NEUROACTIVE COMPOUNDS AND METHODS OF USE THEREOF

Related Applications

This application claims priority to U.S. Provisional Application No. 62/060932, filed October 7, 2014, the entire contents of which are incorporated herein by reference.

Background of the Invention

[0001] NMDA receptors are highly expressed in the CNS and are involved in excitatory synaptic transmission. Activating these receptors contributes to synaptic plasticity in some circumstances and excitotoxicity in others. These receptors are ligand-gated ion channels that admit Ca2+ after binding of the neurotransmitters glutamate and glycine, and are fundamental to excitatory neurotransmission and normal CNS function. NMDA receptors are heteromeric complexes comprised of NR1, NR2, and/or NR3 subunits and possess distinct recognition sites for exogenous and endogenous ligands. These recognition sites include binding sites for glycine, and glutamate modulators. Positive modulators may be useful as therapeutic agents with potential clinical uses as cognitive enhancers and in the treatment of psychiatric disorders in which glutamatergic transmission is reduced or defective (see, *e.g.,* Horak et al., J. of Neuroscience, 2004, 24(46), 10318-10325). In contrast, negative modulators may be useful as therapeutic agents with potential clinical uses in the treatment of psychiatric disorders in which glutamatergic transmission is pathologically increased (*e.g.,* treatment resistant depression).

[0002] NMDA modulator compounds, *e.g.,* neuroactive steroids such as pregnenolone sulfate (PS) have been shown to exert direct modulatory effects on several types of neurotransmitter receptors, such as $GABA_A$, glycine, AMPA, kainate, and NMDA receptors. NMDA receptors are positively modulated by PS; however, the degree of modulation varies considerably, *e.g.,* depending upon the subunit composition of the receptor.

[0003] New and improved neuroactive compounds are needed that modulate brain excitability for the prevention and treatment of CNS-related conditions. The methods described herein are directed toward this end.

Summary of the Invention

[0004] Thus, in one aspect, described herein are methods of treating a sterol synthesis disorder such as SLOS or a sterol deficiency disorder. The methods of treatment can include treating a subject by administering to the subject an NMDA receptor modulating compound. Exemplary compounds are described herein.

[0005] In one aspect, described herein is a method of treating a subject suffering from a sterol synthesis disorder (*e.g.,* disorder of cholesterol biosynthesis; disorder characterized by a significant disruption of sterol biosynthesis) or a sterol deficiency disorder (*e.g.,* abnormal levels of a sterol described herein; *e.g.,* at least 1, e.g., at least 2 standard deviations below normal sterol levels), comprising administering to the subject an effective amount of an NMDA receptor modulating compound or pharmaceutically acceptable salt thereof.

[0006] As used herein, "normal sterol level" varies by age, and is defined, as described in as Björkhem et al., *J. of Lipid Res.* 2001, 42: 366-371; for example, within 2 standard deviations of the values provided in Table 2 (e.g., within 2 standard deviations, within 1.5 standard deviations, or within 1 standard deviation). Normal and abnormal sterol levels (*e.g.,* 24(S)-hydroxycholesterol and 27(S)-hydroxycholesterol) for example in various age groups, have been reported in *e.g.,* Björkhem et al., *J. of Lipid Res.* 2001, 42: 366-371; Bretillon et al., *J. Lipid Res.* 2000, 41: 840-845; Björkhem et al., *J. Lipid Res.* 1998, 39: 1594-1600; Lutjohann et al., *Proc. Natl. Acad. Sci. USA* 1996, 93: 9799-9804, the contents of each of which are incorporated herein by reference.

[0007] In some embodiments, the subject suffers from a sterol synthesis disorder and a 24(S)-hydroxycholesterol deficiency disorder.

[0008] In some embodiments, the sterol deficiency disorder is characterized by the presence of 24(S)-hydroxycholesterol in the plasma of the subject at significantly reduced levels (*e.g.,* at least 1 or 2 standard deviations below) compared with the plasma of a subject not suffering from a sterol deficiency disorder).

[0009] In some embodiments, the metabolic processing of 24(S)-hydroxycholesterol is low as compared with a subject not suffering from the disorder.

[0010] In some embodiments, the compound is 24(S)-hydroxycholesterol. In some embodiments, the compound is not a product of nature. In some embodiments, the sterol is 24(S)-hydroxycholesterol, 25-hydroxycholesterol, or 27(S)-hydroxycholesterol.

[0011] In some embodiments, the sterol disorder is selected from: Smith-Lemli-Opitz syndrome; Conradi-Hunermann syndrome; Greenberg dysplasia; Desmosterolosis; Cerebrotendinous Xanthomatosis (CTX); Mevalonate Kinase Deficiency Syndromes (MKD); SC4MOL gene mutation (SMO Deficiency); lathosterolosis; X-linked dominant chondrodysplasia puncata; CHILD syndrome or CK-syndrome; autism spectrum disorder; Niemann-Pick disease; and disorders of dolichol synthesis or metabolism. In some embodiments, the sterol disorder is Smith-Lemli-Opitz syndrome.

[0012] In some embodiments, the compound has an EC_{50} of 10 μM or less (*e.g.,* 5 μM, 1 μM, 500 nM, 350 nM, 250 nM, 100 nM, 50 nM, 10 nM or less).

[0013] In some embodiments, the compound is present at an effective plasma concentration of 10 to 800 ng/mL of plasma (*e.g.,* 10 to 600 ng/mL, 10 to 500 ng/mL, 25 to 500 ng/mL, 40 to 500 ng/mL, 25 to 350 ng/mL). In some embodiments, the compound is present at an effective plasma concentration of at least 10 ng/mL of plasma (*e.g.,* at least 15 ng/mL, 20 ng/mL, 25 ng/mL, 30 ng/mL, 30 ng/mL, 35 ng/mL, 40 ng/mL, 45 ng/mL, 50 ng/mL, 55 ng/mL).

[0014] In some embodiments, the compound is a NMDA receptor modulator (*e.g.,* positive modulator, negative modulator).

[0015] In some embodiments, the compound is a compound of Formula (**I**), (**II-a**), (**II-b**), (**III**), (**IV**), (**V**), (**VI**), (**VII**), (**VIII**), (**IX-A**), (**IX-B**), (**X**), (**XI-A**), or (**XI-B**) In some embodiments, the compound is a compound of Formula (**I**).

[0016] In some embodiments, the administration to the subject normalizes concentrations of oxysterols in circulation relative to a subject not administered with the compound or administered with a placebo.

[0017] In some embodiments, the administration to the subject elevates levels of cholesterol in tissues and plasma relative to a subject not administered with the compound or administered with a placebo.

[0018] In some embodiments, the subject is an infant. In some embodiments, the subject is less than 21 years old (*e.g.,* less than 18, 15, 13, 12, 10, 8, 6, 4, 3, 2, or 1 year old).

[0019] In some embodiments, the method further comprises administration of an additional therapy. In some embodiments, the additional therapy is dietary cholesterol therapy (*e.g.,* cholesterol supplementation, statin treatment (*e.g.,* 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (*e.g.,* HMG CoA reductase inhibitors), *e.g.,* simvastatin), bile acid supplementation or downstream hormone supplementation, medical therapies, or surgical interventions; antioxidants; gene therapy.

[0020] In one aspect, described herein is a dosage form comprising a compound of Formula (**I**), (**II-a**), (**II-b**), (**III**), (**IV**), (**V**), (**VI**), (**VII**), (**VIII**), (**IX-A**), (**IX-B**), (**X**), (**XI-A**), or (**XI-B**) configured for administration in a subject, wherein the subject is a child. In some embodiments, the dosage form is a

liquid suspension, sprinkle, meltaway, sublingual, or injectable. In some embodiments, the dosage form is a solid dosage form. In some embodiments, the solid dosage form is a tablet, capsule, or pill.

Detailed Description of Certain Embodiments of the Invention

Diseases and disorders

Described herein are methods of treating a sterol synthesis disorder. Exemplary disorders are described herein. The methods include administering to a subject, *e.g.,* a subject suffering from a sterol synthesis disorder such as SLOS, a NMDA receptor modulating compound. Exemplary compounds are described herein. In some embodiments the compounds is 24(S) hydroxyl cholesterol. In some embodiments, the compound is a compound of a formula described herein such as a compound of Formula (**I**), (**II-a**), (**II-b**), (**III**), (**IV**), (**V**), (**VI**), (**VII**), (**VIII**), (**IX-A**), (**IX-B**), (**X**), (**XI-A**), or (**XI-B**).

Sterol Synthesis Disorders

In one aspect, described herein are methods for treating a sterol synthesis disorder. Cholesterol has an essential rule in growth and development. It is a membrance lipid and a precursor to many molecules that play important roles in cellular growth and diffierentiation, protein glycosylation, and signaling pathways. Biosynthesis of cholesterol involves a number of enzymes and intermediates. Disorders resulting from a deficiency in any of the enzymes involved in cholesterol biosynthesis lead to the accumulation of intermediates and imbalance in biomolecules, resulting in disorders including congenital skeletal malformations, dysmorphic facial features, psychomotor retardation, and failure to thrive. In an embodiment, a sterol synthesis disorder or symptom of a sterol synthesis disorder can be treated by administering to a subject suffering from a sterol synthesis disorder a compound described herein, such as a NMDA receptor modulating compound as described herein. Additional disorders are described below.

Smith-Lemli-Opitz Syndrome

In one aspect, described herein are methods for treating Smith-Lemli-Opitz Syndrome (or SLOS, or 7-dehydrocholesterol reductase deficiency). SLOS is an inborn error of cholesterol synthesis. In addition to microcephaly, moderate to severe intellectual disability, sensory hypersensitivity, stereotyped

behaviors, dysmorphic facial features, and syndactyly of the second/third toes, a feature of the disease is reduced cerebrosterol (24(S)-hydroxycholesterol) levels. SLOS is an autosomal recessive genetic condition resulting from deficiency in the final enzyme of the cholesterol synthesis pathway, and causes low or low-normal plasma cholesterol levels and increased 7- and 8-dehydrocholesterol (DHC; 7DHC and 8DHC) levels. Common therapies currently used include dietary cholesterol supplementation, treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG CoA reductase inhibitors, also known as statins), and treatment with agents that enhance cholesterol production and/or accretion; and to decrease the accumulation of 7DHC and 8DHC, the potentially toxic precursors of cholesterol.

Desmosterolosis

Desmosterolosis is a deficiency in desmosterol reductase and has a similar phenotype to SLOS. In one aspect, described herein are methods for treating desmosterolosis.

Sitosterolemia

Sitosterolemia is a rare autosomal recessive disorder caused by mutations in two ATP-binding cassette (ABC) transporter genes (ABCG5 and ABCG8). Sitosterolemia enhances the absorption of plant sterols and cholesterol from the intestines. Patients typically present with tendon and tuberous xanthomas and premature coronary artery disease. In one aspect, described herein are methods for treating sitosterolemia.

Cerebrotendinous xanthomatosis (CTX)

In one aspect, described herein are methods for treating cerebrotendinous xanthomatosis (also referred to as cerebral cholesterosis, or Van Bogaert-Scherer-Epstein syndrome). CTX can be caused by a mutation in the CYP27A1 gene, which produces the sterol 27-hydroxylase enzyme. Sterol 27-hydroxylase metabolizes cholesterol into bile acids (*e.g.,* chenodeoxycholic acid) that are important in the absorption of fats in the intestine. Enzyme dysfunction can lead to cholesterol accumulation in tissues. CTX is characterized by childhood diarrhea, cataracts, tendon xanthomas, reduced mental capability and abnormal movements in adults.

Mevalonate Kinase Deficiency Syndromes (MKD)

Mevalonate Kinase Deficiency (also referred to as mevalonic aciduria (a more severe form of MKD), or Hyper IgD Syndrome (HIDS, or hyperimmunoglobulinemia D) with period fever syndrome (a more benign form of MKD)) causes an accumulation of mevalonic acid in the urine as a result of insufficient acitivity of mevalonate kinase. MKD can result in developmental delay, hypotonia, anemia, hepatosplenomegaly, dysmorphic features, mental retardation, and overall failure to thrive. Mevalonic aciduria is characterized by delayed physical and mental development, failure to thrive, recurrent episodes of fever with vomiting and diarrhea, enlarged liver, spleen and lymph nodes, microcephaly (small head size), cataract, low muscle tone, short statute, distinctfacial features, ataxia, and anemia. HIDS is is characterized by recurrent episodes of fever associated with swollen lymph nodes, joint pain, gastrointestinal issues and skin rash. In one aspect, described herein are methods for treating MKD.

SC4MOL gene mutation (SMO Deficiency)

SC4MOL gene deficiency is a genetic disorder in the cholesterol biosynthesis pathway (*e.g.,* mutations in the SC4MOL gene encoding a novel sterol oxidase). SC$MOL deficiency is characterized by the accumulation of dimethyl and monomethyl sterols that can be detected in blood, skin flakes or primary skin fibroblasts. In one aspect, described herein are methods for treating SMO deficiency.

Niemann-Pick disease

Niemann-Pick disease is a lysosomal storage disease resulting from a genetic mutation that affects metabolism. Niemann-Pick disease leads to abnormal accumulation of cholesterol and other fatty substances (lipids) due to an inability of the body to transport the substances. The accumulation damages the affected areas.

Autism

In one aspect, described herein are methods for treating autism spectrum disorder or autism. Autism spectrum disorder (ASD) and autism refer to a group of complex disorders of brain development. Autism is typically characterized by difficulties in social interaction, for example in verbal and nonverbal communication. Repetitive behaviors are also often seen in indidividuals having autism. Autism can be associated with intellectual disability, difficulties in motor coordination and attention and physical health issues, *e.g.,* sleep and gastrointestinal disturbances. Individuals having autism can also excel in visual

skills, music, math and art. Autism can refer to autistic disorder, childhood disintegrative disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS), and Asperger syndrome. Autism also refers to monogenetic causes of autism such as synaptophathy's, *e.g.,* Rett syndrome, Fragile X syndrome, Angelman syndrome.

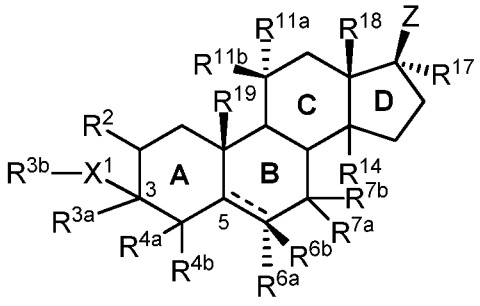
Disorders Associated with Phenylketonuria

In one aspect, described herein are methods for treating disorders associated with phenylketonuria (e.g., cognitive disorders). Phenylketonuria can lead to hypochesterolemia and lowered vitamin D status. Total and low-density cholesterols and 25-hydroxy vitamin D have been found to be decreased in subjects suffering from phenylketonuria as compared with subjects not suffering from phenylketonuria (*Clin. Chim. Acta* 2013, 416: 54-59). 24S-hydroxycholesterol and 27S-hydroxycholesterol and 7α-hydroxycholesterol (e.g., representing peripheral and hepatic cholesterol elimination, respectively) have been shown to be significantly decreased in subjects suffering from phenylketonuria, while 7β-hydroxycholesterol (e.g., reflecting oxidative stress) was increased significantly in subjects suffering from phenylketonuria. Changes in the levels of 24S-OHC and 7β-hydroxycholesterol correlate with phenylalanine level, and 27S-hydroxycholesterol levels may correlate with the 25-hydroxy vitamin D level in subjects suffering from phenylketonuria.

Compounds

[0021] Described herein are methods of treating a sterol synthesis disorder such as SLOS, by administering to a subject an NMDA receptor modulating compound. Exemplary compounds are described herein below. In some embodiments, the compound is a negative modulator (e.g., a negative allosteric modulator). In some embodiments, the compound is a positive modulator (e.g., a positive allosteric modulator). In some embodiments, the compound is an allosteric modulator.

[0022] Exemplary compounds include a compound of Formula (**I**):

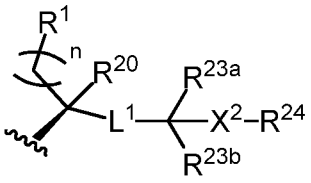


(I)

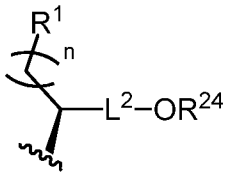
or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof;

wherein:

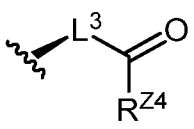
Z is a group of the formula (i), (ii), (iii), (iv), or (v):



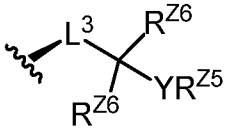
(i),



(ii),

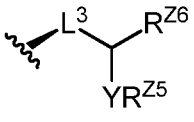


(iii),



(iv),

or



(v)

L^1 and L^2 are selected from a group consisting of a bond, a substituted or unsubstituted C_1–C_6 alkylene, a substituted or unsubstituted C_2–C_6 alkenylene, substituted or unsubstituted C_2–C_6 alkynylene, a substituted or unsubstituted hetero C_1–C_6 alkylene, a substituted or unsubstituted hetero C_2–C_6 alkenylene, and a substituted or unsubstituted hetero C_2–C_6 alkynylene;

L^3 is a substituted or unsubstituted C_1–C_6 alkylene, a substituted or unsubstituted C_2–C_6 alkenylene, substituted or unsubstituted C_2–C_6 alkynylene, a substituted or unsubstituted hetero C_1–C_6 alkylene, a substituted or unsubstituted hetero C_2–C_6 alkenylene, or a substituted or unsubstituted hetero C_2–C_6 alkynylene;

each instance of X^1 and X^2 is independently –O–, –S–, –N(R^X)–, wherein each instance of R^X is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted

heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, or an amino protecting group;

R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, halo, $-N_3$, $-NO_2$, $-SCN$, $-CN$, $-OR^{A1}$, $-SR^{A1}$, $-N(R^{A1})_2$, $-N=NR^{A1}$, $-N=C(R^{A1})_2$, $-N(OR^{A1})(R^{A1})$,$-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-C(=O)N(OR^{A1})(R^{A1})$,$-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)SR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-NR^{A1}C(=O)R^{A1}$, $-NR^{A1}C(=O)OR^{A1}$, $-NR^{A1}C(=O)SR^{A1}$, $-NR^{A1}C(=O)N(R^{A1})_2$, $-SC(=O)R^{A2}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-OS(=O)_2R^{A2}$, $-OS(=O)_2OR^{A1}$, $-S-S(=O)_2R^{A2}$, $-S-S(=O)_2OR^{A1}$, $-S(=O)R^{A2}$, $-SO_2R^{A2}$, $-NR^{A1}SO_2R^{A2}$, or $-SO_2N(R^{A1})_2$, wherein R^{A1} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{A1} groups are joined to form an substituted or unsubstituted heterocyclic ring; and R^{A2} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or an R^{A1} group and an R^{A2} group are joined to form an substituted or unsubstituted heterocyclic ring;

each instance of R^2, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, and R^{11b} is independently hydrogen, –OH, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-N_3$, $-NO_2$, $-SCN$, $-CN$, $-OR^{B1}$, $-SR^{B1}$, $-N(R^{B1})_2$, $-N=NR^{B1}$, $-N=C(R^{B1})_2$, $-N(OR^{B1})(R^{B1})$, $-C(=O)R^{B1}$, $-C(=O)OR^{B1}$, $-C(=O)SR^{B1}$, $-C(=O)N(R^{b1})_2$, $-C(=O)N(OR^{B1})(R^{B1})$,$-OC(=O)R^{B1}$, $-OC(=O)OR^{B1}$, $-OC(=O)SR^{B1}$, $-OC(=O)N(R^{B1})_2$, $-NR^{B1}C(=O)R^{B1}$, $-NR^{B1}C(=O)OR^{B1}$, $-NR^{B1}C(=O)SR^{B1}$, $-NR^{B1}C(=O)N(R^{B1})_2$, $-SC(=O)R^{B2}$, $-SC(=O)OR^{B1}$, $-SC(=O)SR^{B1}$, $-SC(=O)N(R^{B1})_2$, $-OS(=O)_2R^{B2}$, $-OS(=O)_2OR^{B1}$, $-S-S(=O)_2R^{B2}$, $-S-S(=O)_2OR^{B1}$, $-S(=O)R^{B2}$, $-SO_2R^{B2}$, $-NR^{B1}SO_2R^{B2}$, or $-SO_2N(R^{B1})_2$, wherein R^{B1} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group

when attached to a nitrogen atom, or two R^{B1} groups are joined to form an substituted or unsubstituted heterocyclic ring; and R^{B2} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or an R^{B1} group and an R^{B2} group are joined to form an substituted or unsubstituted heterocyclic ring; or optionally wherein each of R^{4a} and R^{4b}, and/or R^{7a} and R^{7b}, and/or R^{11a} and R^{11b} are joined to form an oxo (=O) group;

R^{3a} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{3b} is hydrogen, $–C(=O)R^{C1}$, $–C(=O)OR^{C1}$, $–C(=O)SR^{C1}$, $–C(=O)N(R^{C1})_2$, $–S(=O)_2R^{C2}$, $–S(=O)_2OR^{C1}$, $–P(=O)_2R^{C2}$, $–P(=O)_2OR^{C1}$, $–P(=O)(OR^{C1})_2$, $–P(=O)(R^{C2})_2$, or $–P(=O)(R^{C2})(OR^{C1})$, wherein R^{C1} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{C1} groups are joined to form an substituted or unsubstituted heterocyclic ring; and R^{C2} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each of R^{6a} and R^{6b} is independently hydrogen, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl, and ------ represents a single or double bond, provided if a double bond is present in Ring B, then one of R^{6a} or R^{6b} is absent, and provided if a single bond is present in Ring B, then the hydrogen at C5 is in the *alpha* or *beta* position;

R^{14} is hydrogen or substituted or unsubstituted alkyl;

R^{17} is hydrogen, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or $–OR^{D1}$, wherein R^{D1} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or an oxygen protecting group;

each instance of R^{18}, R^{19}, and R^{20} is independently hydrogen or substituted or unsubstituted alkyl;

and each instance of R^{23a} and R^{23b} is independently hydrogen, halogen, or substituted or unsubstituted alkyl, or R^{23a} and R^{23b} are joined together to form substituted or unsubstituted C_3–C_6 cycloalkyl;

R^{24} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstitued alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstitued aryl, substituted or unsubstituted heteroaryl, $–C(=O)R^{E1}$, $–C(=O)OR^{E1}$, $–C(=O)SR^{E1}$, $–C(=O)N(R^{E1})_2$, $–S(=O)_2R^{E2}$, $–S(=O)_2OR^{E1}$, $–P(=O)_2R^{E2}$, $–P(=O)_2OR^{E1}$, $–P(=O)(OR^{E1})_2$, $–P(=O)(R^{E2})_2$, or $–P(=O)(R^{E2})(OR^{E1})$, wherein R^{E1} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{E1} groups are joined to form an substituted or unsubstituted heterocyclic ring; and R^{E2} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

Y is –O–, –S–, or $–NR^{Z5}–$;

R^{Z4} is independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $–OR^{Z5}$, $–SR^{Z5}$, or $–N(R^{Z5})_2$;

each instance of R^{Z5} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{Z5} groups are joined to form a substituted or unsubstituted heterocyclic ring; and

each instance of R^{Z6} is independently hydrogen or substituted or unsubstituted alkyl, or two R^{Z6} groups are joined to form a C_{3-6} carbocyclic ring; and

the subscript n is 0, 1, 2, or 3.

