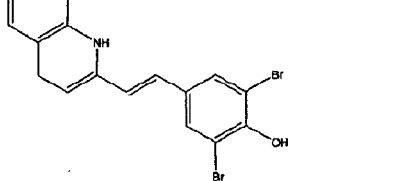
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 Chemical Name 5-((E)-2-(2-((E)-2-(3-hydroxy-4-methoxyphenyl)ethenyl)-1,2-dihydro-4-pyridinyl)ethenyl)-2-methoxyphenol	 Chemical Name 2,6-dibromo-4-((E)-2-(2-((E)-2-(3,5-dibromo-4-hydroxyphenyl)ethenyl)-1,2-dihydro-4-pyridinyl)ethenyl)phenol	 Chemical Name 4-((E)-2-(5-((E)-2-(3,4-dihydroxyphenyl)ethenyl)-1,3,4-thiadiazol-2-yl)ethenyl)-1,2-benzenediol
 Chemical Name 4-((E)-2-(5-((E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl)-1,3,4-thiadiazol-2-yl)ethenyl)-2-methoxyphenol	 Chemical Name 5-((E)-2-(5-((E)-2-(3-hydroxy-4-methoxyphenyl)ethenyl)-1,3,4-thiadiazol-2-yl)ethenyl)-2-methoxyphenol	 Chemical Name 2,6-dibromo-4-((E)-2-(5-((E)-2-(3,5-dibromo-4-hydroxyphenyl)ethenyl)-1,3,4-thiadiazol-2-yl)ethenyl)phenol
 Chemical Name 4-((E)-2-(1,2-dihydro-4-pyridinyl)ethenyl)-1,2-benzenediol	 Chemical Name 2,6-dibromo-4-((E)-2-(1,2-dihydro-4-pyridinyl)ethenyl)phenol	 Chemical Name 4-((E)-2-(1,4-dihydro-4-quinolinyl)ethenyl)-1,2-benzenediol
 Chemical Name 2,6-dibromo-4-((E)-2-(1,4-dihydro-4-quinolinyl)ethenyl)phenol	 Chemical Name 4-((E)-2-(1,4-dihydro-2-quinolinyl)ethenyl)-1,2-benzenediol	 Chemical Name 2,6-dibromo-4-((E)-2-(1,4-dihydro-2-quinolinyl)ethenyl)phenol

FIGURE 4 cont.

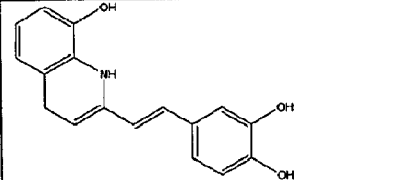
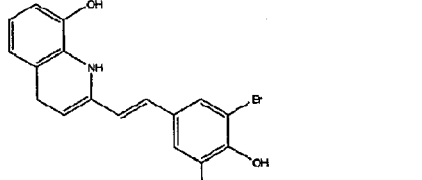
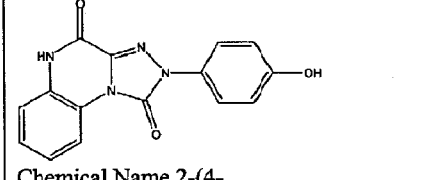
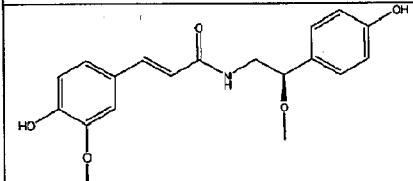
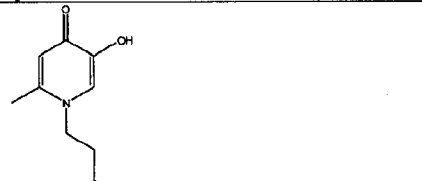
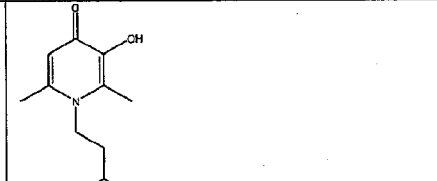
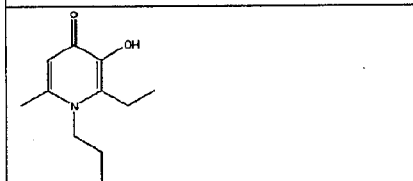
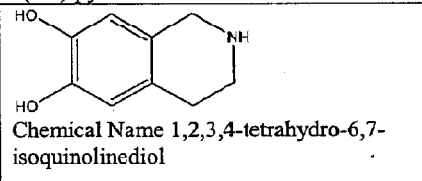
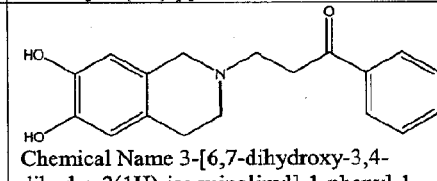
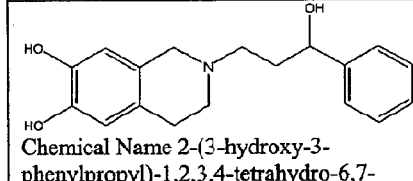
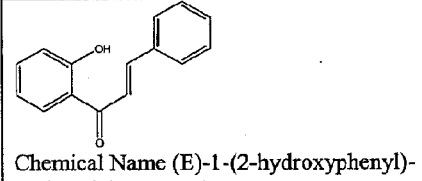
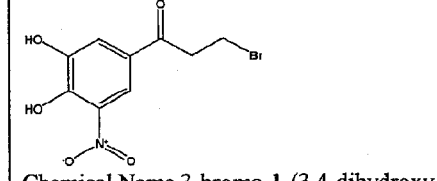
 Chemical Name 4-[(E)-2-(8-hydroxy-1,4-dihydro-2-quinolinyl)ethenyl]-1,2-benzenediol	 Chemical Name 2-[(E)-2-(3,5-dibromo-4-hydroxyphenyl)ethenyl]-1,4-dihydro-8-quinolinol	 Chemical Name 2-(4-hydroxyphenyl)[1,2,4]triazolo[4,3-a]quinoxaline-1,4(2H,5H)-dione
 Chemical Name (E)-3-(4-hydroxy-3-methoxyphenyl)-N-[(2R)-2-(4-hydroxyphenyl)-2-methoxyethyl]-2-propanamide	 Chemical Name 1-(3,4-dihydroxyphenethyl)-5-hydroxy-2-methyl-4(1H)-pyridinone	 Chemical Name 1-(3,4-dihydroxyphenethyl)-3-hydroxy-2,6-dimethyl-4(1H)-pyridinone
 Chemical Name 1-(3,4-dihydroxyphenethyl)-2-ethyl-3-hydroxy-6-methyl-4(1H)-pyridinone	 Chemical Name 1,2,3,4-tetrahydro-6,7-isoquinolinediol	 Chemical Name 3-[6,7-dihydroxy-3,4-dihydro-2(1H)-isoquinolinyl]-1-phenyl-1-propanone
 Chemical Name 2-(3-hydroxy-3-phenylpropyl)-1,2,3,4-tetrahydro-6,7-isoquinolinediol	 Chemical Name (E)-1-(2-hydroxyphenyl)-3-phenyl-2-propen-1-one	 Chemical Name 3-bromo-1-(3,4-dihydroxy-5-nitrophenyl)-1-propanone