[0023] In certain embodiments, when R^{3a} is H, n is 1, and R^{19} is Me; then R^1 is other than H, alkyl, alkenyl, or alkynyl. In certain embodiments, when R^{3a} is H, R^{3b} is –COMe, R^{19} is Me, and n is 0; then R^1 is OH. In certain embodiments, when R^{3a} is H, n is 0, and R^{20} is alkyl; then R^1 is other than OH. In certain embodiments, when R^{19} is Me; then R^1 is other than H, alkyl, alkenyl, or alkynyl. In certain embodiments, R^1 is H; and R^{19} is other than Me. In certain embodiments, each R^1 and R^{3a} is H; and R^{19} is other than Me.

[0024] In certain embodiments, when R^{3a} is H, then R^1 is other than H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl. In certain embodiments, when R^{3a} is H, then R^1 is substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, halo, $–N_3$, $–NO_2$, –SCN, –CN, $–OR^{A1}$, $–SR^{A1}$, $–N(R^{A1})_2$, $–N{=}NR^{A1}$, $–N{=}C(R^{A1})_2$, $–N(OR^{A1})(R^{A1})$,$–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)SR^{A1}$, $–C(=O)N(R^{A1})_2$, $–C(=O)N(OR^{A1})(R^{A1})$,$–OC(=O)R^{A1}$, $–OC(=O)OR^{A1}$, $–OC(=O)SR^{A1}$, $–OC(=O)N(R^{A1})_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}C(=O)SR^{A1}$, $–NR^{A1}C(=O)N(R^{A1})_2$, $–SC(=O)R^{A2}$, $–SC(=O)OR^{A1}$, $–SC(=O)SR^{A1}$, $–SC(=O)N(R^{A1})_2$, $–OS(=O)_2R^{A2}$, $–OS(=O)_2OR^{A1}$, $–S–S(=O)_2R^{A2}$, $–S–S(=O)_2OR^{A1}$, $–S(=O)R^{A2}$, $–SO_2R^{A2}$, $–NR^{A1}SO_2R^{A2}$, or $–SO_2N(R^{A1})_2$.

Various embodiments of R^{3a}

[0025] As generally defined above, R^{3a} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. It is generally understood that R^{3a} may be in the *alpha* (down) or *beta* (up) position. In certain embodiments, R^{3a} is *alpha*. In certain embodiments, R^{3a} is *beta*.

[0026] In certain embodiments, R^{3a} is hydrogen.

[0027] In certain embodiments, R^{3a} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstituted $C_{1–6}$alkyl, substituted or unsubstituted $C_{1–2}$alkyl, substituted or unsubstituted $C_{2–3}$alkyl, substituted or unsubstituted $C_{3–4}$alkyl, substituted or unsubstituted $C_{4–5}$alkyl, or substituted or unsubstituted $C_{5–6}$alkyl. Exemplary R^{3a} $C_{1–6}$alkyl groups include, but are not limited to, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), n–hexyl (C_6), $C_{1–6}$ alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more fluoro groups (*e.g.,* $–CF_3$, $–CH_2F$, $–CHF_2$, difluoroethyl, and 2,2,2–trifluoro–1,1–dimethyl–ethyl), $C_{1–6}$ alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more chloro groups (*e.g.,* $–CH_2Cl$, $–CHCl_2$), and $C_{1–6}$ alkyl substituted with alkoxy groups (*e.g.,* $–CH_2OCH_3$ and $–CH_2OCH_2CH_3$). In certain embodiments, R^{3a} is

substituted alkyl, *e.g.*, R^{3a} is haloalkyl, alkoxyalkyl, or aminoalkyl. In certain embodiments, R^{3a} is Me, Et, n-Pr, n-Bu, i-Bu, fluoromethyl, chloromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, difluoroethyl, 2,2,2-trifluoro-1,1-dimethyl-ethyl, methoxymethyl, methoxyethyl, or ethoxymethyl. In certain embodiments, R^{3a} is Me, Et, n-Pr, n-Bu, or i-Bu. In certain embodiments, R^{3a} is methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, or ethoxyethyl. In certain embodiments, R^{3a} is trifluoromethoxymethyl. In certain embodiments, R^{3a} is fluoromethyl, chloromethyl, difluoromethyl, trifluoromethyl, difluoroethyl, trifluoroethyl, or 2,2,2-trifluoro-1,1-dimethyl-ethyl. In certain embodiments, R^{3a} is trifluoromethyl.

[0028] In certain embodiments, R^{3a} is substituted or unsubstituted alkenyl, *e.g.*, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-3}alkenyl, substituted or unsubstituted C_{3-4}alkenyl, substituted or unsubstituted C_{4-5}alkenyl, or substituted or unsubstituted C_{5-6}alkenyl. In certain embodiments, R^{3a} is ethenyl (C_2), propenyl (C_3), or butenyl (C_4), unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, alkoxyalkyl, or hydroxyl. In certain embodiments, R^{3a} is ethenyl, propenyl, or butenyl, unsubstituted or substituted with alkyl, halo, haloalkyl, alkoxyalkyl, or hydroxy. In certain embodiments, R^{3a} is ethenyl.

[0029] In certain embodiments, R^{3a} is substituted or unsubstituted alkynyl, *e.g.*, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{2-3}alkynyl, substituted or unsubstituted C_{3-4}alkynyl, substituted or unsubstituted C_{4-5}alkynyl, or substituted or unsubstituted C_{5-6}alkynyl. Exemplary substituted or unsubstituted R^{3a} alkynyl groups include, but are not limited to, ethynyl, propynyl, or butynyl, unsubstituted or substituted with alkyl, halo, haloalkyl (*e.g.*, CF_3), alkoxyalkyl, cycloalkyl (*e.g.*, cyclopropyl or cyclobutyl), or hydroxyl. In certain embodiments, R^{3a} is selected from the group consisting of trifluoroethynyl, cyclopropylethynyl, cyclobutylethynyl, and propynyl, fluoropropynyl, and chloroethynyl. In certain embodiments, R^{3a} is ethynyl (C_2), propynyl (C_3), or butynyl (C_4), unsubstituted or substituted with one or more substituents selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl. In certain embodiments, R^{3a} is ethynyl (C_2), propynyl (C_3), or butynyl (C_4) substituted with substituted phenyl. In certain embodiment, the phenyl substitutent is further substituted with one or more substituents selected from the group consisting of halo, alkyl, trifluoroalkyl, alkoxy, acyl, amino or amido. In certain embodiments, R^{3a} is ethynyl (C_2), propynyl (C_3), or butynyl (C_4) substituted with substituted or unsubstituted pyrrolyl, imidazolyl, pyrazolyl, oxazoyl, thiazolyl, isoxazoyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, or tetrazolyl.

[0030] In certain embodiments, R^{3a} is ethynyl, propynyl, or butynyl, unsubstituted or substituted with alkyl, halo, haloalkyl, alkoxyalkyl, or hydroxyl. In certain embodiments, R^{3a} is ethynyl or propynyl,

substituted with substituted or unsubstituted aryl. In certain embodiments, R^{3a} is ethynyl or propynyl, substituted with phenyl unsubstituted or substituted with halo, alkyl, alkoxy, haloalkyl, trihaloalkyl, or acyl. In certain embodiments, R^{3a} is ethynyl or propynyl, substituted with substituted or unsubstituted carbocyclyl. In certain embodiments, R^{3a} is ethynyl or propynyl, substituted with substituted or unsubstituted cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In certain embodiments, R^{3a} is ethynyl or propynyl, substituted with substituted or unsubstituted heteroaryl. In certain embodiments, R^{3a} is ethynyl or propynyl, substituted with substituted or unsubstituted pyridinyl, or pyrimidinyl. In certain embodiments, R^{3a} is ethynyl or propynyl, substituted with substituted or unsubstituted pyrrolyl, imidazolyl, pyrazolyl, oxazoyl, thiazolyl, isoxazoyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl. In certain embodiments, R^{3a} is ethynyl or propynyl, substituted with substituted or unsubstituted heterocyclyl. In certain embodiments, R^{3a} is ethynyl or propynyl, substituted with substituted or unsubstituted pyrrolidinyl, piperidinyl, piperazinyl, or mopholinyl. In certain embodiments, R^{3a} is propynyl or butynyl, substituted with hydroxyl or alkoxy. In certain embodiments, R^{3a} is propynyl or butynyl, substituted with methoxy or ethoxy. In certain embodiments, R^{3a} is ethynyl or propynyl, substituted with Cl. In certain embodiments, R^{3a} is ethynyl or propynyl, substituted with trifluoromethyl.

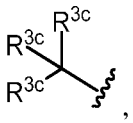
[0031] In certain embodiments, R^{3a} is substituted or unsubstituted carbocyclyl, *e.g.,* substituted or unsubstituted C_{3-6}carbocyclyl, substituted or unsubstituted C_{3-4}carbocyclyl, substituted or unsubstituted C_{4-5} carbocyclyl, or substituted or unsubstituted C_{5-6} carbocyclyl.

[0032] In certain embodiments, R^{3a} is substituted or unsubstituted heterocyclyl, *e.g.,* substituted or unsubstituted 3–6 membered heterocyclyl, substituted or unsubstituted 3–4 membered heterocyclyl, substituted or unsubstituted 4–5 membered heterocyclyl, or substituted or unsubstituted 5–6 membered heterocyclyl.

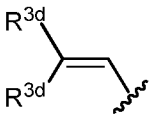
[0033] In certain embodiments, R^{3a} is substituted or unsubstituted aryl. In certain embodiments, R^{3a} is substituted or unsubstituted phenyl.

[0034] In certain embodiments, R^{3a} is substituted or unsubstituted heteroaryl, *e.g.,* optionally substituted 5– to 6–membered heteroaryl.

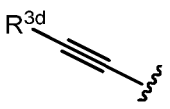
[0035] Further embodiments of R^{3a}, as a substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl groups, are depicted below:



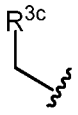
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wherein each instance of R^{3c} is hydrogen, halo, or $-OR^{F1}$, wherein R^{F1} is substituted or unsubstituted alkyl; and each instance of R^{3d} is hydrogen, halo, or substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl.

[0036] In certain embodiments, at least one R^{3c} is hydrogen. In certain embodiments, at least two R^{3c} is hydrogen. In certain embodiments, each R^{3c} is hydrogen. In certain embodiments, at least one R^{3c} is halogen (*e.g.,* fluoro, chloro, bromo, iodo). In certain embodiments, at least two R^{3c} are halogen (*e.g.,* fluoro, chloro, bromo, iodo). In certain embodiments, each R^{3c} is halogen (*e.g.,* fluoro, to provide the group $-CF_3$). In certain embodiments, at least one R^{3c} is $-OR^{F1}$ (*e.g.,* OMe or OEt). In certain embodiments, at least two R^{3c} is $-OR^{F1}$ (*e.g.,* OMe or OEt). In certain embodiments, at least one R^{3c} is hydrogen, F, –OMe, or –OEt. In certain embodiments, one of R^{3c} is F, –OMe, or OEt; and the rest are H.

[0037] In certain embodiments, at least one R^{3d} is hydrogen. In certain embodiments, each R^{2c} is hydrogen. In certain embodiments, at least one R^{3d} is halogen (*e.g.,* fluoro, chloro, bromo, iodo). In certain embodiments, each R^{3d} is halogen (*e.g.,* fluoro, chloro, bromo, iodo). In certain embodiments, each of R^{3d} is alkyl, *e.g.,* each of R^{2c} is Me. In certain embodiments, one of R^{3d} is alkyl; and the other is hydrogen, *e.g.,* one of R^{3d} is Me; and the other is hydrogen. In certain embodiments, one of R^{3d} is substituted or unsubstituted carbocyclyl, *e.g.,* cyclopropyl or cyclobutyl, and the other is hydrogen. In certain embodiments, at least one R^{3d} is hydrogen, –F, –Br, –Cl, –I, $-CH_3$, $-CF_3$, cyclopropyl, or cyclobutyl. In certain embodiments, each instance of R^{3d} is H. In certain embodiments, each instance of R^{3d} is halogen (*e.g.,* fluoro, chloro, bromo, iodo). In certain embodiments, each instance of R^{3d} is alkyl, *e.g.,* $-CH_3$, $-CF_3$, $-CH_2CH_2Cl$. In certain embodiments, each instance of R^{3d} is substituted or unsubstituted carbocyclyl, *e.g.,* cyclopropyl or cyclobutyl. In certain embodiments, R^{3d} is substituted or unsubstituted cyclopropyl. In certain embodiments, each instance of R^{3d} is hydrogen, –F, –Br, –Cl, –I, $-CH_3$, $-CF_3$, $-CH_2CH_2Cl$, cyclopropyl, or cyclobutyl. In certain embodiments, R^{3d} is Me or Cl. In certain embodiments, R^{3d} is substituted or unsubstituted heterocyclyl.

Various embodiments of $-X^1$-R^{3b}

[0038] As generally defined above, for group $-X^1R^{3b}$, X^1 is independently –O–, –S–, or $-N(R^X)-$, wherein each instance of R^X is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl,

substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, or an amino protecting group; and R^{3b} is hydrogen, $-C(=O)R^{C1}$, $-C(=O)OR^{C1}$, $-C(=O)SR^{C1}$, $-C(=O)N(R^{C1})_2$, $-S(=O)_2R^{C1}$, $-S(=O)_2OR^{C1}$, $-P(=O)_2R^{C1}$, $-P(=O)_2OR^{C1}$, $-P(=O)(OR^{C1})_2$, $-P(=O)(R^{C1})_2$, or $-P(=O)(R^{C1})(OR^{C1})$, wherein R^{C1} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{C1} groups are joined to form an substituted or unsubstituted heterocyclic ring. It is generally understood that the group $-X^1$-R^{3b} may be in the *alpha* (down) or *beta* (up) position. In certain embodiments, the group $-X^1$-R^{3b} is *alpha*. In certain embodiments, the group $-X^1$-R^{3b} is *beta*.

[0039] In certain embodiments, X^1 is –O–. In certain embodiments, X^1 is –S–. In certain embodiments, X^1 is $-N(R^X)-$. In certain embodiments, R^X is alkyl. In certain embodiments, R^X is Me, Et, or i-Pr. In certain embodiments, R^X is H, *i.e.,* wherein X^1 is –NH–.

[0040] In certain embodiments, R^{3b} is hydrogen. For example, in certain embodiments, the group $-X^1R^{3b}$ is –OH. In certain embodiments, the group $-X^1R^{3b}$ is –SH. In certain embodiments, the group $-X^1R^{3b}$ is $-NH_2$ or $-NHR^X$.

[0041] In certain embodiments, R^{3b} is $-C(=O)R^{C1}$, $-C(=O)OR^{C1}$, $-C(=O)SR^{C1}$, $-C(=O)N(R^{C1})_2$, $-S(=O)_2R^{C1}$, $-S(=O)_2OR^{C1}$, $-P(=O)_2R^{C1}$, $-P(=O)_2OR^{C1}$, $-P(=O)(OR^{C1})_2$, $-P(=O)(R^{C1})_2$, or $-P(=O)(R^{C1})(OR^{C1})$.

[0042] In certain embodiments, at least one instance of R^{C1} is hydrogen or a protecting group, *i.e.,* an oxygen protecting group when attached to an oxygen atom, sulfur protecting group when attached to an sulfur atom, or a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one instance of R^{C1} is hydrogen.

[0043] In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl. Exemplary R^{C1} C_{1-6}alkyl groups include, but are not limited to, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), n–hexyl (C_6), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more fluoro groups (*e.g.,* $-CF_3$, $-CH_2F$, $-CHF_2$, difluoroethyl, and 2,2,2–trifluoro–1,1–dimethyl–ethyl),

C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more chloro groups (*e.g.*, $-CH_2Cl$, $-CHCl_2$), and C_{1-6} alkyl substituted with alkoxy groups (*e.g.*, $-CH_2OCH_3$ and $-CH_2OCH_2CH_3$).

[0044] In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted alkenyl, *e.g.,* substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-3}alkenyl, substituted or unsubstituted C_{3-4}alkenyl, substituted or unsubstituted C_{4-5}alkenyl, or substituted or unsubstituted C_{5-6}alkenyl.

[0045] In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted alkynyl, *e.g.,* substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{2-3}alkynyl, substituted or unsubstituted C_{3-4}alkynyl, substituted or unsubstituted C_{4-5}alkynyl, or substituted or unsubstituted C_{5-6}alkynyl.

[0046] In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted carbocyclyl, *e.g.,* substituted or unsubstituted C_{3-6}carbocyclyl, substituted or unsubstituted C_{3-4}carbocyclyl, substituted or unsubstituted C_{4-5} carbocyclyl, or substituted or unsubstituted C_{5-6} carbocyclyl.

[0047] In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted heterocyclyl, *e.g.,* substituted or unsubstituted 3–6 membered heterocyclyl, substituted or unsubstituted 3–4 membered heterocyclyl, substituted or unsubstituted 4–5 membered heterocyclyl, or substituted or unsubstituted 5–6 membered heterocyclyl.

[0048] In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted aryl, *e.g.,* substituted or unsubstituted phenyl.

[0049] In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted heteroaryl, *e.g.,* optionally substituted 5– to 6–membered heteroaryl.

[0050] In certain embodiments, two R^{C1} groups are joined to form a substituted or unsubstituted heterocyclic ring, *e.g.,* a substituted or unsubstituted piperidinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted morpholinyl ring.

[0051] In certain embodiments, R^{3b} is $-C(=O)R^{C1}$, $-C(=O)OR^{C1}$, $-C(=O)N(R^{C1})_2$ or $-C(=O)N(OR^{C1})(R^{C1})$, wherein R^{C1} is as defined herein.

[0052] In certain embodiments, R^{3b} is $-C(=O)R^{C1}$, *e.g.,* for example, wherein R^{C1} is, for example, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), or n–hexyl (C_6). In certain embodiments, R^{3b} is $-C(=O)CH_3$. In certain embodiments, R^{3b} is $-C(=O)(CH_2)_mCO_2H$, wherein m is an integer between 2 and

5, inclusive. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 4. In certain embodiments, m is 5. In certain embodiments, R^{3b} is $-C(=O)CH_2CH_2C(=O)OH$.

[0053] In certain embodiments, R^{3b} is $-C(=O)OR^{C1}$, *e.g.,* for example, wherein R^{C1} is, for example, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), or n–hexyl (C_6).

[0054] In certain embodiments, R^{3b} is $-C(=O)SR^{C1}$, *e.g.,* for example, wherein R^{C1} is, for example, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), or n–hexyl (C_6).

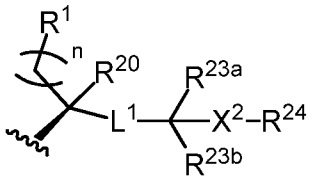
[0055] In certain embodiments, R^{3b} is $-C(=O)N(R^{C1})_2$, *e.g.,* $-C(=O)NH_2$ or $-C(=O)NHR^{C1}$, wherein R^{C1} is, for example, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), or n–hexyl (C_6), or R^1 is $-C(=O)N(R^{C1})_2$ wherein the two R^{C1} groups are joined to form a substituted or unsubstituted heterocyclic ring, *e.g.,* substituted or unsubstituted piperidinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted morpholinyl ring.

[0056] In certain embodiments, R^{3b} is $-S(=O)_2R^{C1}$ or $-S(=O)_2OR^{C1}$, wherein R^{C1} is, for example, hydrogen, or substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), or n–hexyl (C_6), or substituted or unsubstituted phenyl. In certain embodiments, R^{3b} is $-S(=O)_2R^{C1}$. In certain embodiments, R^{3b} is $-S(=O)_2OR^{C1}$, *e.g.,* $-SO_3H$.

[0057] In certain embodiments, R^{3b} is $-P(=O)_2R^{C1}$, $-P(=O)_2OR^{C1}$, $-P(=O)(OR^{C1})_2$, $-P(=O)(R^{C1})_2$, or $-P(=O)(R^{C1})(OR^{C1})$, wherein each R^{C1} is, for example, independently hydrogen, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), or n–hexyl (C_6), or substituted or unsubstituted phenyl. In certain embodiments, R^{3b} is $-P(=O)_2R^{C1}$. In certain embodiments, R^1 is $-P(=O)_2OR^{C1}$. In certain embodiments, R^{3b} is $-P(=O)(OR^{C1})_2$. In certain embodiments, R^1 is $-P(=O)(R^{C1})_2$. In certain embodiments, R^{3b} is $-P(=O)(R^{C1})(OR^{C1})$.

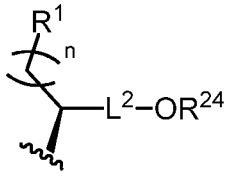
Various embodiments wherein Z is a group of formula (i) or (ii)

[0058] In certain embodiments, Z is a group of formula (i):



(i).

[0059] In other embodiments, Z is a group of formula (ii):



(ii).

[0060] As generally defined above, L^1 and L^2 is a bond (*i.e.,* in other words, is absent) or is a substituted or unsubstituted C_1–C_6 alkylene, a substituted or unsubstituted C_2–C_6 alkenylene, substituted or unsubstituted C_2–C_6 alkynylene, a substituted or unsubstituted hetero C_1–C_6 alkylene, a substituted or unsubstituted hetero C_2–C_6 alkenylene, or a substituted or unsubstituted hetero C_2–C_6 alkynylene.

[0061] In certain embodiments, L^1 or L^2 is a bond.

[0062] In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_1–C_6 alkylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_1–C_4 alkylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_1–C_3 alkylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_1–C_2 alkylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_1 alkylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_2 alkylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_3 alkylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_4 alkylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_5 alkylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_6 alkylene. In certain embodiments, L^1 or L^2 is an alkylene group, as described above, substituted with one or more substituents selected from the group consisting of substituted or unsubstituted alkyl and halo. In certain embodiments, L^1 or L^2 is -CH_2-, -CHMe-, -CMe_2-, -CH_2-CH_2-, -CF_2-CH_2-, -CH_2-CMe_2-, -CH_2-CH_2-CH_2-, or -CH_2-CH_2-CMe_2-.

[0063] In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_2–C_6 alkenylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_2–C_5 alkenylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_2–C_4 alkenylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_2–C_3 alkenylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_2 alkenylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_3 alkenylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_4 alkenylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_5 alkenylene. In certain embodiments, L^1 or L^2 is

a substituted or unsubstituted C_6 alkenylene. In certain embodiments, L^1 or L^2 is an alkenylene group, as described above, substituted with one or more substituents selected from the group consisting of substituted or unsubstituted alkyl and halo.

[0064] In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_2–C_6 alkynylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_2–C_5 alkynylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_2–C_4 alkynylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_2–C_3 alkynylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_2 alkynylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_3 alkynylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_4 alkynylene. In certain embodiments, L^1 is a substituted or unsubstituted C_5 alkynylene. In certain embodiments, L^1 or L^2 is a substituted or unsubstituted C_6 alkynylene. In certain embodiments, L^1 or L^2 is an alkynylene group, as described above, substituted with one or more substituents selected from the group consisting of substituted or unsubstituted alkyl and halo.

[0065] Furthermore, in certain embodiments, L^1 or L^2 is substituted or unsubstituted heteroC_{1-6}alkylene, *e.g.,* substituted or unsubstituted heteroC_{1-2}alkylene, substituted or unsubstituted heteroC_{2-3}alkylene, substituted or unsubstituted heteroC_{3-4}alkylene, substituted or unsubstituted heteroC_{4-5}alkylene, or substituted or unsubstituted heteroC_{5-6}alkylene. In certain embodiments, L^1 or L^2 is substituted or unsubstituted heteroC_{2-6}alkyenlene, *e.g.,* substituted or unsubstituted heteroC_{2-3}alkenylene, substituted or unsubstituted heteroC_{3-4}alkenylene, substituted or unsubstituted heteroC_{4-5}alkenylene, or substituted or unsubstituted heteroC_{5-6}alkenylene. In certain embodiments, L^1 or L^2 is substituted or unsubstituted heteroC_{2-6}alkynylene, *e.g.,* substituted or unsubstituted heteroC_{2-3}alkynylene, substituted or unsubstituted heteroC_{3-4}alkynylene, substituted or unsubstituted heteroC_{4-5}alkynylene, or substituted or unsubstituted heteroC_{5-6}alkynylene. In any of the above instances, in certain embodiments, L^1 or L^2 is heteroalkylene, heteroalkenylene, or heteroalkynylene unsubstituted or substituted with halo (*e.g.,* fluoro) or substituted or unsubstituted C_{1-6} alkyl.

[0066] As generally defined above, R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, halo, $–N_3$, $–NO_2$, –SCN, –CN, $–OR^{A1}$, $–SR^{A1}$, $–N(R^{A1})_2$, $–N{=}NR^{A1}$, $–N{=}C(R^{A1})_2$, $–N(OR^{A1})(R^{A1})$,$–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)SR^{A1}$, $–C(=O)N(R^{A1})_2$, $–C(=O)N(OR^{A1})(R^{A1})$,$–OC(=O)R^{A1}$, $–OC(=O)OR^{A1}$, $–OC(=O)SR^{A1}$, $–OC(=O)N(R^{A1})_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}C(=O)SR^{A1}$, $–NR^{A1}C(=O)N(R^{A1})_2$, $–SC(=O)R^{A2}$, $–SC(=O)OR^{A1}$, $–SC(=O)SR^{A1}$, $–SC(=O)N(R^{A1})_2$, $–OS(=O)_2R^{A2}$, $–OS(=O)_2OR^{A1}$, $–S–S(=O)_2R^{A2}$, $–S–S(=O)_2OR^{A1}$, $–S(=O)R^{A2}$, $–SO_2R^{A2}$, $–NR^{A1}SO_2R^{A2}$, or –

$SO_2N(R^{A1})_2$, wherein R^{A1} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{A1} groups are joined to form an substituted or unsubstituted heterocyclic ring; and R^{A2} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or an R^{A1} group and an R^{A2} group are joined to form an substituted or unsubstituted heterocyclic ring.

[0067] In certain embodiments, R^1 is hydrogen.

[0068] In certain embodiments, R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl. In certain embodiments, R^1 is substituted or unsubstituted alkyl, *e.g.,* Me, Et, or i-Pr. In certain embodiments, R^1 is substituted or unsubstituted alkenyl, *e.g.,* substituted or unsubstituted ethenyl or substituted or unsubstituted propenyl. In certain embodiments, R^1 is substituted or unsubstituted alkynyl.

[0069] In certain embodiments, R^1 is selected from substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl.

[0070] In certain embodiments, R^1 is substituted or unsubstituted aryl, *e.g.,* phenyl.

[0071] In certain embodiments, R^1 is substituted or unsubstituted heteroaryl, *e.g.,* a substituted or unsubstituted heteroaryl selected from pyrrolyl, imidazolyl, pyrazolyl, oxazoyl, thiazolyl, isoxazoyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl, quinazonyl, quinoxilinyl, naphthyridinyl, indolyl, indazolyl, benzimidazloyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyridopyrimidinyl, or purinyl. In certain embodiments, the heteroaryl group is substituted with one or more groups selected from substituted or unsubstituted alkyl, haloalkyl, alkenyl, substituted or unsubstituted alkynyl, oxo, hydoxy, halo, alkoxy, -S-alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -SO-alkyl, substituted or unsubstituted $-SO_2$-alkyl, substituted or unsubstituted -SO-aryl, substituted or unsubstituted $-SO_2$-aryl, substituted or unsubstituted -SO-heteroaryl, substituted or unsubstituted $-SO_2$-heteroaryl, amino, cyano, and acyl. In certain embodiments, R^1 is imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, or tetrazolyl; each unsubstitued or substituted with one or two groups independently selected from oxo, Me, F, Cl, -CN, and $-CF_3$. In certain embodiments, R^1 is quinolinyl,

isoquinolinyl or purinyl; each unsubstitued or substituted with one or two groups independently selected from oxo, Me, F, Cl, -CN, and -CF_3.

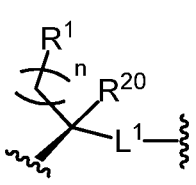
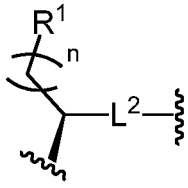
[0072] In certain embodiments, R^1 is $-OR^{A1}$. In certain embodiments, R^1 is -O-quinolinyl, -O-isoquinolinyl,- O-purinyl, each unsubstitued or substituted with one or two groups independently selected from Me, F, Cl, -CN, and -CF_3. In certain embodiments, R^1 is –OH or -O-CO-CH_2-CH_2-CO_2H.

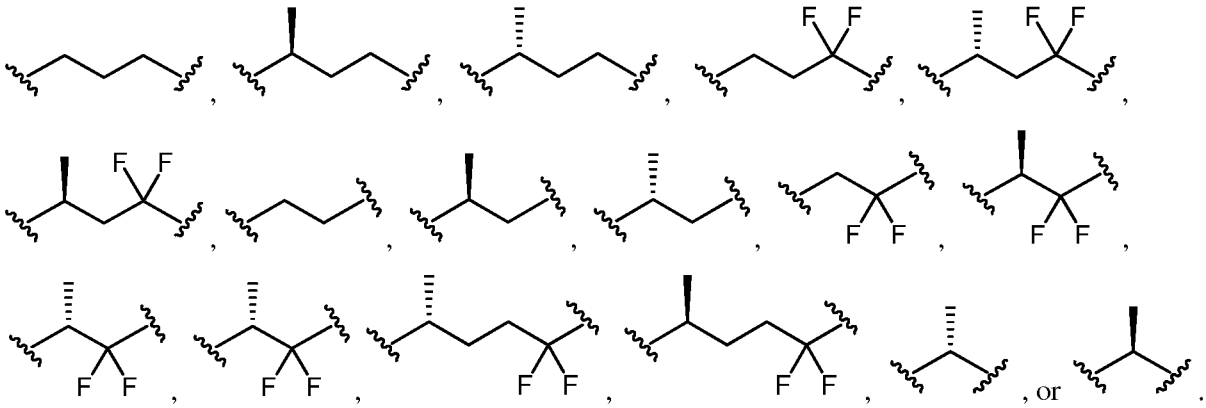
[0073] In certain embodiments, R^1 is $-SR^{A1}$. In certain embodiments, R^1 is S-quinolinyl, -S-isoquinolinyl, or -S-purinyl, each unsubstitued or substituted with one or two groups independently selected from Me, F, Cl, -CN, and -CF_3. In certain embodiments, R^1 is –SH.

[0074] In certain embodiments, R^1 is $-OS(=O)_2R^{A2}$. In certain embodiments, R^1 is $-OS(=O)_2OR^{A1}$; *e.g.*, -O-SO_3H. In certain embodiments, R^1 is $-S-S(=O)_2R^{A2}$. In certain embodiments, R^1 is $-S-S(=O)_2OR^{A1}$; *e.g.*, -S-SO_3H.

[0075] As generally defined above, R^{20} is independently hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^{20} is hydrogen. In certain embodiments, R^{20} is substituted or unsubstituted alkyl (*e.g.*, -CH_3).

[0076] As generally defined above each instance of R^{23a} and R^{23b} is independently hydrogen, halogen, or substituted or unsubstituted alkyl, or R^{23a} and R^{23b} are joined together to form substituted or unsubstituted C_3–C_6 cycloalkyl. In certain embodiments, each instance of R^{23a} and R^{23b} is hydrogen. In certain embodiments, one of R^{23a} and R^{23b} is halogen, *e.g.*, fluoro, and the other of R^{23a} and R^{23b} is hydrogen, halogen, or substituted or unsubstituted alkyl. In certain embodiments, each instance of R^{23a} and R^{23b} is halogen, *e.g.*, fluoro. In certain embodiments, each instance of R^{23a} and R^{23b} is independently substituted or unsubstituted alkyl. In certain embodiments, each of R^{23a} and R^{23b} is Me. In certain embodiments, one of R^{23a} and R^{23b} is H. In certain embodiments, one of R^{23a} and R^{23b} is H; and the other is substituted or unsubstituted alkyl. In certain embodiments, one of R^{23a} and R^{23b} is H; and the other is Me or Et. In certain embodiments, R^{23a} and R^{23b} are joined together to form substituted or unsubstituted C_3–C_6 cycloalkyl. In certain embodiments, R^{23a} and R^{23b} are joined together to form a substituted or unsubstituted cyclopropyl.

[0077] In certain embodiments, the group  or  is of the formula:



[0078] As generally defined above, X^2 is independently –O–, –S–, or –N(R^X)–, wherein each instance of R^X is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, or an amino protecting group.

[0079] In certain embodiments, X^2 is –O–. In certain embodiments, X^2 is –S–. In certain embodiments, X^2 is –N(R^X)–. In certain embodiments, R^X is alkyl. In certain embodiments, R^X is Me, Et, or i-Pr. In certain embodiments, R^X is hydrogen.

[0080] In certain embodiments, X^1 is –O– and X^2 is –O–. In certain embodiments, X^1 is –O– and X^2 is –S–. In certain embodiments, X^1 is –O– and X^2 is –N(R^X)–. In certain embodiments, X^1 is –S– and X^2 is –O–. In certain embodiments, X^1 is –S– and X^2 is –S–. In certain embodiments, X^1 is –S– and X^2 is –N(R^X)–. In certain embodiments, X^1 is –N(R^X)– and X^2 is –O–. In certain embodiments, X^1 is –N(R^X)– and X^2 is –S–. In certain embodiments, X^1 is –N(R^X)– and X^2 is –N(R^X)–.

[0081] As generally defined above, R^{24} is H, substituted or unsubstituted alkyl, substituted or unsubstitued alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstitued aryl, substituted or unsubstituted heteroaryl, –C(=O)R^{E1}, –C(=O)OR^{E1}, –C(=O)SR^{E1}, –C(=O)N(R^{E1})$_2$, –S(=O)$_2R^{E2}$, –S(=O)$_2$OR^{E1}, –P(=O)$_2R^{E2}$, –P(=O)$_2$OR^{E1}, –P(=O)(OR^{E1})$_2$, –P(=O)(R^{E2})$_2$, or –P(=O)(R^{E2})(OR^{E1}).

[0082] In certain embodiments, R^{24} is hydrogen.

[0083] In certain embodiments, R^{24} is substituted or unsubstituted alkyl. In certain embodiments, R^{24} is alkyl unsubstituted or substituted with one or more substituents selected from the group consisting of halo or and hydroxyl. In certain embodiments, R^{24} is substituted or unsubstitued alkenyl. In certain embodiments, R^{24} is substituted or unsubstituted alkynyl. In certain embodiments, R^{24} is substituted or unsubstituted carbocyclyl. In certain embodiments, R^{24} is substituted or unsubstituted

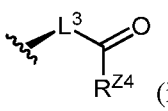
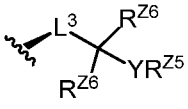
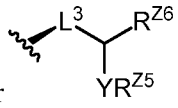
heterocyclyl. In certain embodiments, R^{24} is substituted or unsubstitued aryl. In certain embodiments, R^{24} is substituted or unsubstituted heteroaryl.

[0084] In certain embodiments, R^{24} is $-C(=O)R^{E1}$, *e.g.,* R^{24} is $-C(=O)(CH_2)_pCO_2H$, wherein p is an integer between 2 and 5, inclusive. In certain embodiments, p is 2. In certain embodiments, p is 3. In certain embodiments, p is 4. In certain embodiments, p is 5. In certain embodiments, R^{24} is $-C(=O)OR^{E1}$. In certain embodiments, R^{24} is $-C(=O)SR^{E1}$. In certain embodiments, R^{24} is $-C(=O)N(R^{E1})_2$. In certain embodiments, R^{24} is $-S(=O)_2R^{E2}$. In certain embodiments, R^{24} is $-S(=O)_2OR^{E1}$; *e.g.,* $-SO_3H$. In certain embodiments, R^{24} is $-P(=O)_2R^{E2}$. In certain embodiments, R^{24} is $-P(=O)_2OR^{E1}$. In certain embodiments, R^{24} is $-P(=O)(OR^{E1})_2$. In certain embodiments, R^{24} is $-P(=O)(R^{E2})_2$. In certain embodiments, R^{24} is $-P(=O)(R^{E2})(OR^{E1})$.

[0085] As generally defined above, the subscript n is 0, 1, 2, or 3. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is 3.

Various embodiments wherein Z is a group of formula (iii), (iv), or (v)

[0086] In certain embodiments, Z is a group of formula (iii), (iv), or (v):


(iii),

(iv), or

(v).

[0087] In certain embodiments, L^3 is substituted or unsubstituted C_{1-6}alkylene, *e.g.,* substituted or unsubstituted C_{1-2}alkylene, substituted or unsubstituted C_{2-3}alkylene, substituted or unsubstituted C_{3-4}alkylene, substituted or unsubstituted C_{4-5}alkylene, or substituted or unsubstituted C_{5-6}alkylene. In certain embodiments, L^3 is substituted or unsubstituted C_{2-6}alkyenlene, *e.g.,* substituted or unsubstituted C_{2-3}alkenylene, substituted or unsubstituted C_{3-4}alkenylene, substituted or unsubstituted C_{4-5}alkenylene, or substituted or unsubstituted C_{5-6}alkenylene. In certain embodiments, L^3 is substituted or unsubstituted C_{2-6}alkynylene, *e.g.,* substituted or unsubstituted C_{2-3}alkynylene, substituted or unsubstituted C_{3-4}alkynylene, substituted or unsubstituted C_{4-5}alkynylene, or substituted or unsubstituted C_{5-6}alkynylene. In any of the above instances, in certain embodiments, L^3 is alkylene, alkenylene, or alkynylene unsubstituted or substituted with halo (*e.g.,* fluoro), substituted or unsubstituted C_{1-6} alkyl, and/or $-OR^{Z5}$.

[0088] Furthermore, in certain embodiments, L^3 is substituted or unsubstituted heteroC_{1-6}alkylene, *e.g.,* substituted or unsubstituted heteroC_{1-2}alkylene, substituted or unsubstituted heteroC_{2-3}alkylene, substituted or unsubstituted heteroC_{3-4}alkylene, substituted or unsubstituted heteroC_{4-5}alkylene, or substituted or unsubstituted heteroC_{5-6}alkylene. In certain embodiments, L^3 is substituted or unsubstituted heteroC_{2-6}alkyenlene, *e.g.,* substituted or unsubstituted heteroC_{2-3}alkenylene, substituted or unsubstituted heteroC_{3-4}alkenylene, substituted or unsubstituted heteroC_{4-5}alkenylene, or substituted or

unsubstituted heteroC_{5-6}alkenylene. In certain embodiments, L^3 is substituted or unsubstituted heteroC_{2-6}alkynylene, *e.g.,* substituted or unsubstituted heteroC_{2-3}alkynylene, substituted or unsubstituted heteroC_{3-4}alkynylene, substituted or unsubstituted heteroC_{4-5}alkynylene, or substituted or unsubstituted heteroC_{5-6}alkynylene. In any of the above instances, in certain embodiments, L^3 is heteroalkylene, heteroalkenylene, or heteroalkynylene unsubstituted or substituted with halo (*e.g.,* fluoro), substituted or unsubstituted C_{1-6} alkyl, and/or $-OR^{Z5}$.

[0089] In any of the above or below instances, in certain embodiments, at least one R^{Z5} is hydrogen.

[0090] In any of the above or below instances, in certain embodiments, at least one instance of R^{Z5} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl. Exemplary R^{Z5} C_{1-6}alkyl groups include, but are not limited to, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), n–hexyl (C_6), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more fluoro groups (*e.g.,* $-CF_3$, $-CH_2F$, $-CHF_2$, difluoroethyl, and 2,2,2–trifluoro–1,1–dimethyl–ethyl), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more chloro groups (*e.g.,* $-CH_2Cl$, $-CHCl_2$), and C_{1-6} alkyl substituted with alkoxy groups (*e.g.,* $-CH_2OCH_3$ and $-CH_2OCH_2CH_3$).