FIGURE 4 cont.

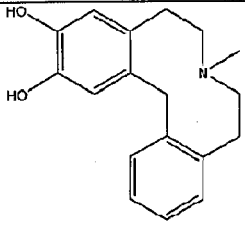
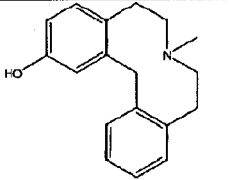
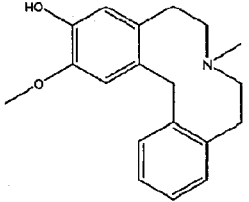
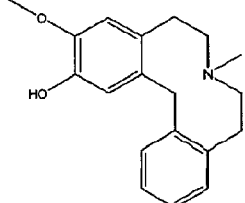
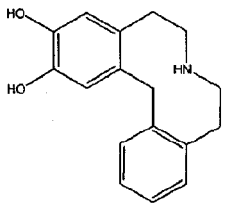
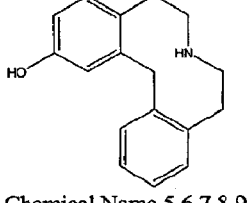
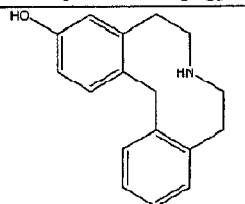
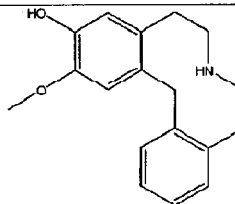
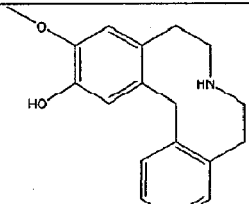
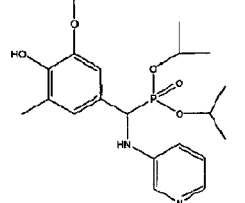
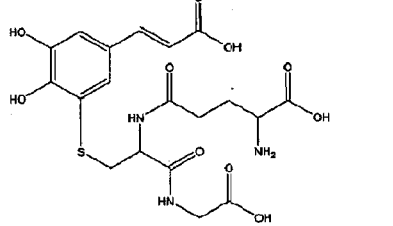
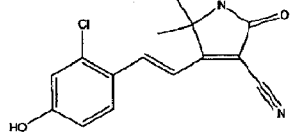
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 Chemical Name 3-methoxy-7-methyl-5,6,7,8,9,14-hexahydrodibenzo[d,g]azecine-2-ol	 Chemical Name 5,6,7,8,9,14-hexahydrodibenzo[d,g]azecine-2,3-diol	 Chemical Name 5,6,7,8,9,14-hexahydrodibenzo[d,g]azecine-2-ol
 Chemical Name 5,6,7,8,9,14-hexahydrodibenzo[d,g]azecine-3-ol	 Chemical Name 2-methoxy-5,6,7,8,9,14-hexahydrodibenzo[d,g]azecine-3-ol	 Chemical Name 3-methoxy-5,6,7,8,9,14-hexahydrodibenzo[d,g]azecine-2-ol
 Chemical Name diisopropyl (4-hydroxy-3-methoxy-5-methylphenyl)(3-pyridinylamino)methylphosphonate	 Chemical Name (E)-3-[3-((2-((4-amino-4-carboxybutanoyl)amino)-3-((carboxymethyl)amino)-3-oxopropyl)sulfanyl)-4,5-dihydroxyphenyl]-2-propenoic acid	 Chemical Name 4-[(E)-2-(2-chloro-4-hydroxyphenyl)ethenyl]-5,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile

FIGURE 4 cont.

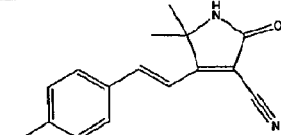
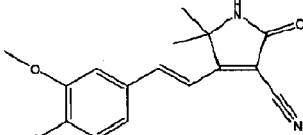
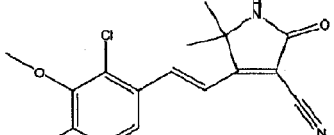
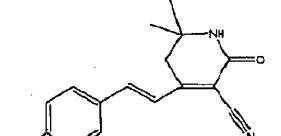
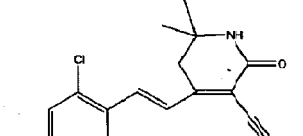
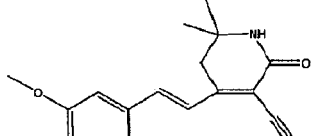
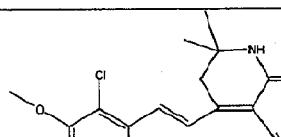
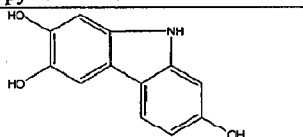
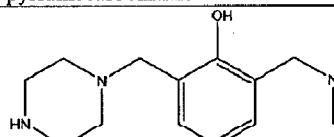
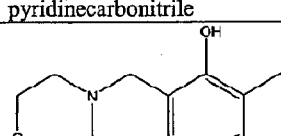
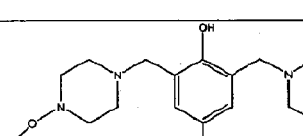
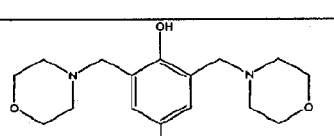
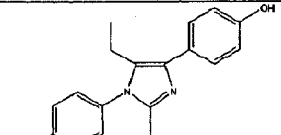
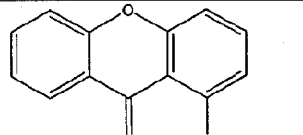
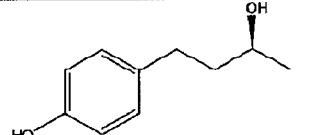
 Chemical Name 4-[(E)-2-(4-hydroxyphenyl)ethenyl]-5,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile	 Chemical Name 4-[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-5,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile	 Chemical Name 4-[(E)-2-(2-chloro-4-hydroxy-3-methoxyphenyl)ethenyl]-5,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile
 Chemical Name 4-[(E)-2-(4-hydroxyphenyl)ethenyl]-6,6-dimethyl-2-oxo-1,2,5,6-tetrahydro-3-pyridinecarbonitrile	 Chemical Name 4-[(E)-2-(2-chloro-4-hydroxyphenyl)ethenyl]-6,6-dimethyl-2-oxo-1,2,5,6-tetrahydro-3-pyridinecarbonitrile	 Chemical Name 4-[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-6,6-dimethyl-2-oxo-1,2,5,6-tetrahydro-3-pyridinecarbonitrile
 Chemical Name 4-[(E)-2-(2-chloro-4-hydroxy-3-methoxyphenyl)ethenyl]-6,6-dimethyl-2-oxo-1,2,5,6-tetrahydro-3-pyridinecarbonitrile	 Chemical Name 9H-carbazole-2,3,7-triol	 Chemical Name 2,6-bis(1-piperazinylmethyl)phenol
 Chemical Name 2,6-bis(4-morpholinylmethyl)phenol	 Chemical Name 4-methoxy-2,6-bis[(4-methoxy-1-piperazinyl)methyl]phenol	 Chemical Name 4-methoxy-2,6-bis(4-morpholinylmethyl)phenol
 Chemical Name 4-[5-ethyl-4-(4-hydroxyphenyl)-2-phenyl-1H-imidazol-1-yl]phenol	 Chemical Name 1-hydroxy-9H-xanthen-9-one	 Chemical Name 4-[(3S)-3-hydroxybutyl]phenol

FIGURE 4 cont.