[0091] In any of the above or below instances, in certain embodiments, at least one instance of R^{Z5} is substituted or unsubstituted alkenyl, *e.g.,* substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-3}alkenyl, substituted or unsubstituted C_{3-4}alkenyl, substituted or unsubstituted C_{4-5}alkenyl, or substituted or unsubstituted C_{5-6}alkenyl.

[0092] In any of the above or below instances, in certain embodiments, at least one instance of R^{Z5} is substituted or unsubstituted alkynyl, *e.g.,* substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{2-3}alkynyl, substituted or unsubstituted C_{3-4}alkynyl, substituted or unsubstituted C_{4-5}alkynyl, or substituted or unsubstituted C_{5-6}alkynyl.

[0093] In any of the above or below instances, in certain embodiments, at least one instance of R^{Z5} is substituted or unsubstituted carbocyclyl, *e.g.,* substituted or unsubstituted C_{3-6}carbocyclyl, substituted or unsubstituted C_{3-4}carbocyclyl, substituted or unsubstituted C_{4-5} carbocyclyl, or substituted or unsubstituted C_{5-6} carbocyclyl.

[0094] In any of the above or below instances, in certain embodiments, at least one instance of R^{Z5} is substituted or unsubstituted heterocyclyl, *e.g.,* substituted or unsubstituted 3–6 membered

heterocyclyl, substituted or unsubstituted 3–4 membered heterocyclyl, substituted or unsubstituted 4–5 membered heterocyclyl, or substituted or unsubstituted 5–6 membered heterocyclyl.

[0095] In any of the above or below instances, in certain embodiments, at least one instance of R^{Z5} is substituted or unsubstituted aryl, *e.g.,* substituted or unsubstituted phenyl.

[0096] In any of the above or below instances, in certain embodiments, at least one instance of R^{Z5} is substituted or unsubstituted heteroaryl, *e.g.,* optionally substituted 5–6 membered heteroaryl.

[0097] In any of the above or below instances, in certain embodiments, R^{Z5} is a protecting group, *e.g.,* an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom.

[0098] In certain embodiments, wherein two R^{Z5} are attached to a nitrogen atom, the two R^{Z5} groups are joined to form a substituted or unsubstituted heterocyclic ring, *e.g.,* a substituted or unsubstituted piperidinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted morpholinyl ring.

[0099] Furthermore, in any of the above or below instances, in certain embodiments, each instance of R^{Z6} is independently hydrogen, substituted or unsubstituted alkyl, or two R^{Z6} groups are joined to form a C_{3-6} carbocyclic ring.

[00100] In certain embodiments, at least one instance of R^{Z6} is hydrogen.

[00101] In certain embodiments, at least one instance of R^{Z6} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl. Exemplary R^{Z4} C_{1-6}alkyl groups include, but are not limited to, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), n–hexyl (C_6), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more fluoro groups (*e.g.,* $–CF_3$, $–CH_2F$, $–CHF_2$, difluoroethyl, and 2,2,2–trifluoro–1,1–dimethyl–ethyl), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more chloro groups (*e.g.,* $–CH_2Cl$, $–CHCl_2$), and C_{1-6} alkyl substituted with alkoxy groups (*e.g.,* $–CH_2OCH_3$ and $–CH_2OCH_2CH_3$).

[00102] In certain embodiments, two R^{Z6} groups are joined to form a C_{3-6} carbocyclic ring, *e.g.,* for example, a substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl ring.

[00103] In certain embodiments, R^{Z4} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or

unsubstituted C_{5-6}alkyl. Exemplary R^{Z4} C_{1-6}alkyl groups include, but are not limited to, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), n–hexyl (C_6), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more fluoro groups (*e.g.*, $–CF_3$, $–CH_2F$, $–CHF_2$, difluoroethyl, and 2,2,2–trifluoro–1,1–dimethyl–ethyl), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more chloro groups (*e.g.*, $–CH_2Cl$, $–CHCl_2$), and C_{1-6} alkyl substituted with alkoxy groups (*e.g.*, $–CH_2OCH_3$ and $–CH_2OCH_2CH_3$).

[00104] In certain embodiments, R^{Z4} is substituted or unsubstituted alkenyl, *e.g.*, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-3}alkenyl, substituted or unsubstituted C_{3-4}alkenyl, substituted or unsubstituted C_{4-5}alkenyl, or substituted or unsubstituted C_{5-6}alkenyl.

[00105] In certain embodiments, R^{Z4} is substituted or unsubstituted alkynyl, *e.g.*, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{2-3}alkynyl, substituted or unsubstituted C_{3-4}alkynyl, substituted or unsubstituted C_{4-5}alkynyl, or substituted or unsubstituted C_{5-6}alkynyl.

[00106] In certain embodiments, R^{Z4} is substituted or unsubstituted carbocyclyl, *e.g.*, substituted or unsubstituted C_{3-6}carbocyclyl, substituted or unsubstituted C_{3-4}carbocyclyl, substituted or unsubstituted C_{4-5} carbocyclyl, or substituted or unsubstituted C_{5-6} carbocyclyl.

[00107] In certain embodiments, R^{Z4} is substituted or unsubstituted heterocyclyl, *e.g.*, substituted or unsubstituted 3–6 membered heterocyclyl, substituted or unsubstituted 3–4 membered heterocyclyl, substituted or unsubstituted 4–5 membered heterocyclyl, or substituted or unsubstituted 5–6 membered heterocyclyl.

[00108] In certain embodiments, R^{Z4} is substituted or unsubstituted aryl, *e.g.*, substituted or unsubstituted phenyl.

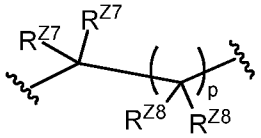
[00109] In certain embodiments, R^{Z4} is substituted or unsubstituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00110] In certain embodiments, R^{Z4} is $–OR^{Z5}$, wherein R^{Z5} is as defined herein, *e.g.*, for example, R^{Z5} is hydrogen, methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), or n–hexyl (C_6).

[00111] In certain embodiments, R^{Z4} is $–SR^{Z5}$, wherein R^{Z5} is as defined herein, *e.g.*, for example, R^{Z5} is hydrogen, methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), or n–hexyl (C_6).

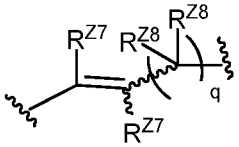
[00112] In certain embodiments, R^{Z4} is $-N(R^{Z5})_2$, *e.g.*, R^{Z4} is $-NH_2$, or $-NHR^{Z5}$, wherein R^{Z5} is as defined herein, *e.g.*, for example, R^{Z5} is hydrogen, methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), or n–hexyl (C_6), or R^{Z4} is $-N(R^{Z5})_2$ wherein the two R^{Z5} groups are joined to form a substituted or unsubstituted heterocyclic ring, *e.g.*, a substituted or unsubstituted piperidinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted morpholinyl ring.

[00113] Specific L^3 alkylene groups are contemplated herein. For example, in certain embodiments, L^3 is an alkylene group of the formula:



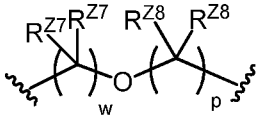
wherein p is 1, 2, or 3; and each instance of R^{Z7} and R^{Z8} is, independently, hydrogen, halo, substituted or unsubstituted C_{1-6} alkyl, or $-OR^{Z5}$. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 3.

[00114] Specific L^3 alkenylene groups are also contemplated herein. For example, in certain embodiments, L^3 is an alkenylene group of the formula:



wherein q is 0, 1, or 2; and each instance of R^{Z7} and R^{Z8} is, independently, hydrogen, halo, substituted or unsubstituted C_{1-6} alkyl, or $-OR^{Z5}$. In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2.

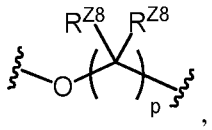
[00115] Specific L^3 heteroalkylene groups are also contemplated herein, *e.g.*, for example, in certain embodiments, L^3 is a heteroalkylene group of the formula:



wherein w is 0 or 1 and p is 1, 2, or 3, or w is 1 and p is 0, 1, 2, or 3; and each instance of R^{Z7} and R^{Z8} is independently hydrogen, halo, substituted or unsubstituted C_{1-6} alkyl, or $-OR^{Z5}$.

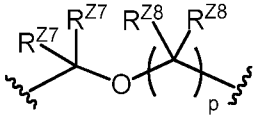
[00116] In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 3. In certain embodiments, w is 0. In certain embodiments, w is 1. In certain embodiments, w is 0, and p is 1. In certain embodiments, w is 0, and p is 2. In certain embodiments, w is 0, and p is 3. In certain embodiments, w is 1, and p is 1. In certain embodiments, w is 1, and p is 2. In certain embodiments, w is 1, and p is 3.

[00117] For example, in certain embodiments wherein w is 0, provided is an L^3 heteroalkylene group of the formula:



wherein p and R^{Z8} are as defined herein.

[00118] In certain embodiments wherein w is 1, provided is an L^3 heteroalkylene group of the formula:

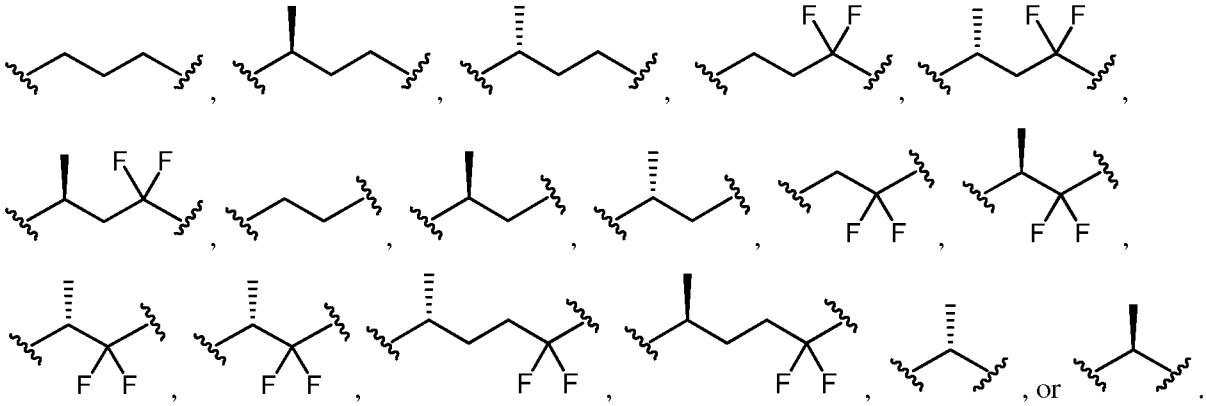


wherein p, R^{27}, and R^{Z8} are as defined herein.

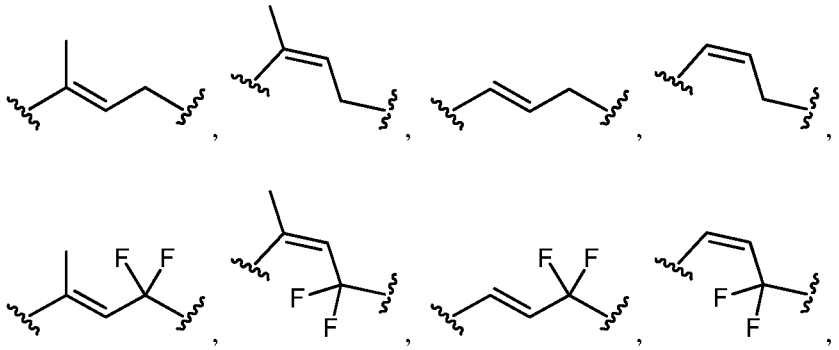
[00119] In certain embodiments, at least one instance of R^{Z7} is hydrogen. In any of the above instances, in certain embodiments, at least one instance of R^{Z7} is halo, *e.g.,* fluoro. In any of the above instances, in certain embodiments, at least one instance of R^{Z7} is substituted or unsubstituted C_{1-6} alkyl, *e.g.,* substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl. Exemplary R^{Z7} C_{1-6}alkyl groups include, but are not limited to, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), n–hexyl (C_6), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more fluoro groups (*e.g.,* $–CF_3$, $–CH_2F$, $–CHF_2$, difluoroethyl, and 2,2,2–trifluoro–1,1–dimethyl–ethyl), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more chloro groups (*e.g.,* $–CH_2Cl$, $–CHCl_2$), and C_{1-6} alkyl substituted with alkoxy groups (*e.g.,* $–CH_2OCH_3$ and $–CH_2OCH_2CH_3$). In any of the above instances, in certain embodiments, at least one instance of R^{Z7} is $–CH_3$, $–CF_3$, $–CH_2CH_3$ (Et), or $–CH(CH_3)_2$ (iPr). In any of the above instances, in certain embodiments, at least one instance of R^{Z7} is $–OR^{Z5}$, *e.g.,* –OH.

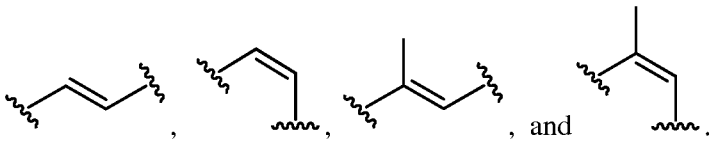
[00120] In certain embodiments, at least one instance of R^{Z8} is hydrogen. In any of the above instances, in certain embodiments, at least one instance of R^{Z8} is halo, *e.g.*, fluoro. In any of the above instances, in certain embodiments, at least one instance of R^{Z8} is substituted or unsubstituted C_{1-6} alkyl, *e.g.*, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl. Exemplary R^{Z8} C_{1-6}alkyl groups include, but are not limited to, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), n–hexyl (C_6), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more fluoro groups (*e.g.*, $–CF_3$, $–CH_2F$, $–CHF_2$, difluoroethyl, and 2,2,2–trifluoro–1,1–dimethyl–ethyl), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more chloro groups (*e.g.*, $–CH_2Cl$, $–CHCl_2$), and C_{1-6} alkyl substituted with alkoxy groups (*e.g.*, $–CH_2OCH_3$ and $–CH_2OCH_2CH_3$). In any of the above instances, in certain embodiments, at least one instance of R^{Z8} is $–CH_3$, $–CF_3$, $–CH_2CH_3$ (Et), or $–CH(CH_3)_2$ (iPr). In any of the above instances, in certain embodiments, at least one instance of R^{Z8} is $–OR^{Z5}$, *e.g.*, –OH.

[00121] Exemplary L^3 alkylene groups include, but are not limited to:

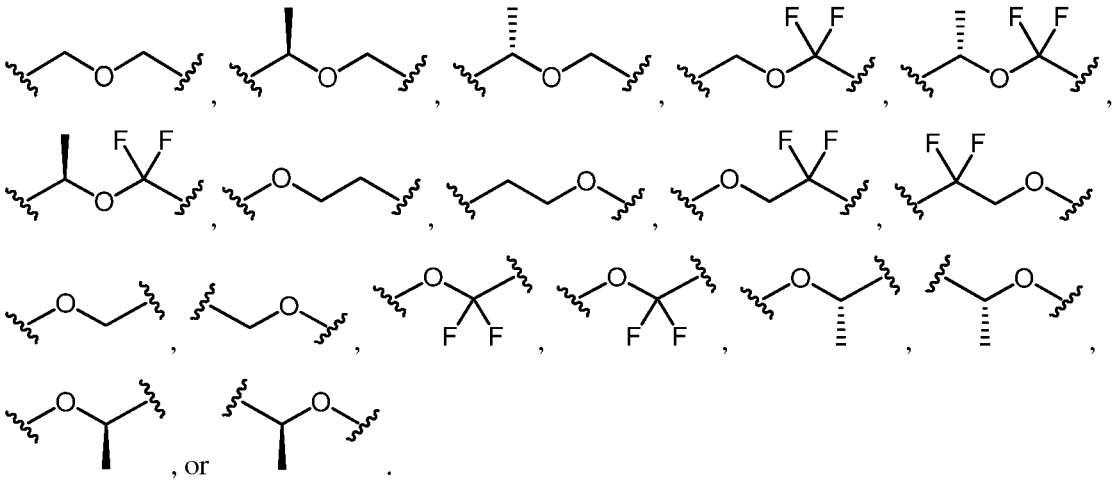


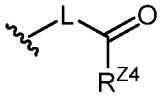
[00122] Exemplary L^3 alkenylene groups include, but are not limited to:

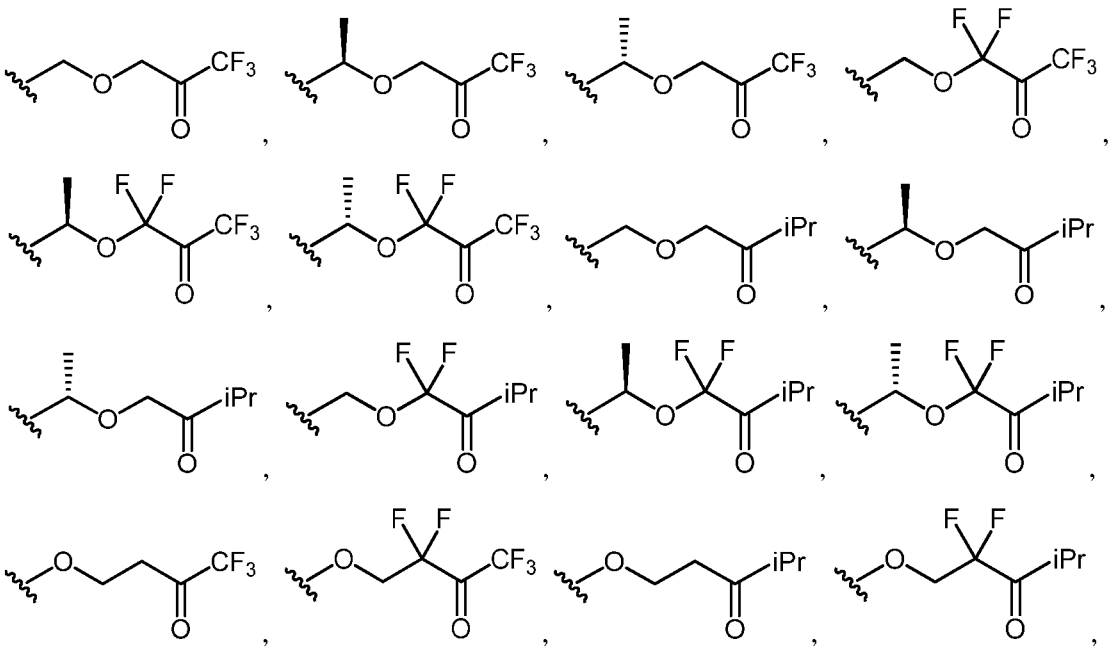


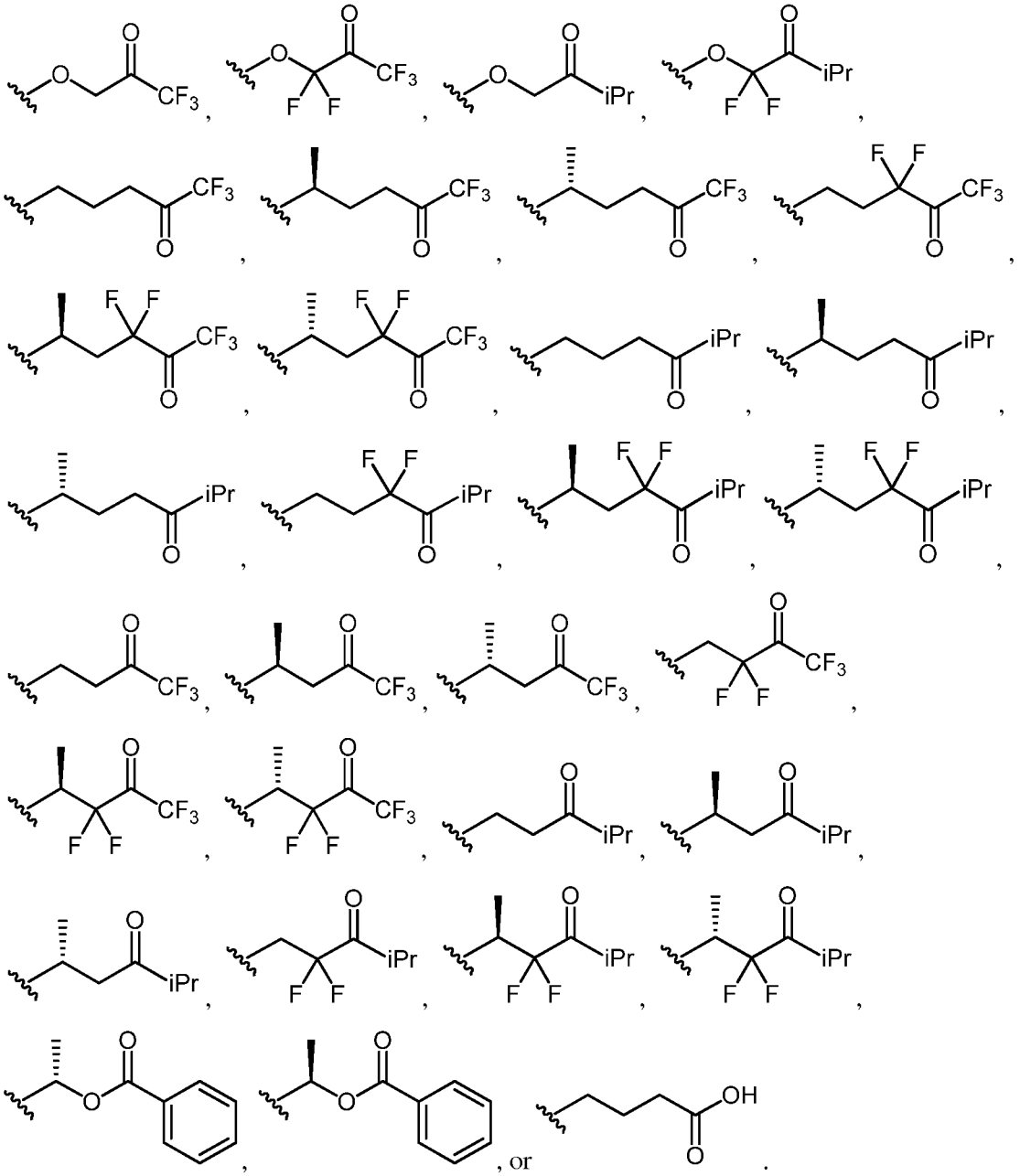


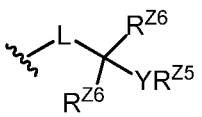
[00123] Exemplary L^3 heteroalkylene groups include, but are not limited to:

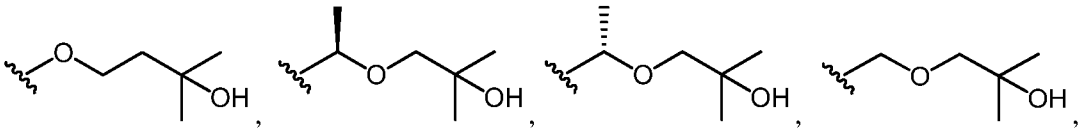


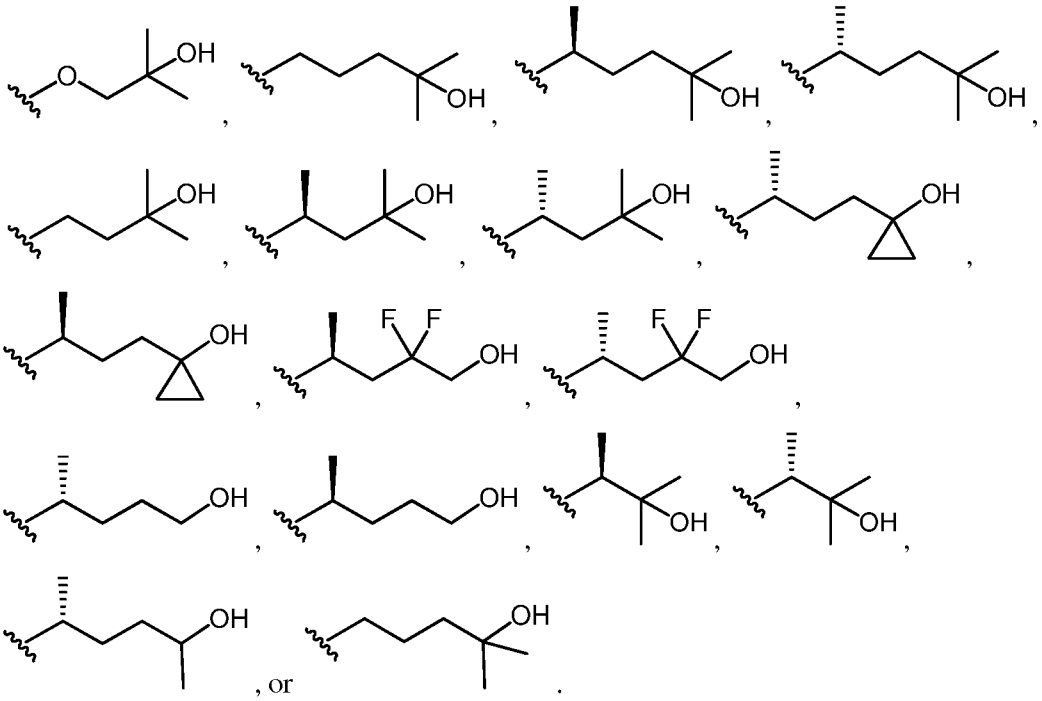
[00124] In certain embodiments, the group , wherein L^3 is an alkylene or heteroalkylene group, is of the formula:

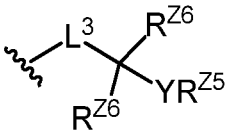


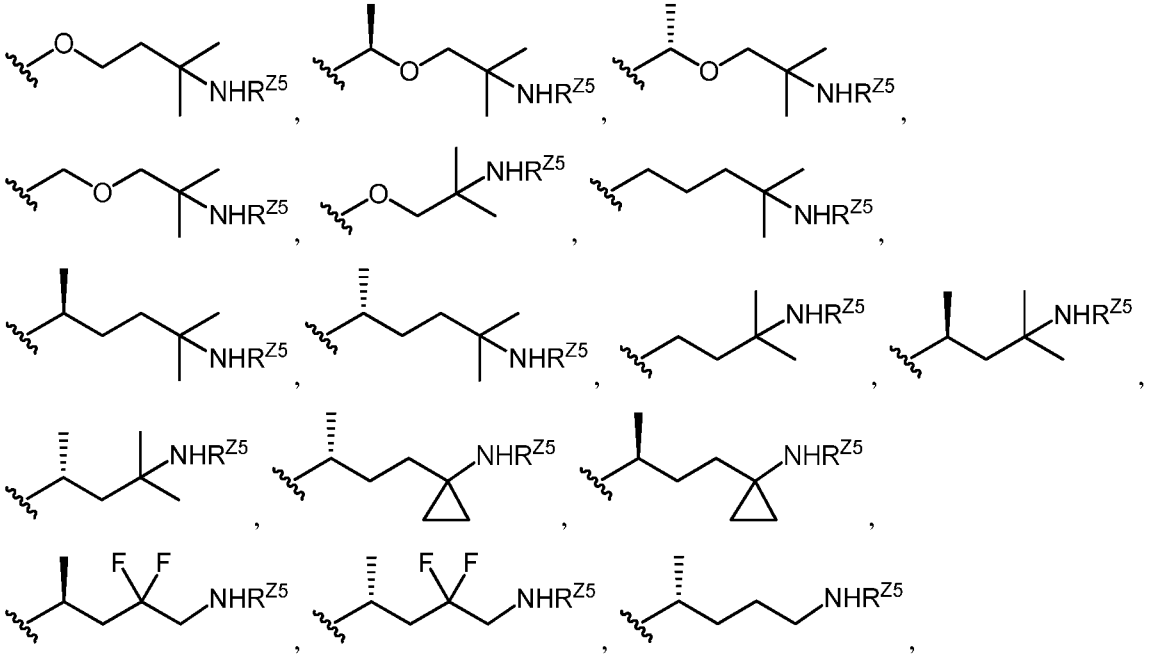


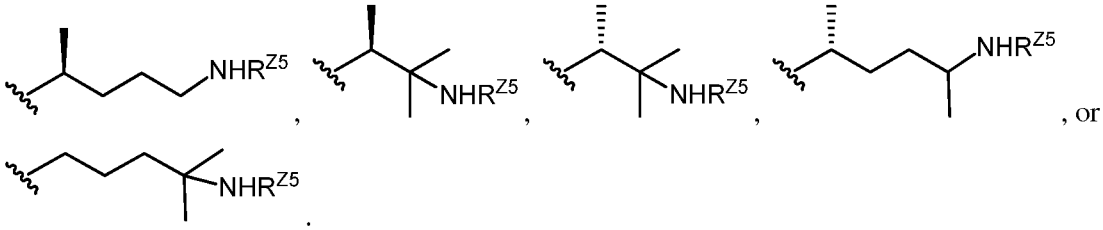
[00125] In certain embodiments, the group , wherein Y is –O– and L^3 is an alkylene or heteroalkylene group, is of the formula:



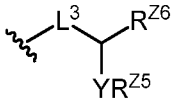


[00126] In certain embodiments, the group  , wherein Y is –NH– and L^3 is an alkylene or heteroalkylene group, is of the formula

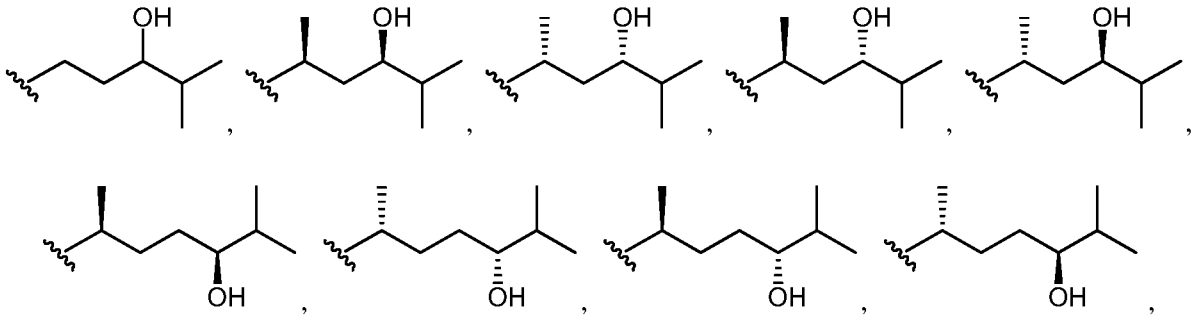




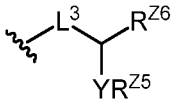
, or .

[00127] In certain embodiments, the group 

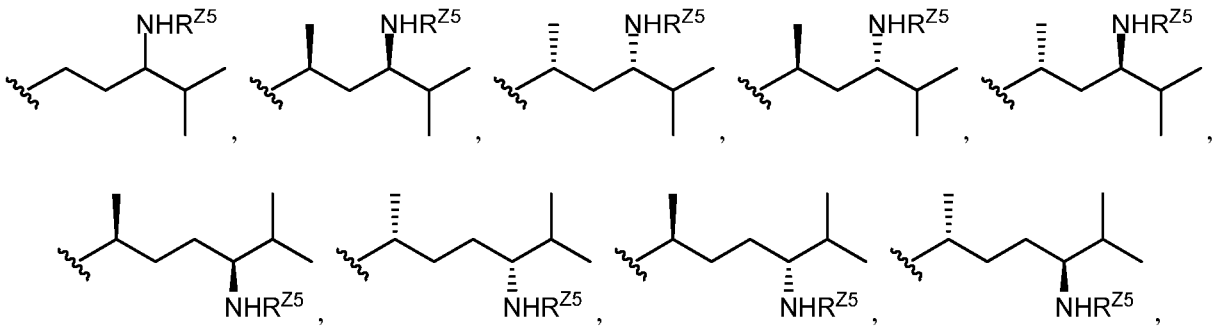
, wherein Y is –O– and L^3 is an alkylene or heteroalkylene group, is of the formula:



or .

[00128] In certain embodiments, the group 

, wherein Y is –NH– and L^3 is an alkylene or heteroalkylene group, is of the formula:



or .

Various embodiments of R^2, R^{11a}, and R^{11b}

[00129] As generally defined above, each instance of R^2, R^{11a}, and R^{11b} is independently H, –OH, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $–N_3$, $–NO_2$, –SCN, –CN, $–OR^{B1}$, $–SR^{B1}$, $–N(R^{B1})_2$, $–N=NR^{B1}$, $–N=C(R^{B1})_2$, $–N(OR^{B1})(R^{B1})$, $–C(=O)R^{B1}$, $–C(=O)OR^{B1}$, $–C(=O)SR^{B1}$, $–C(=O)N(R^{b1})_2$, $–C(=O)N(OR^{B1})(R^{B1})$,$–OC(=O)R^{B1}$, $–OC(=O)OR^{B1}$, $–OC(=O)SR^{B1}$, $–OC(=O)N(R^{B1})_2$, $–NR^{B1}C(=O)R^{B1}$, $–NR^{B1}C(=O)OR^{B1}$, $–NR^{B1}C(=O)SR^{B1}$, $–NR^{B1}C(=O)N(R^{B1})_2$, $–SC(=O)R^{B2}$, $–SC(=O)OR^{B1}$, $–SC(=O)SR^{B1}$, $–SC(=O)N(R^{B1})_2$, $–OS(=O)_2R^{B2}$, $–OS(=O)_2OR^{B1}$, $–S–S(=O)_2R^{B2}$, $–S–S(=O)_2OR^{B1}$, $–S(=O)R^{B2}$, $–SO_2R^{B2}$, $–NR^{B1}SO_2R^{B2}$, or $–SO_2N(R^{B1})_2$, and/or R^{11a} and R^{11b} are joined to form an oxo (=O) group

[00130] In certain embodiments, R^2 is H. In certain embodiments, R^2 is substituted or unsubstituted alkyl. In certain embodiments, R^2 is substituted or unsubstituted alkenyl. In certain embodiments, R^2 is substituted or unsubstituted alkynyl. In certain embodiments, R^2 is $–OR^{B1}$. In certain embodiments, R^2 is $–SR^{B1}$. In certain embodiments, R^2 is $–N(R^{B1})_2$. In certain embodiments, R^2 is H, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, $–OR^{B1}$, $–SR^{B1}$, or $–N(R^{B1})_2$. In certain embodiments, R^2 is F, Cl, Me, Et, n-Pr, methoxy, ethoxy, propoxy, butoxy, ethynyl, hydroxybutynyl, methoxypropynyl, chloroethynyl, or cyclopropynyl. In certain embodiments, R^2 is CF_3, amino, or dimethylamino. In certain embodiments, R^2 is a non-hydrogen group in the *alpha* position. In certain embodiments, R^2 is a non-hydrogen group in the *beta* position.

[00131] In certain embodiments, each instance of R^{11a} and R^{11b} is hydrogen. In certain embodiments, one of R^{11a} and R^{11b} is hydrogen. In certain embodiments, one of R^{11a} and R^{11b} is hydrogen; and the other is $–OR^{B1}$, $–SR^{B1}$, or $–N(R^{B1})_2$. In certain embodiments, one of R^{11a} and R^{11b} is H; and the other is -OH, -OMe, amino, or dialkylamino. In certain embodiments, R^{11b} is a non-hydrogen group, and R^{11a} is hydrogen. In certain embodiments, R^{11a} is a non-hydrogen group, and R^{11b} is hydrogen.

[00132] In certain embodiments, R^{11a} and R^{11b} together form an oxo group.

Various embodiments of R^{4a}, R^{4b}, R^6, R^{7a}, R^{7b}, R^{14}, R^{17}, R^{18}, and R^{19}

[00133] As generally defined above, each instance of R^{4a}, R^{4b}, R^{7a}, and R^{7b} is independently hydrogen, –OH, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $–N_3$, $–NO_2$, –SCN,

–CN, –OR^{B1}, –SR^{B1}, –$N(R^{B1})_2$, –$N{=}NR^{B1}$, –$N{=}C(R^{B1})_2$, –$N(OR^{B1})(R^{B1})$, –$C(=O)R^{B1}$, –$C(=O)OR^{B1}$, –$C(=O)SR^{B1}$, –$C(=O)N(R^{b1})_2$, –$C(=O)N(OR^{B1})(R^{B1})$,–$OC(=O)R^{B1}$, –$OC(=O)OR^{B1}$, –$OC(=O)SR^{B1}$, –$OC(=O)N(R^{B1})_2$, –$NR^{B1}C(=O)R^{B1}$, –$NR^{B1}C(=O)OR^{B1}$, –$NR^{B1}C(=O)SR^{B1}$, –$NR^{B1}C(=O)N(R^{B1})_2$, –$SC(=O)R^{B2}$, –$SC(=O)OR^{B1}$, –$SC(=O)SR^{B1}$, –$SC(=O)N(R^{B1})_2$, –$OS(=O)_2R^{B2}$, –$OS(=O)_2OR^{B1}$, –$S–S(=O)_2R^{B2}$, –$S–S(=O)_2OR^{B1}$, –$S(=O)R^{B2}$, –SO_2R^{B2}, –$NR^{B1}SO_2R^{B2}$, or –$SO_2N(R^{B1})_2$, wherein R^{B1} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{B1} groups are joined to form an substituted or unsubstituted heterocyclic ring; and R^{B2} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or an R^{B1} group and an R^{B2} group are joined to form an substituted or unsubstituted heterocyclic ring; or optionally wherein each of R^{4a} and R^{4b}, and/or R^{7a} and R^{7b} are joined to form an oxo (=O) group.

[00134] In certain embodiments, each instance of R^{4a} and R^{4b} is hydrogen. In certain embodiments, one of R^{4a} and R^{4b} is hydrogen. In certain embodiments, one of R^{4a} and R^{4b} is hydrogen; and the other is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl. In certain embodiments, one of R^{4a} and R^{4b} is hydrogen; and the other is Me, Et, ethenyl, ethynyl, propenyl, or propynyl. In certain embodiments, each of R^{4a} and R^{4b} is independently substituted or unsubstituted alkyl. In certain embodiments, each of R^{4a} and R^{4b} is Me.

[00135] In certain embodiments, each instance of R^{7a} and R^{7b} is hydrogen.

[00136] As generally defined above, each of R^{6a} and R^{6b} is independently hydrogen, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl, and ------ represents a single or double bond, provided if a double bond is present in Ring B, then one of R^{6a} or R^{6b} is absent, and provided if a single bond is present in Ring B, then the hydrogen at C5 is in the *alpha* or *beta* position.

[00137] In certain embodiments, wherein ------ represents a single bond, each instance of R^{6a} and R^{6b} is hydrogen. In certain embodiments, each instance of R^{6a} and R^{6b} is halo, *e.g.,* fluoro.

[00138] In certain embodiments, wherein ------ represents a single bond, R^{6a} is hydrogen, and R^{6b} is halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl. In certain embodiments, R^{6a} is hydrogen, and R^{6b} is halo (*e.g.,* fluoro). In certain embodiments, R^{6a} is hydrogen, and R^{6b} is substituted or unsubstituted alkyl, *e.g.,* substituted or

unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl, *e.g.,* methyl, ethyl, propyl, or isopropyl. In certain embodiments, R^{6a} is hydrogen, and R^{6b} is substituted or unsubstituted alkenyl. In certain embodiments, R^{6a} is hydrogen, and R^{6b} is substituted or unsubstituted alkynyl.

[00139] In certain embodiments, wherein ------ represents a single bond, R^{6b} is hydrogen, and R^{6a} is halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl. In certain embodiments, R^{6b} is hydrogen, and R^{6a} is halo (*e.g.,* fluoro). In certain embodiments, R^{6b} is hydrogen, and R^{6a} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl, *e.g.,* methyl, ethyl, propyl, or isopropyl. In certain embodiments, R^{6b} is hydrogen, and R^{6a} is substituted or unsubstituted alkenyl. In certain embodiments, R^{6b} is hydrogen, and R^{6a} is substituted or unsubstituted alkynyl.

[00140] In certain embodiments, wherein ------ represents a double bond, R^{6a} is hydrogen. In certain embodiments, wherein ------ represents a double bond, R^{6a} is halo, *e.g.,* fluoro. In certain embodiments, wherein ------ represents a double bond, R^{6a} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl, *e.g.,* methyl, ethyl, propyl, or isopropyl. In certain embodiments, wherein ------ represents a double bond, R^{6a} is substituted or unsubstituted alkenyl. In certain embodiments, wherein ------ represents a double bond, R^{6a} is substituted or unsubstituted alkynyl.

[00141] As generally defined above, R^{17} is hydrogen, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or $-OR^{D1}$. In certain embodiments, R^{17} is hydrogen. In certain embodiments, R^{17} is halo. In certain embodiments, R^{17} is substituted or unsubstituted alkyl. In certain embodiments, R^{17} is substituted or unsubstituted alkenyl. In certain embodiments, R^{17} is substituted or unsubstituted alkynyl. In certain embodiments, R^{17} is substituted or unsubstituted carbocyclyl. In certain embodiments, R^{17} is substituted or unsubstituted heterocyclyl. In certain embodiments, R^{17} is substituted or unsubstituted aryl. In certain embodiments, R^{17} is substituted or unsubstituted heteroaryl. In certain embodiments, R^{17} is $-OR^{D1}$ (*e.g.,* -OH).

[00142] As generally defined above, R^{14} is H or substituted or unsubstituted alkyl. In certain embodiments, R^{14} is H. In certain embodiments, R^{14} is substituted or unsubstituted alkyl (*e.g.*, $-CH_3$).

[00143] As generally defined above, R^{18} is independently hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^{18} is hydrogen. In certain embodiments, R^{18} is substituted or unsubstituted alkyl (*e.g.*, $-CH_3$).