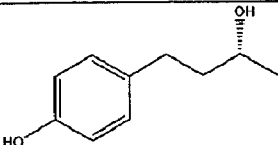
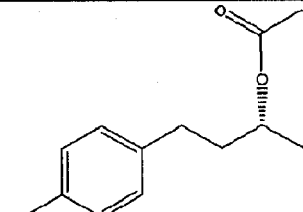
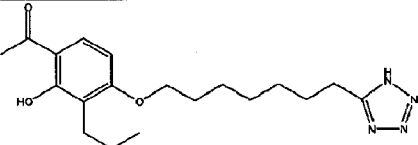
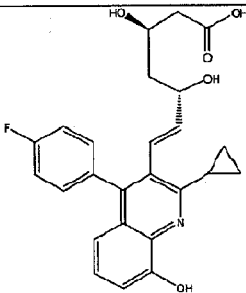
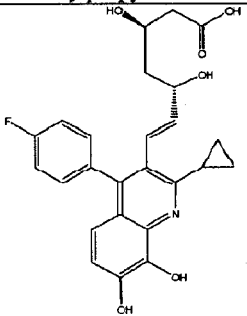
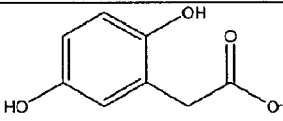
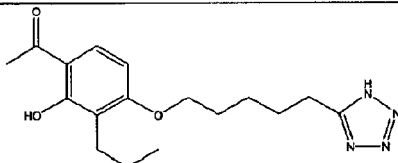
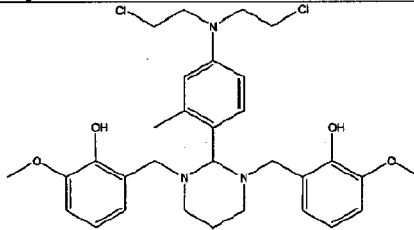
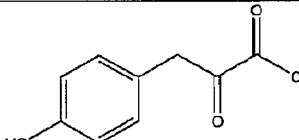
 Chemical Name 4-[(3R)-3-hydroxybutyl]phenol	 Chemical Name (1R)-3-(4-hydroxyphenyl)-1-methylpropyl acetate	 Chemical Name 1-(2-hydroxy-3-propyl-4-[[7-(1H-1,2,3,4-tetrazol-5-yl)heptyl]oxy]phenyl)-1-ethanone
 Chemical Name (3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-8-hydroxy-3-quinolinyl]-3,5-dihydroxy-6-heptenoic acid	 Chemical Name (3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-7,8-dihydroxy-3-quinolinyl]-3,5-dihydroxy-6-heptenoic acid	 Chemical Name 2-(2,5-dihydroxyphenyl)acetate
 Chemical Name 1-(2-hydroxy-3-propyl-4-[[5-(1H-1,2,3,4-tetrazol-5-yl)pentyl]oxy]phenyl)-1-ethanone	 Chemical Name 2-{[2-{4-[bis(2-chloroethyl)amino]-2-methylphenyl]-3-(2-hydroxy-3-methoxybenzyl)tetrahydro-1(2H)-pyrimidinyl]methyl}-6-methoxyphenol	 Chemical Name 3-(4-hydroxyphenyl)-2-oxopropanoate

FIGURE 4 cont.

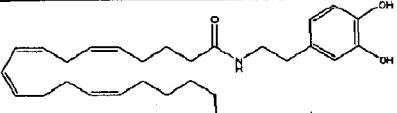
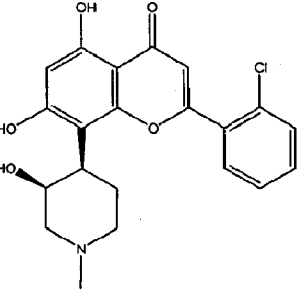
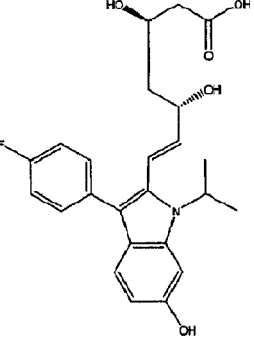
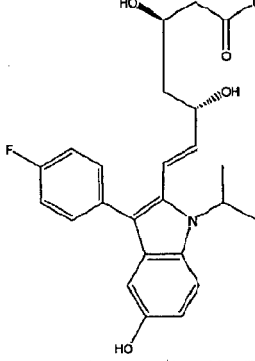
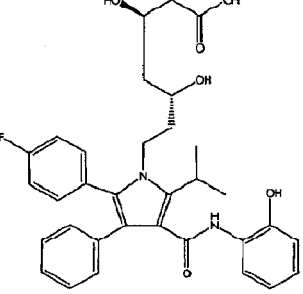
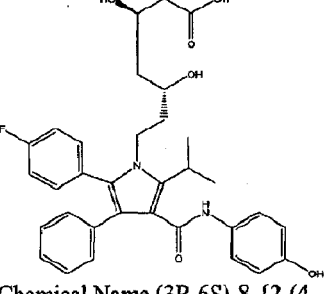
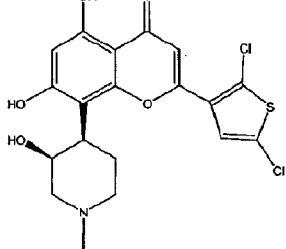
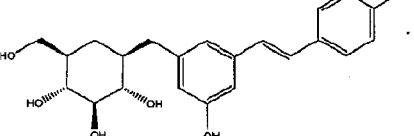
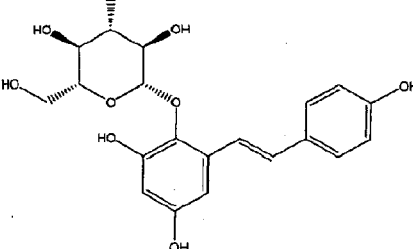
 Chemical Name (5Z,8Z,10Z,14Z)-N-(3,4-dihydroxyphenethyl)-5,8,10,14-icosatetraenamide	 Chemical Name 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methylpiperidinyl]-4H-chromen-4-one	 Chemical Name (3R,6S,7E)-8-[3-(4-fluorophenyl)-6-hydroxy-1-isopropyl-1H-indol-2-yl]-3,6-dihydroxy-7-octenoic acid
 Chemical Name (3R,6S,7E)-8-[3-(4-fluorophenyl)-5-hydroxy-1-isopropyl-1H-indol-2-yl]-3,6-dihydroxy-7-octenoic acid	 Chemical Name (3R,6S)-8-{2-(4-fluorophenyl)-4-[(2-hydroxyanilino)carbonyl]-5-isopropyl-3-phenyl-1H-pyrrol-1-yl}-3,6-dihydroxyoctanoic acid	 Chemical Name (3R,6S)-8-{2-(4-fluorophenyl)-4-[(4-hydroxyanilino)carbonyl]-5-isopropyl-3-phenyl-1H-pyrrol-1-yl}-3,6-dihydroxyoctanoic acid
 Chemical Name 2-(2,5-dichloro-3-thienyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methylpiperidinyl]-4H-chromen-4-one	 Chemical Name (1R,2R,3S,4S,6R)-4-{3-hydroxy-5-[(E)-2-(4-hydroxyphenyl)ethenyl]benzyl}-6-(hydroxymethyl)-1,2,3-cyclohexanetriol	 Chemical Name (2S,3R,4S,5S,6R)-2-{2,4-dihydroxy-6-[(E)-2-(4-hydroxyphenyl)ethenyl]phenoxy}-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol

FIGURE 4 cont.

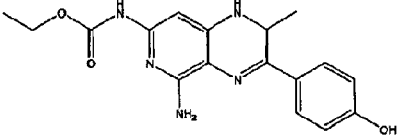
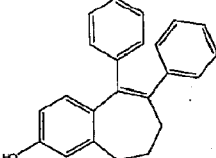
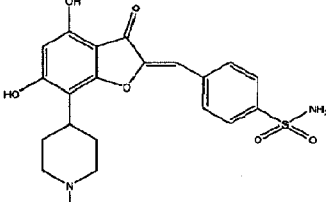
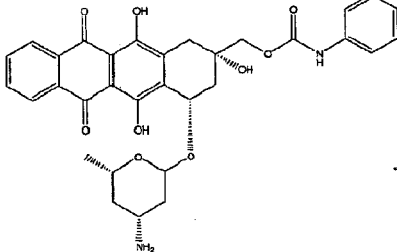
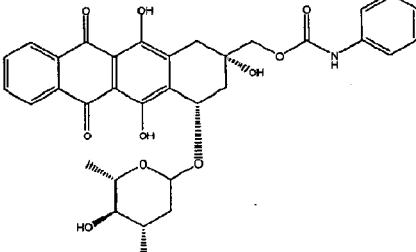
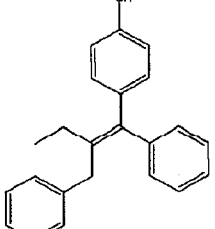
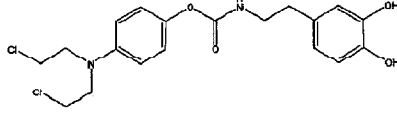
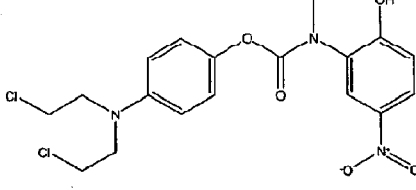
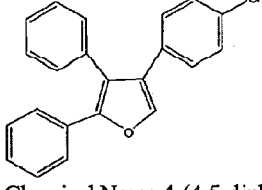
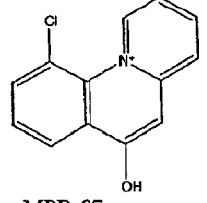
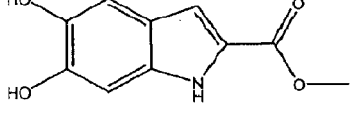
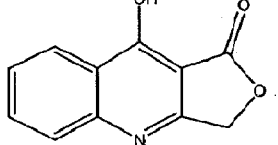
 Chemical Name ethyl 5-amino-3-(4-hydroxyphenyl)-2-methyl-1,2-dihydropyrido[3,4-b]pyrazin-7-ylcarbamate	 Chemical Name 8,9-diphenyl-6,7-dihydro-5H-benzo[a]cyclohepten-3-ol	 Chemical Name 4-([4,6-dihydroxy-7-(1-methyl-4-piperidinyl)-3-oxo-1-benzofuran-2(3H)-ylidene]methyl)benzenesulfonamide
		 Chemical Name 4-[(E)-2-benzyl-1-phenyl-1-butenyl]phenol
		 Chemical Name 4-(4,5-diphenyl-3-furyl)phenol
 Drug Name MPB-07 Chemical Name 10-Chloro-6-hydroxybenzo[c]quinolizinium chloride		 Chemical Name 9-hydroxyfuro[3,4-b]quinolin-1(3H)-one Cognition enhancer

FIGURE 4 cont.