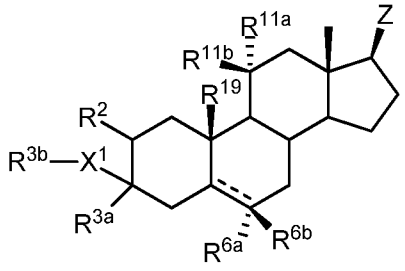
[00144] As generally defined above, R^{19} is independently hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^{19} is hydrogen. In certain embodiments, R^{19} is substituted or unsubstituted alkyl (*e.g.*, $-CH_3$).

[00145] In certain embodiments, R^{14} is hydrogen, R^{18} is $-CH_3$ and R^{19} is $-CH_3$.

[00146] In certain embodiments, R^{14} is hydrogen, R^{18} is $-CH_3$ and R^{19} is hydrogen.

Additional embodiments of Formula (I)

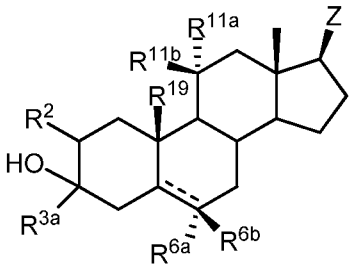
[00147] Various combinations of the above embodiments are futher contemplated herein. For example, in certain embodiments, the compound of Formula (**I**) is of Formula (**I-w**):



(**I-w**)

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, R^{3b} is hydrogen. In certain embodiments, the group $-X^1R^{3b}$ at the C3 position is *beta*. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen or $-OR^{B1}$. In certain embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, ------ represents a single bond, R^5 is *alpha* (down) and R^{6a} is hydrogen. In certain embodiments, ------ represents a double bond. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain embodiments, R^{6a} is halo, *e.g.*, fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.*, fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.*, fluoro. In certain embodiments, R^{19} is methyl.

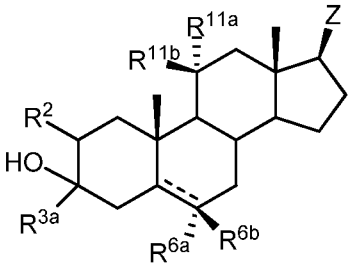
[00148] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-x**):



(I-x)

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, the group –OH at the C3 position is *beta*. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen or $-OR^{B1}$. In certain embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, ------ represents a single bond, R^5 is *alpha* (down) and R^{6a} is hydrogen. In certain embodiments, ------ represents a double bond. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain embodiments, R^{6a} is halo, *e.g.*, fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.*, fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.*, fluoro. In certain embodiments, R^{19} is methyl.

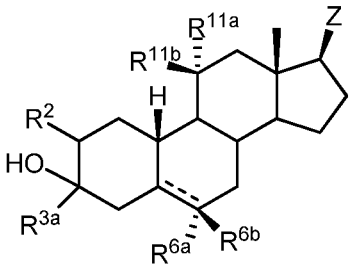
[00149] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-y**):



(I-y)

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, the group –OH at the C3 position is *beta*. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen or $-OR^{B1}$. In certain embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, ------ represents a single bond, R^5 is *alpha* (down) and R^{6a} is hydrogen. In certain embodiments, ------ represents a double bond. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain embodiments, R^{6a} is halo, *e.g.*, fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.*, fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.*, fluoro.

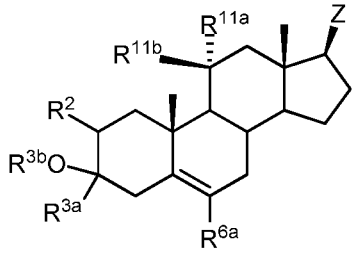
[00150] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-z**):



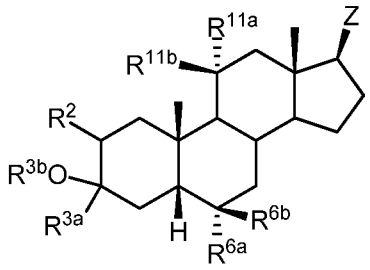
(I-z)

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, the group –OH at the C3 position is *beta*. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen or $-OR^{B1}$. In certain embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, ------ represents a single bond, R^5 is *alpha* (down) and R^{6a} is hydrogen. In certain embodiments, ------ represents a double bond. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain embodiments, R^{6a} is halo, *e.g.*, fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.*, fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.*, fluoro.

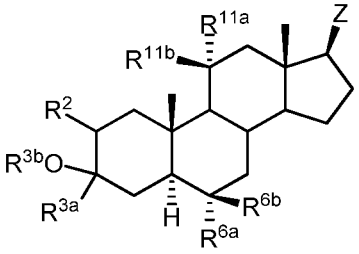
[00151] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-a1**), (**I-a2**), or (**I-a3**):



(I-a1),



(I-a2),

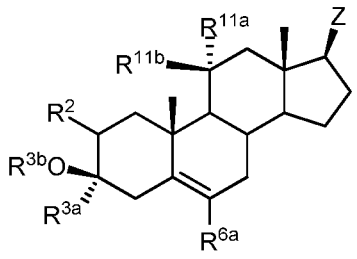


(I-a3)

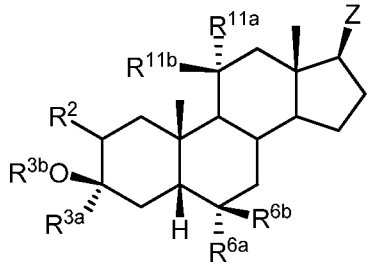
or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, R^{3b} is hydrogen. In certain embodiments, the group $-OR^{3b}$ at the C3 position is *beta*. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen or $-OR^{B1}$. In certain

embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain embodiments, R^{6a} is halo, *e.g.*, fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.*, fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.*, fluoro.

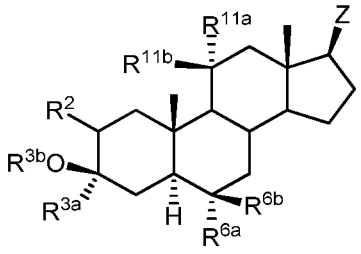
[00152] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-b1**), (**I-b2**), or (**I-b3**):



(**I-b1**),



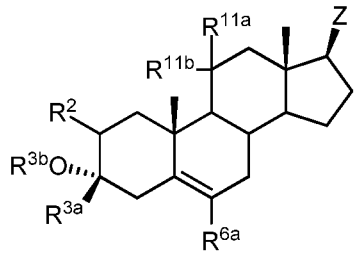
(**I-b2**),



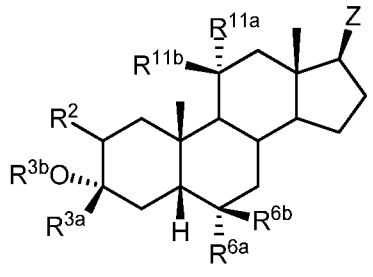
(**I-b3**)

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, R^{3b} is hydrogen. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^{2} is hydrogen or $-OR^{B1}$. In certain embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain embodiments, R^{6a} is halo, *e.g.*, fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.*, fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.*, fluoro.

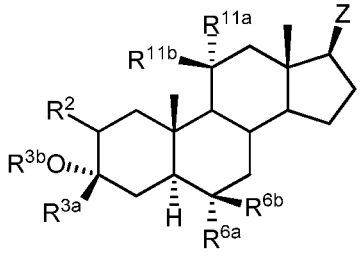
[00153] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-c1**), (**I-c2**), or (**I-c3**):



(**I-c1**),



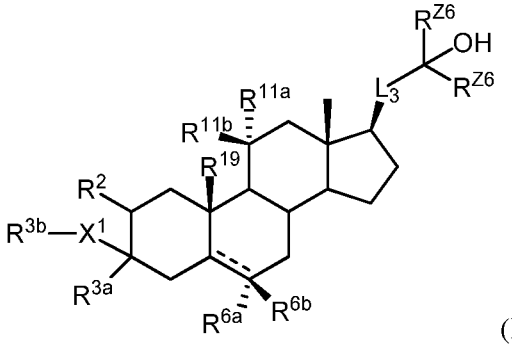
(I-c2),



(I-c3)

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, R^{3b} is hydrogen. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen or $-OR^{B1}$. In certain embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain embodiments, R^{6a} is halo, *e.g.*, fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.*, fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.*, fluoro.

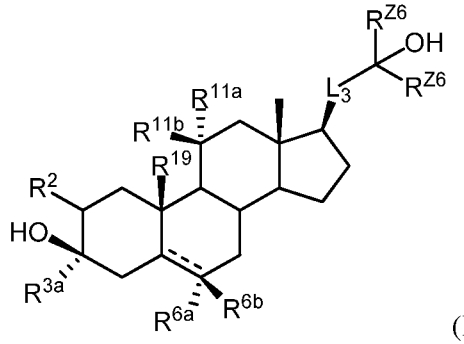
[00154] In certain embodiments, the compound is of Formula (**I-d**):



(**I-d**)

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, R^{3b} is hydrogen. In certain embodiments, the group $-X^1R^{3b}$ at the C3 position is *beta*. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen or $-OR^{B1}$. In certain embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, ------ represents a single bond, R^5 is *alpha* (down) and R^{6a} is hydrogen. In certain embodiments, ------ represents a double bond. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain embodiments, R^{6a} is halo, *e.g.*, fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.*, fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.*, fluoro. In certain embodiments, R^{19} is methyl. In certain embodiments, each R^{Z6} is independently hydrogen or methyl.

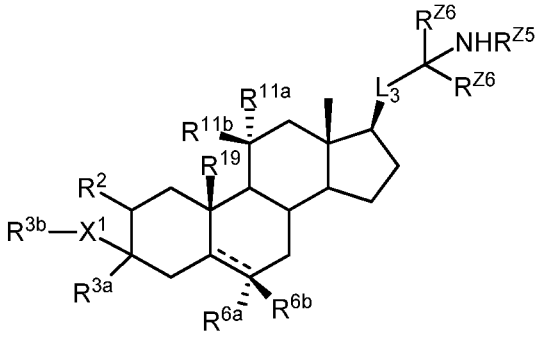
[00155] In certain embodiments, the compound is of Formula (**I-e**):



(**I-e**)

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen or $-OR^{B1}$. In certain embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, ------ represents a single bond, R^5 is *alpha* (down) and R^{6a} is hydrogen. In certain embodiments, ------ represents a double bond. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain embodiments, R^{6a} is halo, *e.g.,* fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.,* fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.,* fluoro. In certain embodiments, R^{19} is methyl. In certain embodiments, each R^{Z6} is independently hydrogen or methyl.

[00156] In certain embodiments, the compound is of Formula (**I-f**):

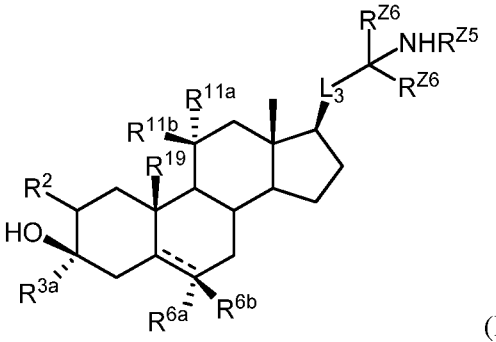


(**I-f**)

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, R^{3b} is hydrogen. In certain embodiments, the group $-X^1R^{3b}$ at the C3 position is *beta*. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen or $-OR^{B1}$. In certain embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, ------ represents a single bond, R^5 is *alpha* (down) and R^{6a} is hydrogen. In certain embodiments, ------ represents a double bond. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain

embodiments, R^{6a} is halo, *e.g.*, fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.*, fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.*, fluoro. In certain embodiments, R^{19} is methyl. In certain embodiments, each R^{Z6} is independently hydrogen or methyl. In certain embodiments, R^{Z5} is hydrogen or methyl.

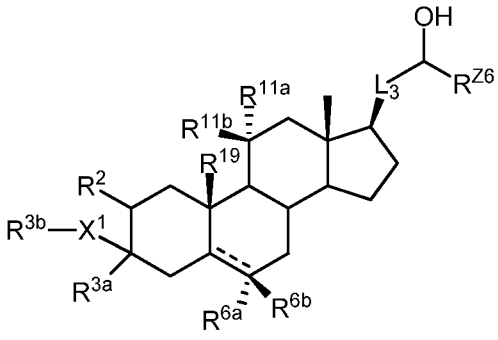
[00157] In certain embodiments, the compound is of Formula (**I-g**):



(**I-g**)

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen or $-OR^{B1}$. In certain embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, ====== represents a single bond, R^5 is *alpha* (down) and R^{6a} is hydrogen. In certain embodiments, ====== represents a double bond. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain embodiments, R^{6a} is halo, *e.g.*, fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.*, fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.*, fluoro. In certain embodiments, R^{19} is methyl. In certain embodiments, each R^{Z6} is independently hydrogen or methyl. In certain embodiments, R^{Z5} is hydrogen or methyl.

[00158] In certain embodiments, the compound is of Formula (**I-h**):

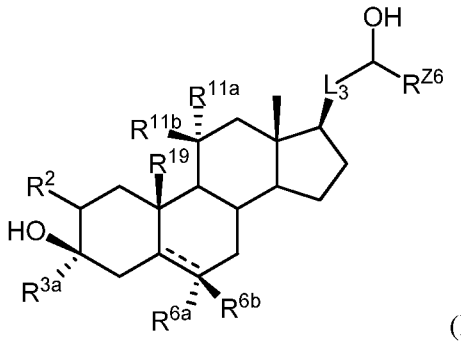


(**I-h**)

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, R^{3b} is hydrogen. In certain

embodiments, the group $-X^1R^{3b}$ at the C3 position is *beta*. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen or $-OR^{B1}$. In certain embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, ------ represents a single bond, R^5 is *alpha* (down) and R^{6a} is hydrogen. In certain embodiments, ------ represents a double bond. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain embodiments, R^{6a} is halo, *e.g.*, fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.*, fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.*, fluoro. In certain embodiments, R^{19} is methyl. In certain embodiments, R^{Z6} is isopropyl.

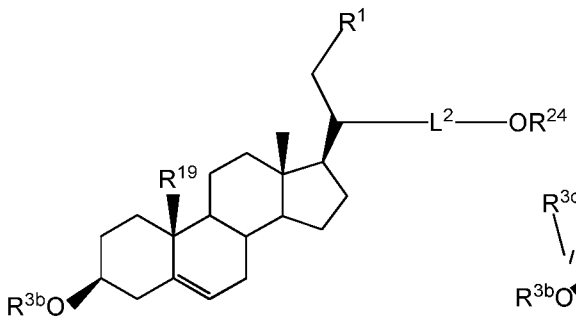
[00159] In certain embodiments, the compound is of Formula (**I-i**):



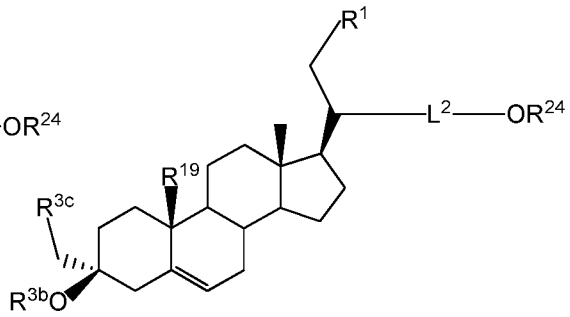
(**I-i**)

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof. In certain embodiments, R^{3a} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen or $-OR^{B1}$. In certain embodiments, R^{11a} is hydrogen and R^{11b} is hydrogen or $-OR^{B1}$. In certain embodiments, ------ represents a single bond, R^5 is *alpha* (down) and R^{6a} is hydrogen. In certain embodiments, ------ represents a double bond. In certain embodiments, R^{6a} and R^{6b} are both hydrogen. In certain embodiments, R^{6a} is halo, *e.g.*, fluoro, or alkyl. In certain embodiments, R^{6b} is halo, *e.g.*, fluoro, or alkyl, and R^{6a} is hydrogen. In certain embodiments, R^{6a} and R^{6b} are both halo, *e.g.*, fluoro. In certain embodiments, R^{19} is methyl. In certain embodiments, R^{Z6} is isopropyl.

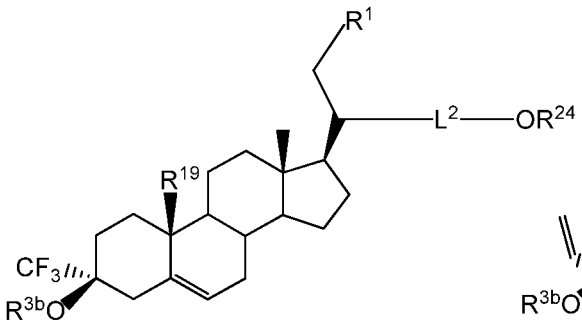
[00160] Additional embodiments of Formula (**I**) include compounds of the following formula:



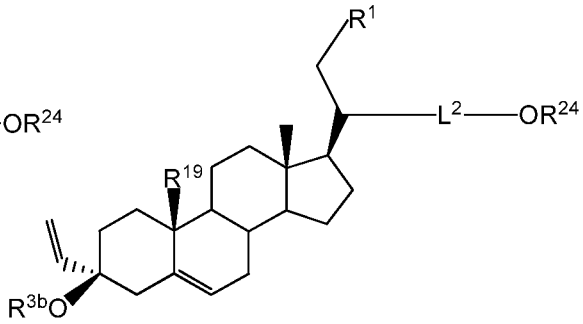
(IV-a) ,



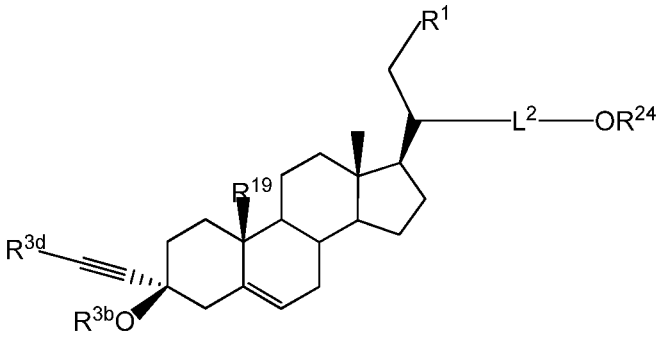
(IV-b) ,



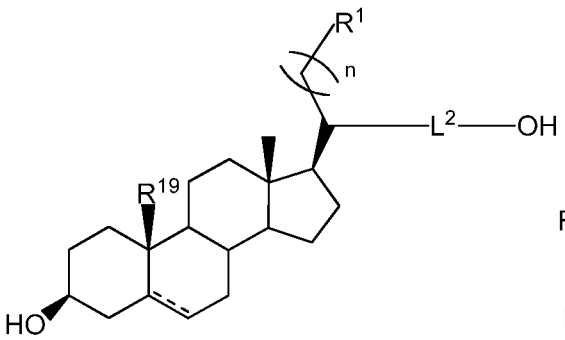
(IV-c) ,



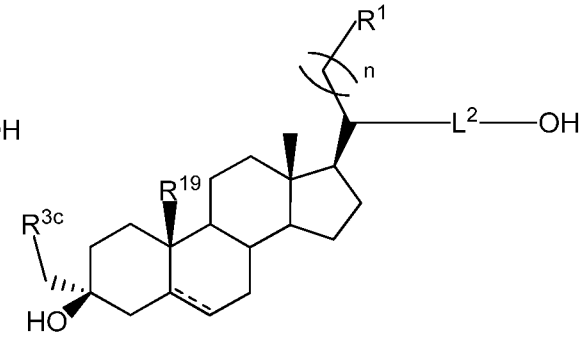
(IV-d) or



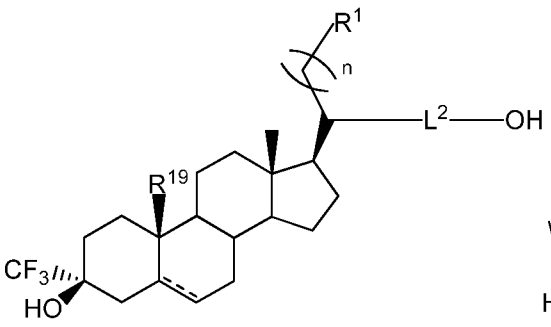
(IV-e)