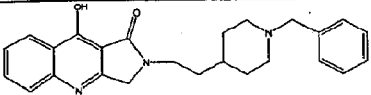
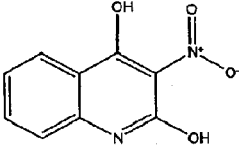
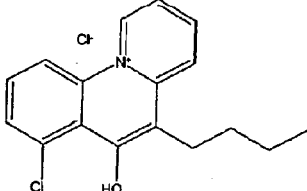
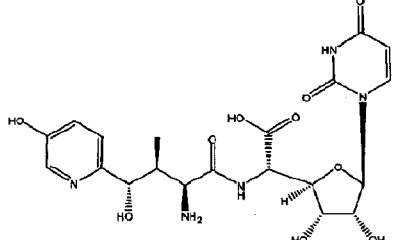
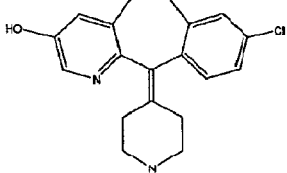
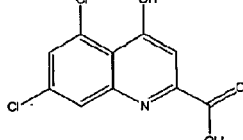
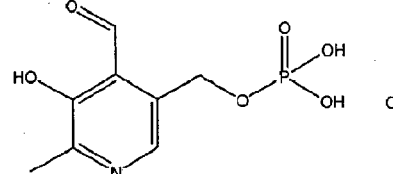
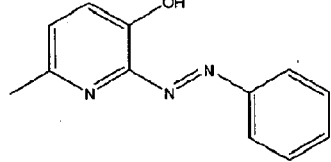
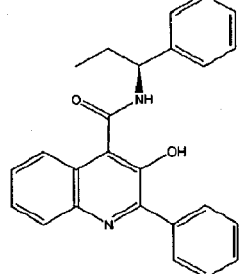
 Chemical Name 2-[2-(1-benzyl-4-piperidinyl)ethyl]-9-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one	 Chemical Name 3-nitro-2,4-quinolinediol	 Drug Name MPB-104 Chemical Name 5-Butyl-7-chloro-6-hydroxypyrido[1,2-a]quinolinium chloride
 Drug Name Nikkomycin Z Chemical Name 5-[[[(2S,3S,4S)-2-Amino-4-hydroxy-4-(5-hydroxy-2-pyridinyl)-3-methyl-1-oxobutyl]amino]-1,5-dideoxy-1-(1,2,3,4-tetrahydro-2,4-dioxo-1-pyrimidinyl)-D-allofuranuronic acid	 Chemical Name 8-Chloro-11-(4-piperidinylidene)-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-3-ol	 Chemical Name 5,7-dichloro-4-hydroxy-2-quinolinecarboxylic acid
 Drug Name p5p, MC-1, Cardoxal Chemical Name Pyridoxal-5'-phosphate monohydrate	 Drug Name SIB-1757 Chemical Name 6-Methyl-2-[(E)-2-phenyldiazenyl]-3-pyridinol	 Drug Name Talnetant, SB-223412 Chemical Name (-)-3-Hydroxy-2-phenyl-N-[1(S)-phenylpropyl]quinoline-4-carboxamide

FIGURE 4 cont.

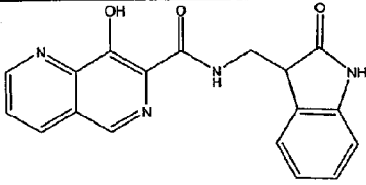
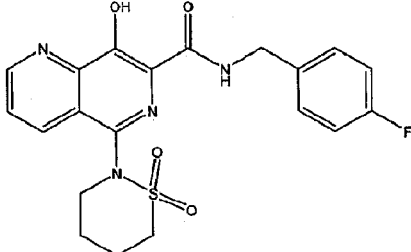
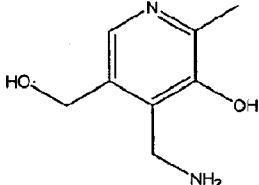
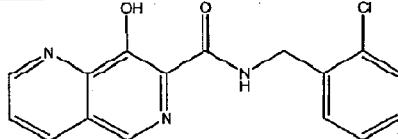
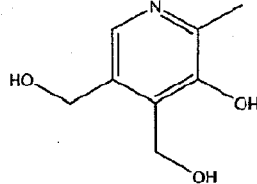
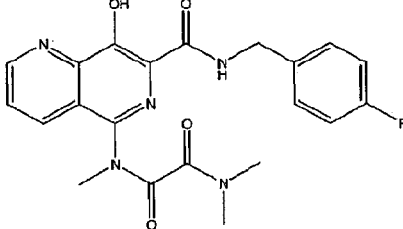
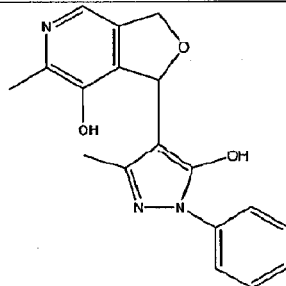
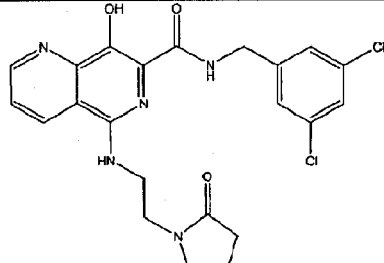
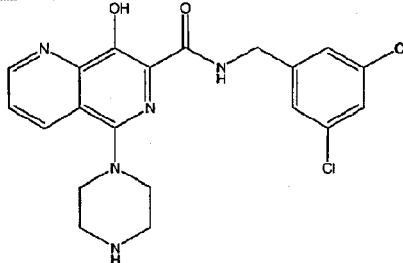
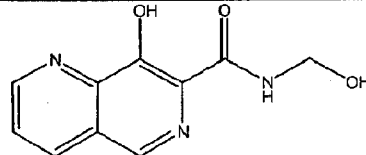
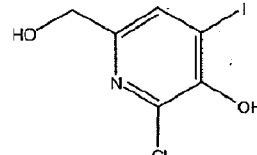
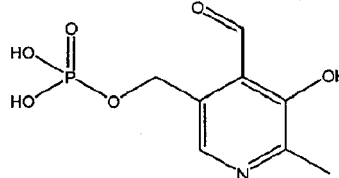
 Chemical Name 8-Hydroxy-N-(2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-1,6-naphthyridine-7-carboxamide	 Drug Name L-000870810, L-870810 Chemical Name 5-(1,1-Dioxoperhydro-1,2-thiazin-2-yl)-N-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide	 Drug Name Pyridoxylamine, Pyridoxamine, K-163, Pyridorin Chemical Name 4-(Aminomethyl)-5-(hydroxymethyl)-2-methylpyridin-3-ol
 Chemical Name N-(2-Chlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide Novel aryl diketo-containing inhibitors of HIV-1 integrase	 Chemical Name 4,5-Bis(hydroxymethyl)-2-methylpyridin-3-ol	 Drug Name L-870812 Chemical Name N1-[7-[N-(4-Fluorobenzyl)carbamoyl]-8-hydroxy-1,6-naphthyridin-5-yl]-N1,N2,N2-trimethyloxamide
 Drug Name Pyridavone Chemical Name 1-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-6-methyl-1,3-dihydrofuro[3,4-c]pyridin-7-ol	 Chemical Name N-(3,5-Dichlorobenzyl)-8-hydroxy-5-[2-(2-oxopyrrolidin-1-yl)ethylamino]-1,6-naphthyridine-7-carboxamide	 Chemical Name N-(3,5-Dichlorobenzyl)-8-hydroxy-5-(piperazin-1-yl)-1,6-naphthyridine-7-carboxamide
 Chemical Name 8-hydroxy-N-(hydroxymethyl)-1,6-naphthyridine-7-carboxamide	 Chemical Name 2-chloro-6-(hydroxymethyl)-4-iodo-3-pyridinol	 Chemical Name (4-formyl-5-hydroxy-6-methyl-3-pyridinyl)methyl dihydrogen phosphate

FIGURE 4 cont.

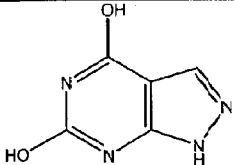
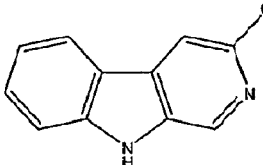
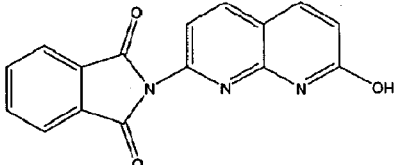
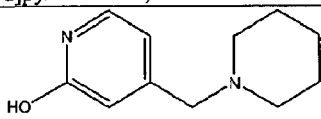
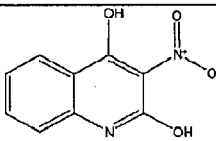
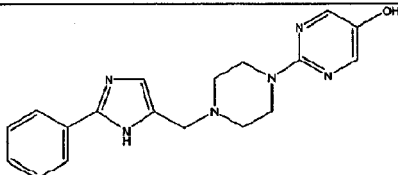
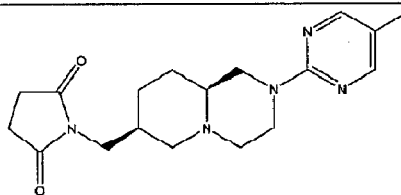
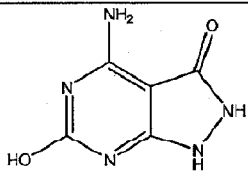
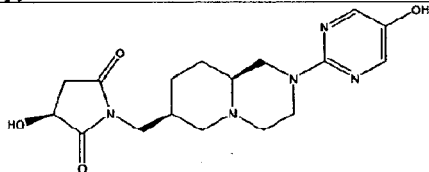
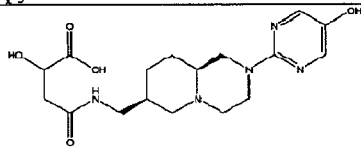
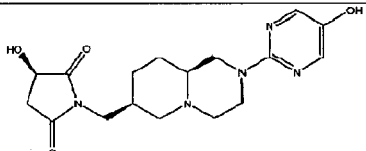
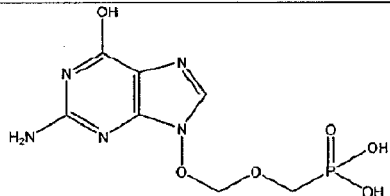
 Drug Name Oxipurinol, Oxypurinol, NSC-76239, Oxyprim Chemical Name 1H-Pyrazolo[3,4- d]pyrimidine-4,6-diol	 Chemical Name 9H-beta-Carbolin-3-ol	 Chemical Name 2-(7- hydroxy[1,8]naphthyridin-2-yl)-1H- isoindole-1,3(2H)-dione
 Chemical Name 4-(1-piperidinylmethyl)- 2-pyridinol	 Chemical Name 3-nitro-2,4-quinolinediol	 Chemical Name 2-{4-[(2-phenyl-1H- imidazol-5-yl)methyl]-1-piperazinyl}-5- pyrimidinol
 Chemical Name 1-{[(7S,9aS)-2-(5- hydroxy-2-pyrimidinyl)octahydro-2H- pyrido[1,2-a]pyrazin-7-yl]methyl}-2,5- pyrrolidinedione	 Drug Name Hydroxyakalone Chemical Name 4-Amino-6-hydroxy-2,3- dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-one	 Chemical Name (3S)-1-{[(7S,9aS)-2-(5- hydroxy-2-pyrimidinyl)octahydro-2H- pyrido[1,2-a]pyrazin-7-yl]methyl}-3- hydroxy-2,5-pyrrolidinedione
 Chemical Name 4-({[(7R,9aS)-2-(5- hydroxy-2-pyrimidinyl)octahydro-2H- pyrido[1,2-a]pyrazin-7-yl]methyl} amino)-2-hydroxy-4- oxobutanoic acid	 Chemical Name (3R)-1-{[(7S,9aS)-2-(5- hydroxy-2-pyrimidinyl)octahydro-2H- pyrido[1,2-a]pyrazin-7-yl]methyl}-3- hydroxy-2,5-pyrrolidinedione	 Chemical Name 9- (Phosphonomethoxymethoxy)guanine

FIGURE 4 cont.