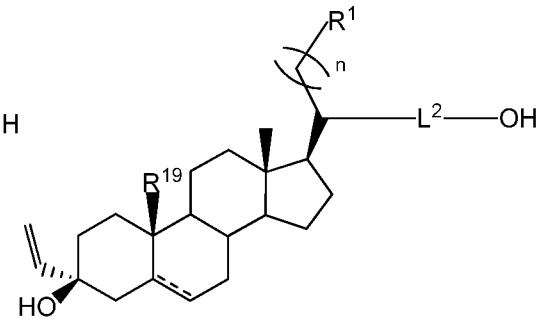
(V-a) ,



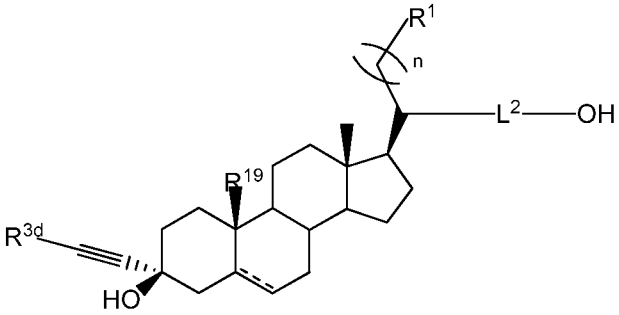
(V-b) ,



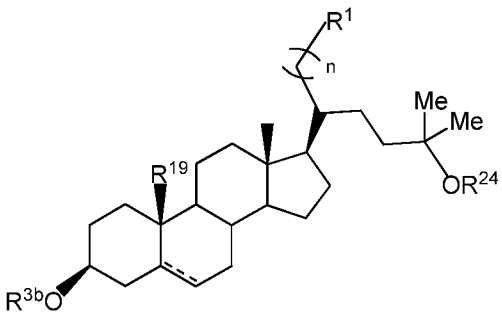
(V-c) ,



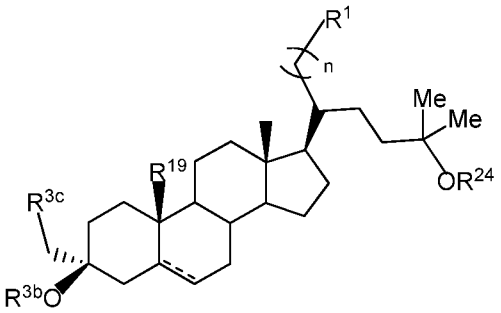
(V-d) or



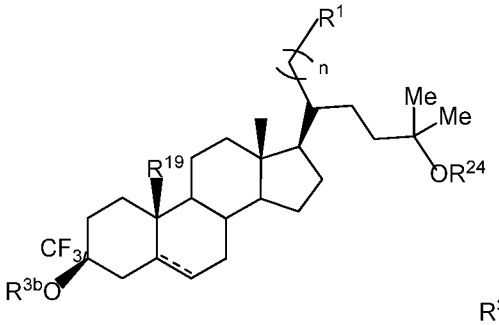
(V-e)



(VI-a) ,

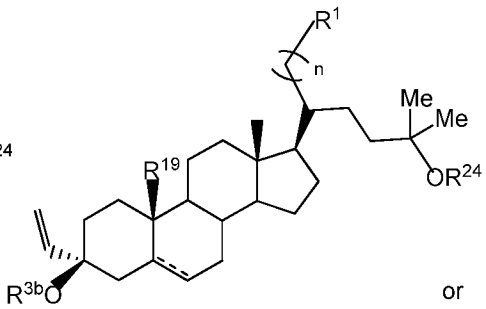


(VI-b) ,



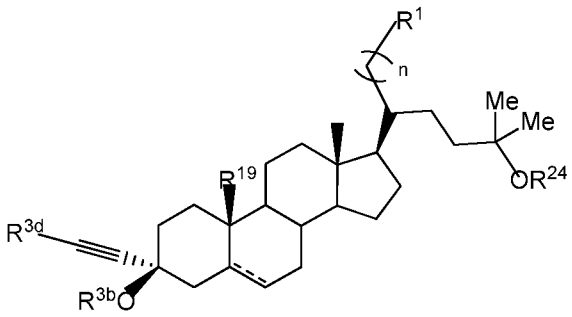
(VI-c)

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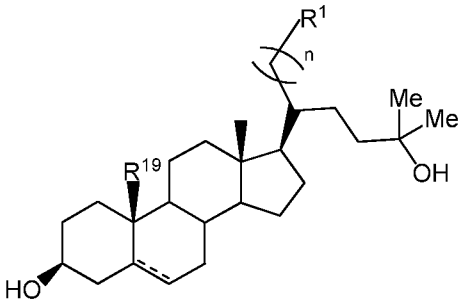


(VI-d)

or

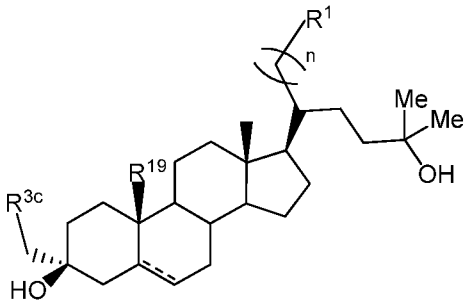


(VI-e)



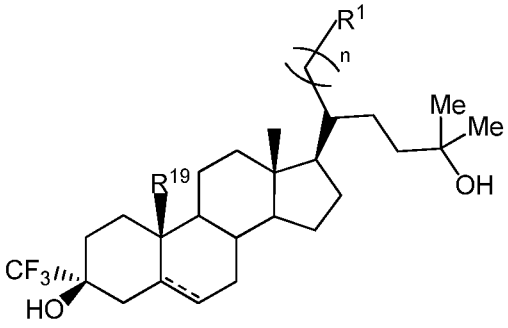
(VII-a)

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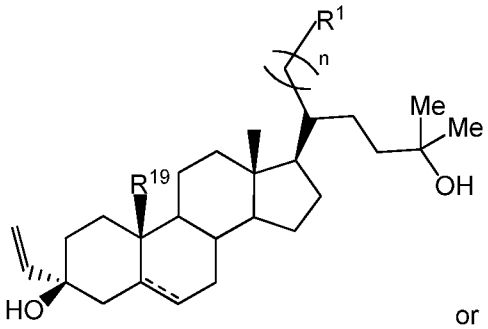


(VII-b)

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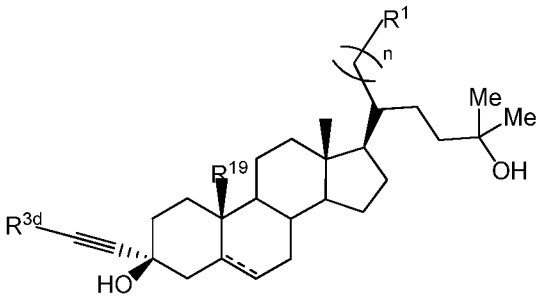


(VII-c)

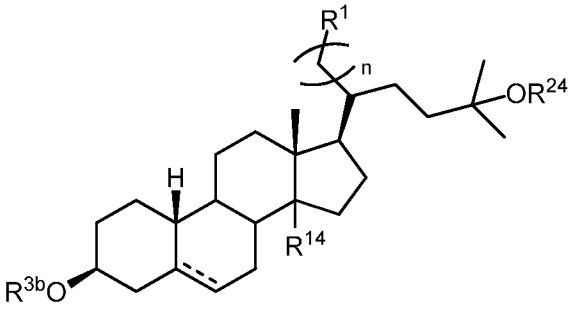


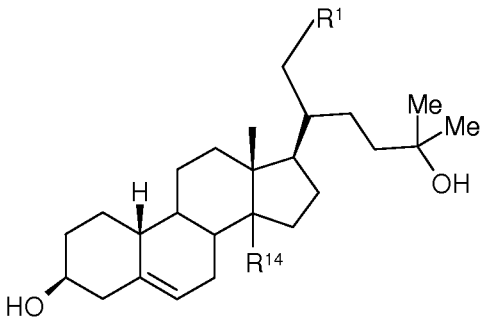
or

(VII-d)

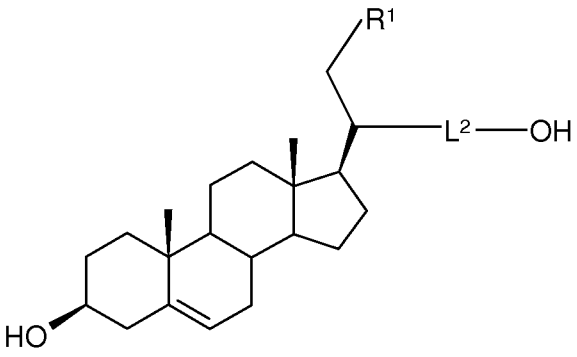


(VII-e)

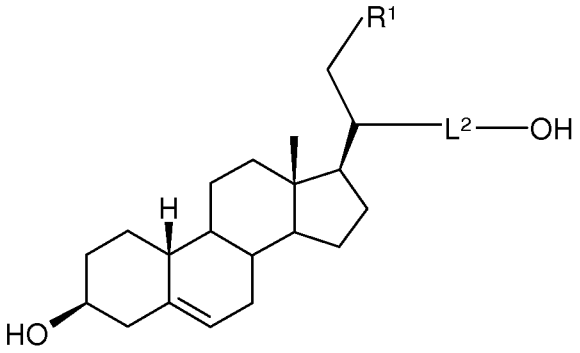




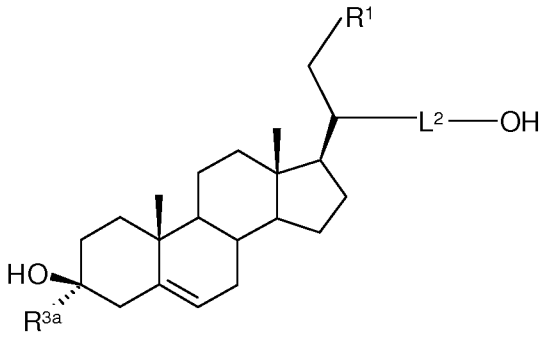
(IX)



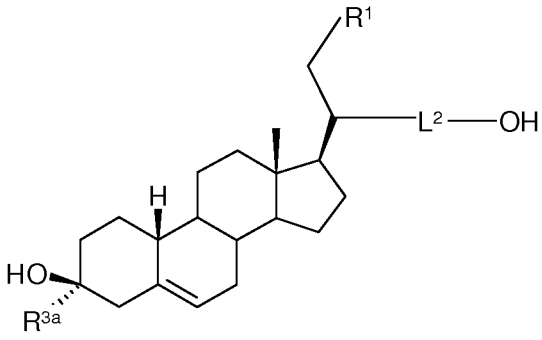
X



XI

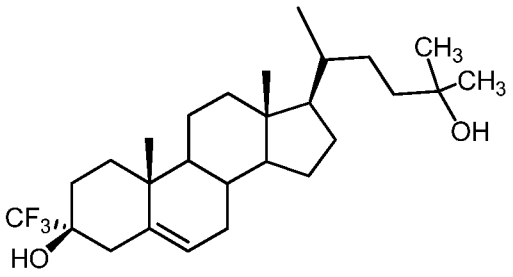


XIIa or

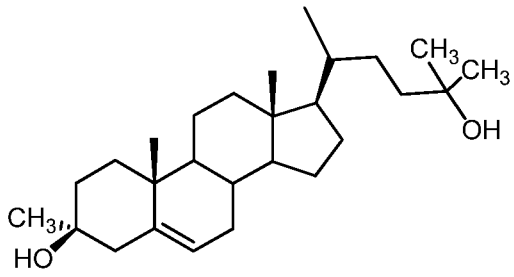


XIIb

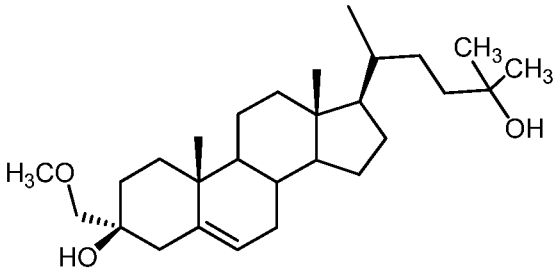
[00161] In certain embodiments the compound is any one of the following compounds:



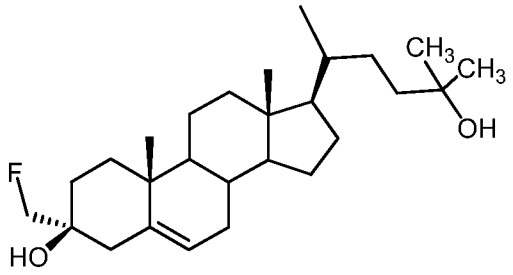
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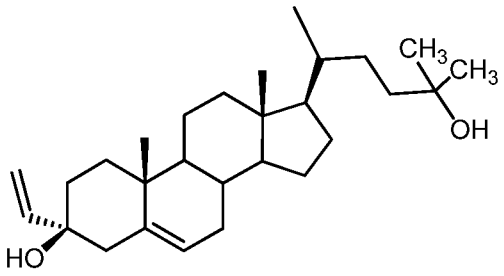
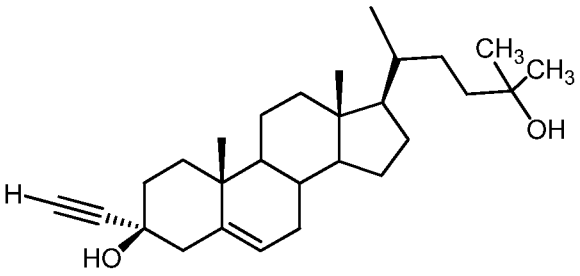
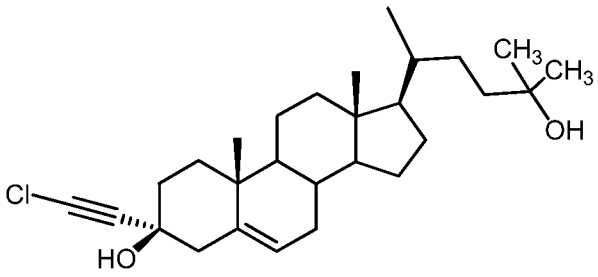
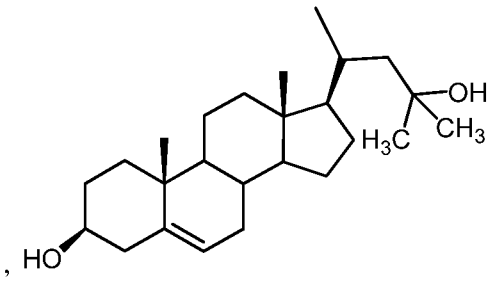
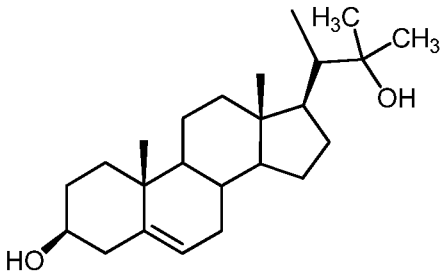
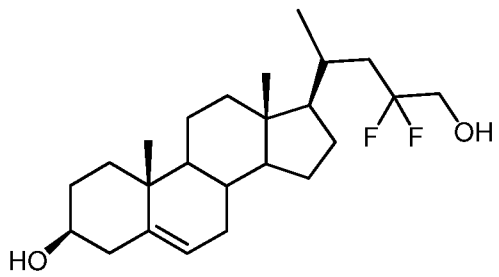
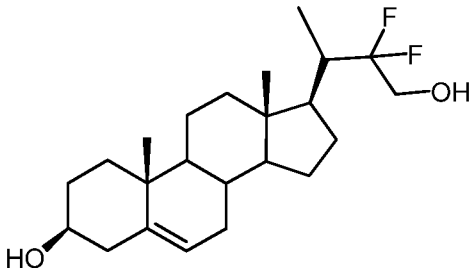
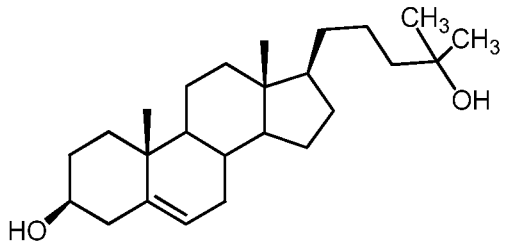
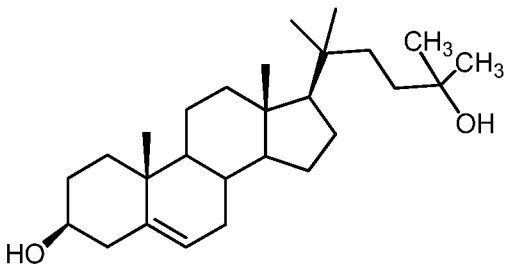
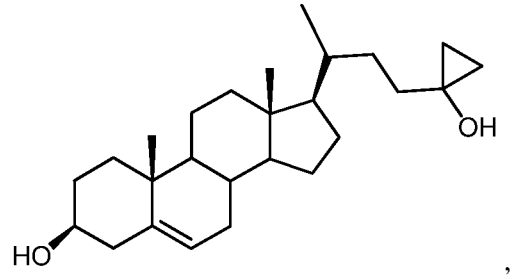
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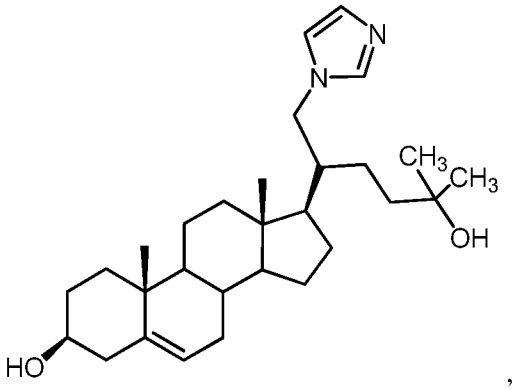
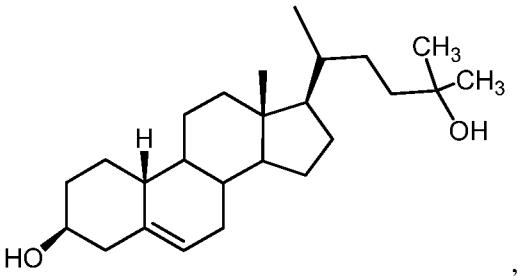
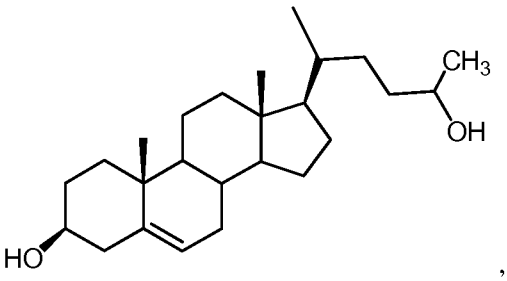
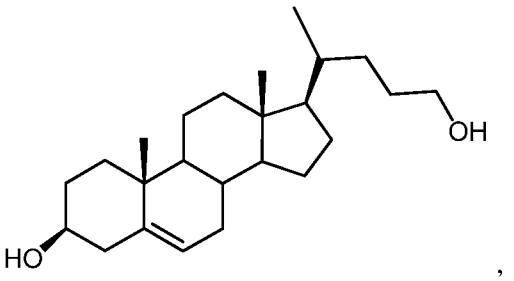
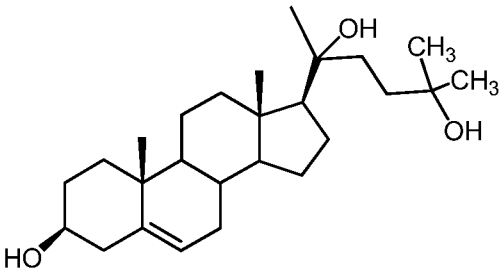
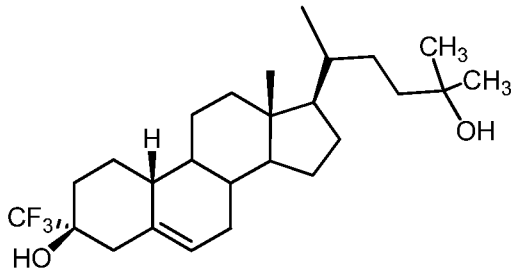
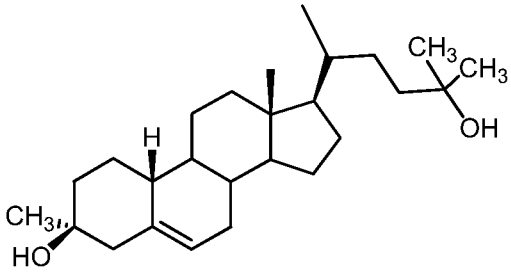
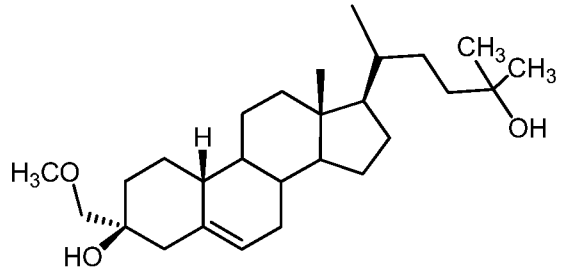
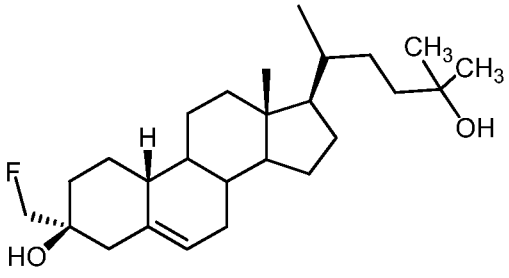
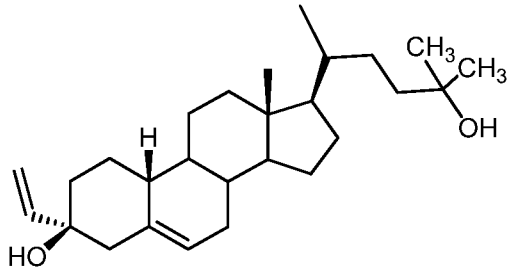