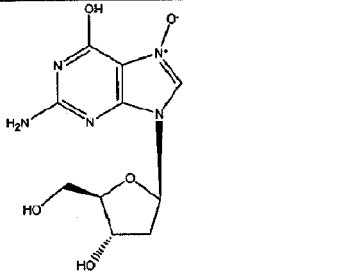
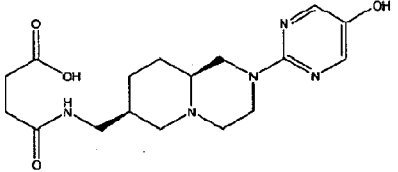
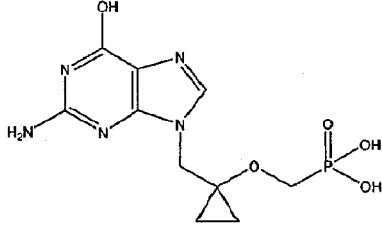
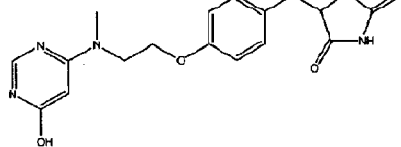
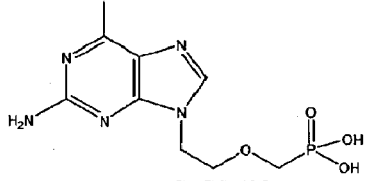
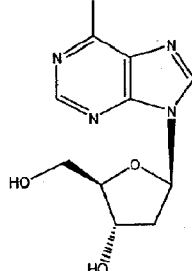
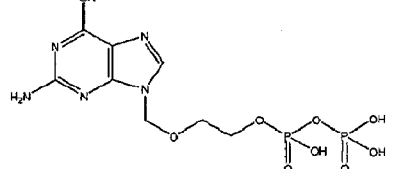
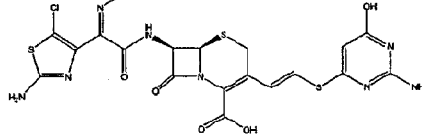
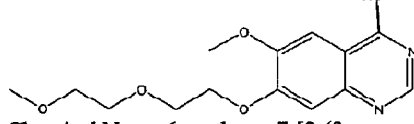
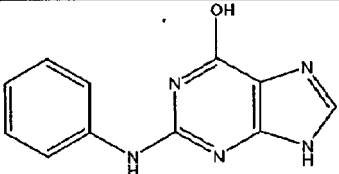
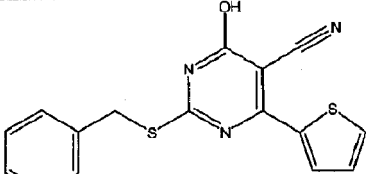
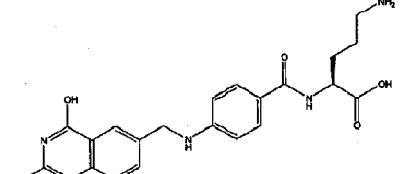
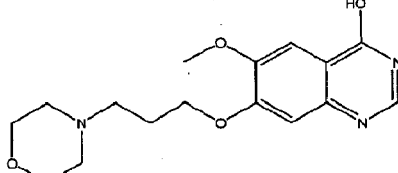
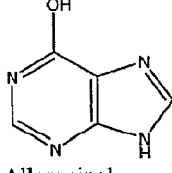
 Chemical Name 7-Hydroxyguanine deoxyriboside	 Chemical Name 4-(((7R,9aS)-2-(5-hydroxy-2-pyrimidinyl)octahydro-2H-pyrido[1,2-a]pyrazin-7-yl)methyl)amino-4-oxobutanoic acid	 Drug Name ANA-317, LB-80317 Chemical Name 1-(Guanin-9-ylmethyl)cyclopropyloxymethylphosphonic acid; 1-(2-Amino-6-hydroxy-9H-purin-9-ylmethyl)cyclopropyloxymethylphosphonic acid
 Chemical Name 5-[4-[2-(6-Hydroxypyrimidin-4-yl)-N-methylamino]ethoxy]benzyl]thiazolidine-2,4-dione	 Drug Name PMEG, GS-438 Chemical Name 2-(Guanin-9-yl)ethoxymethylphosphonic acid	 Chemical Name 9-[(2R,4S,5R)-4-Hydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-9H-purin-6-ol
 Chemical Name 2-(Guanin-9-yl-methoxy)ethyl diphosphate	 Drug Name LB-11058 Chemical Name (6R,7R)-7-[(Z)-2-(2-Amino-5-chlorothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(E)-2-(2-amino-6-hydroxypyrimidin-4-ylsulfanyl)vinyl]-3-cephem-4-carboxylic acid	 Chemical Name 6-methoxy-7-[2-(2-methoxyethoxy)ethoxy]-4-quinazolinol

FIGURE 4 cont.

 Chemical Name 2-anilino-9H-purin-6-ol	 Chemical Name 2-(Benzylsulfanyl)-4-hydroxy-6-(2-thienyl)pyrimidine-5-carbonitrile	 Folypolyglutamate synthase as a target for therapeutic intervention <i>Drugs Fut</i> 2003, 28(10): 967. See p. 970; Fig.2; comp.; 5,8-Dideazapteroyl-Orn
 Chemical Name 6-methoxy-7-[3-(4-morpholinyl)propoxy]-4-quinazolinol	 Allopurinol	