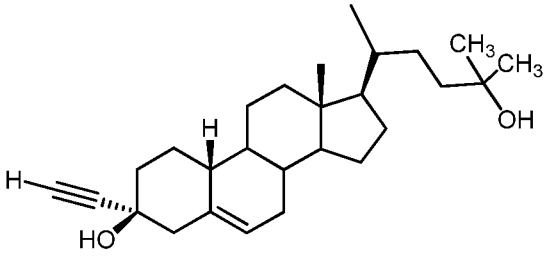
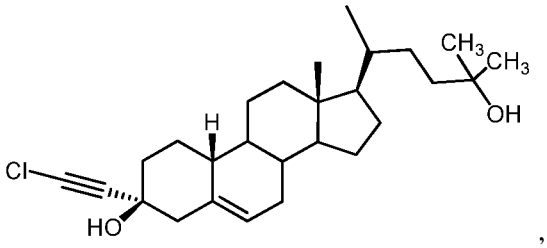
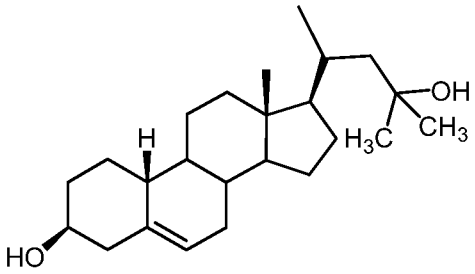
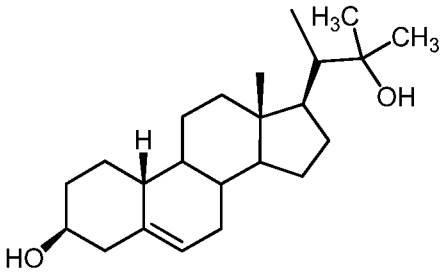
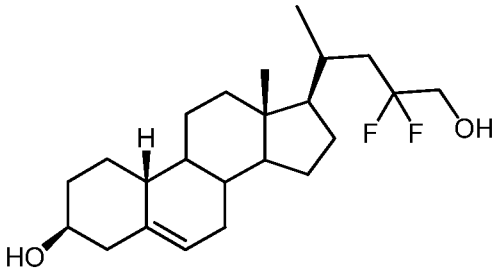
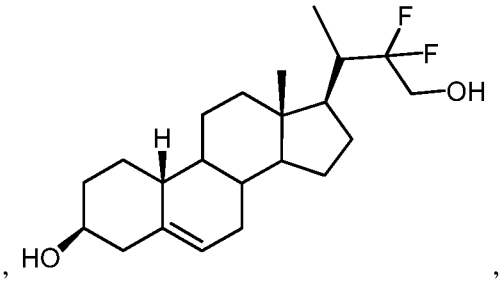
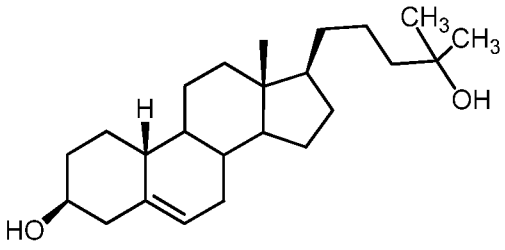
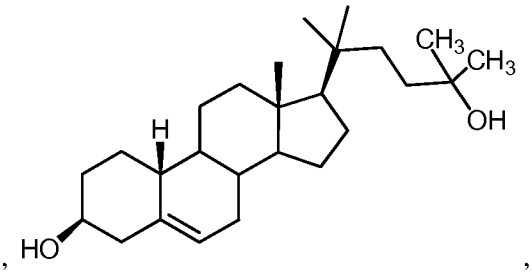
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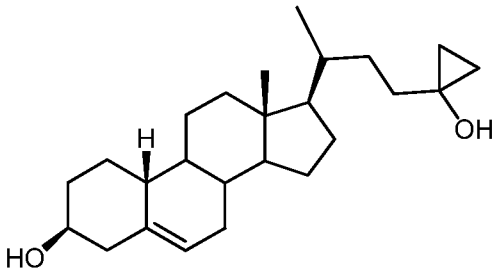
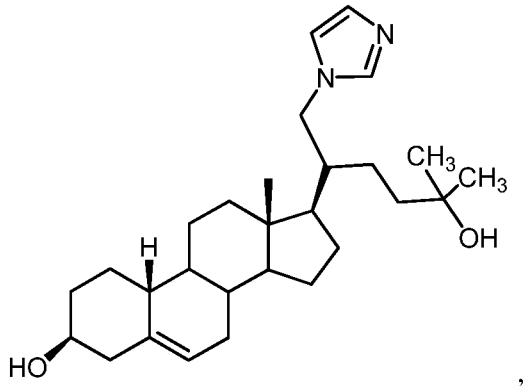
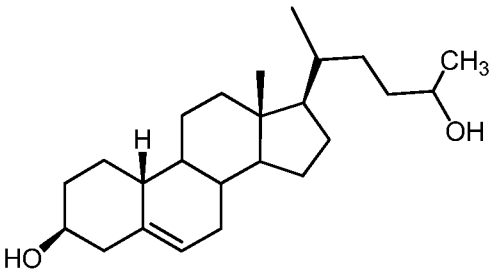
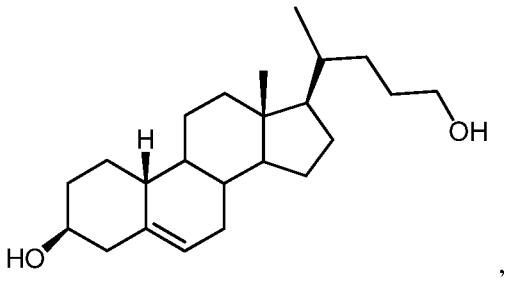
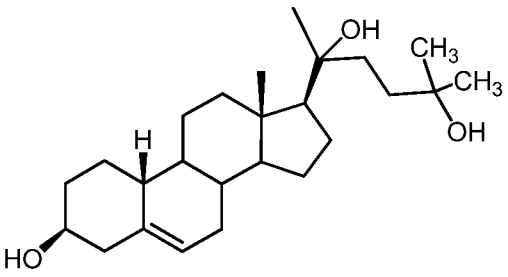
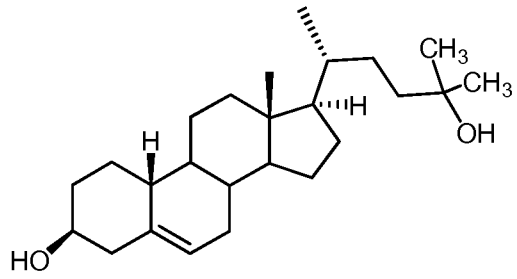
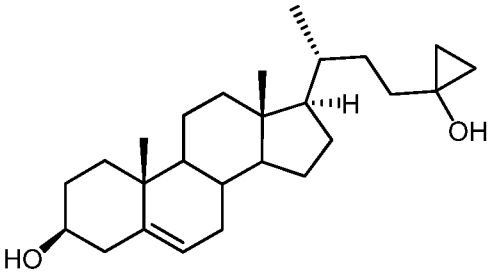
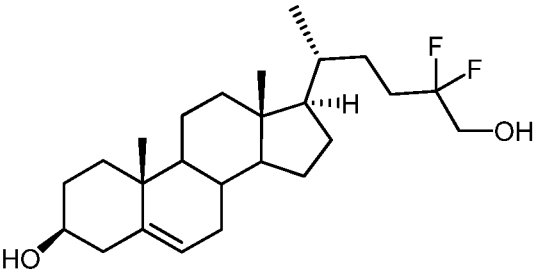


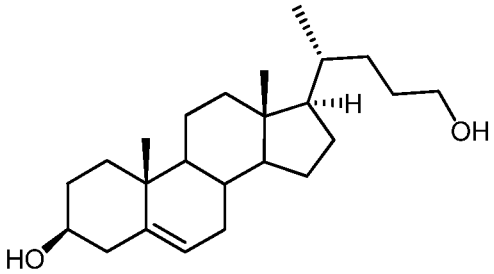
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CH3
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OH
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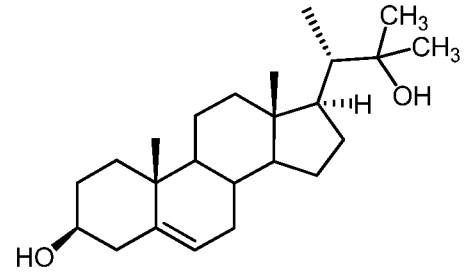

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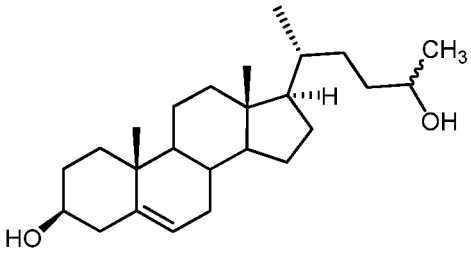

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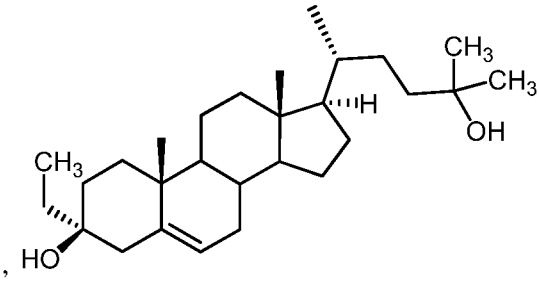
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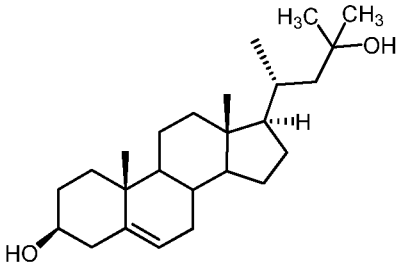
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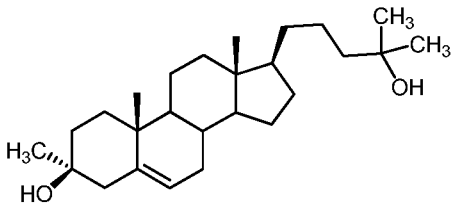
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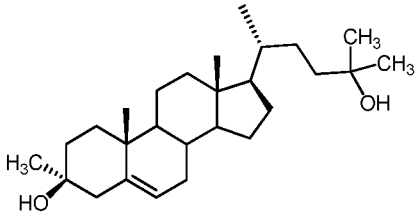
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CH3

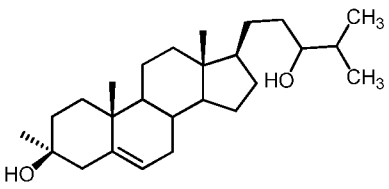
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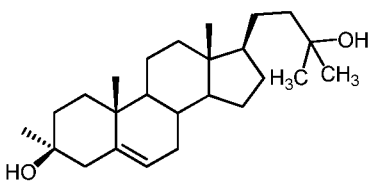
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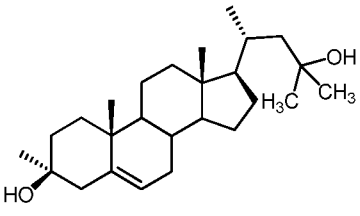
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CH3
CH3

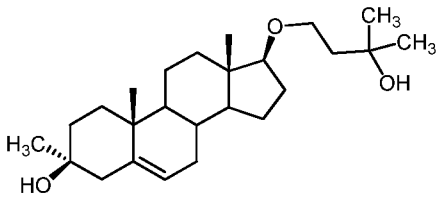
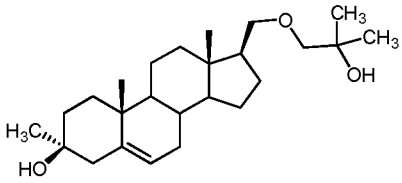
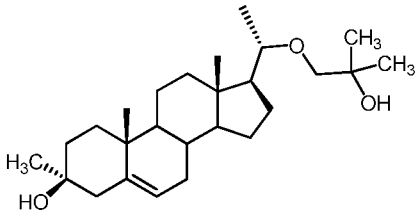
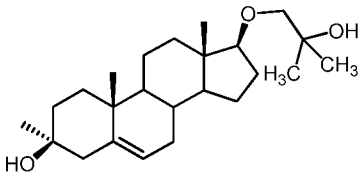
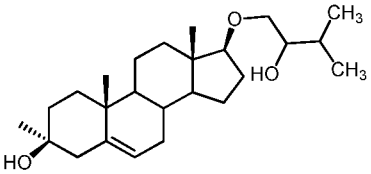
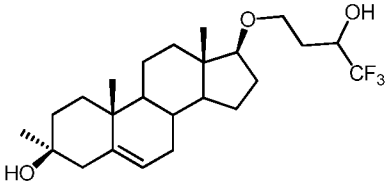
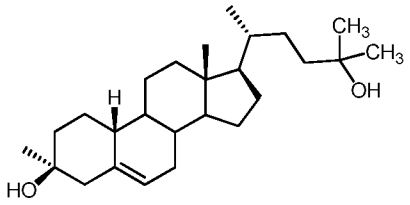
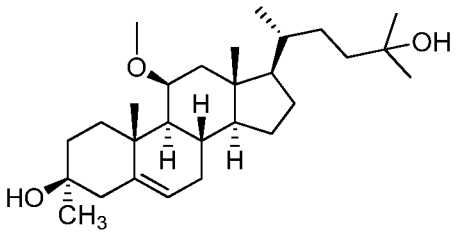
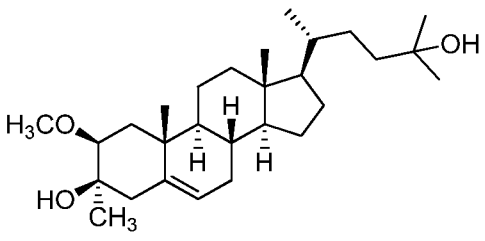
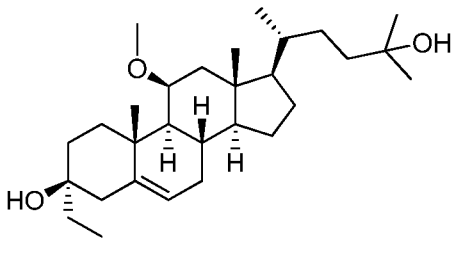
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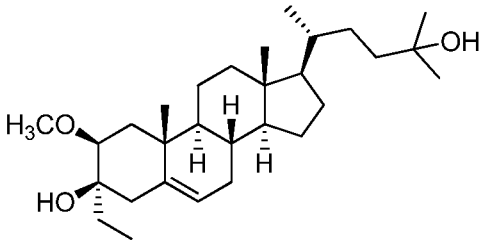

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H3C
CH3

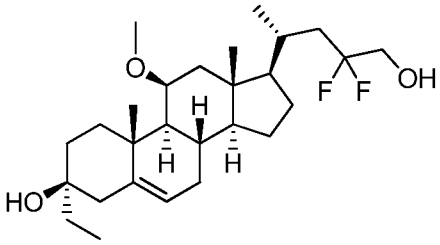
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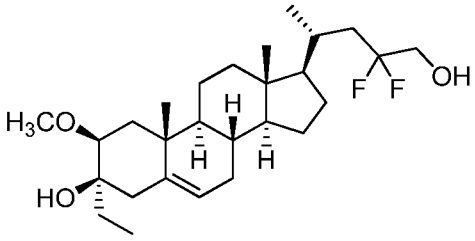

HO
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H3C
CH3

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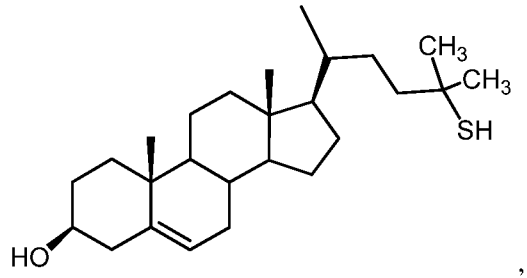


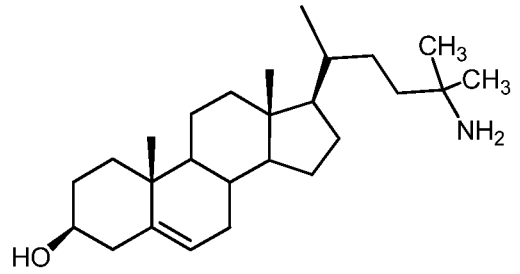
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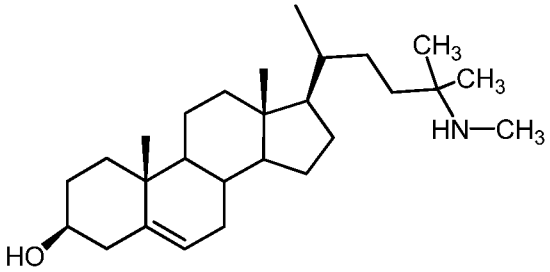
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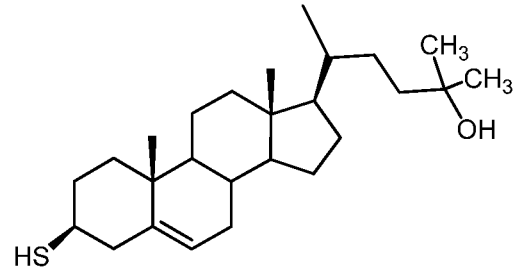
, or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof.

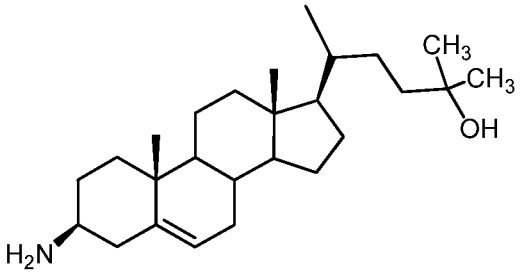
[00162] In certain embodiments the compound is any one of the following compounds:

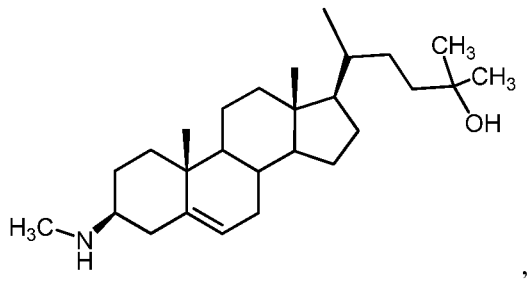


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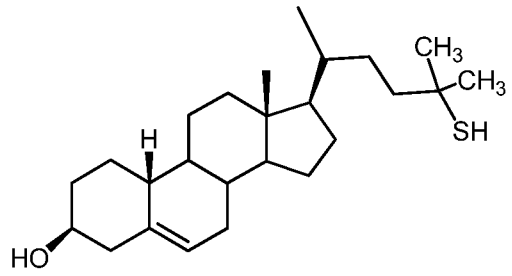
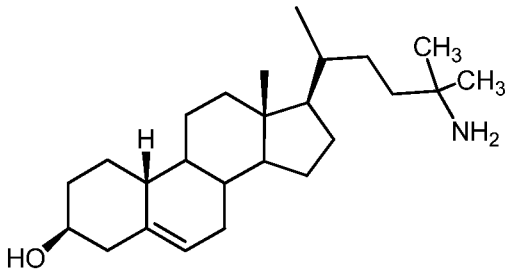
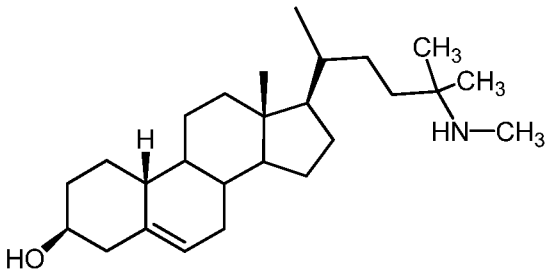
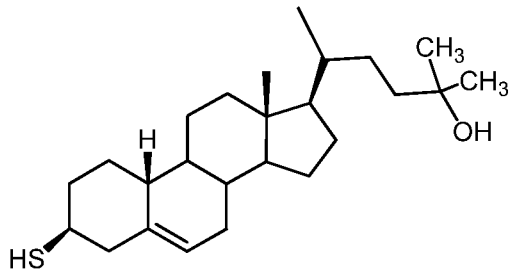
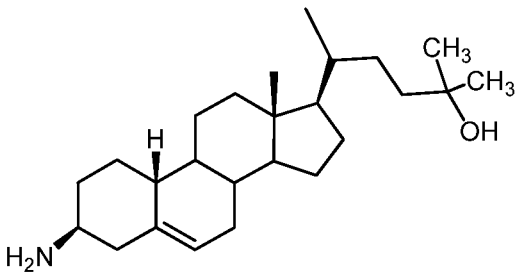
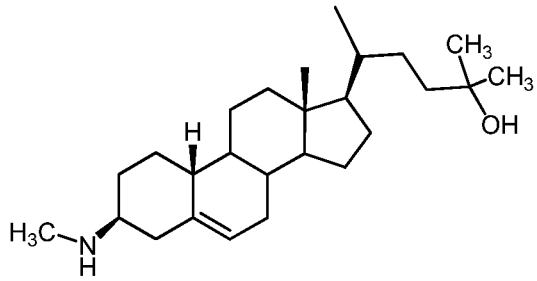
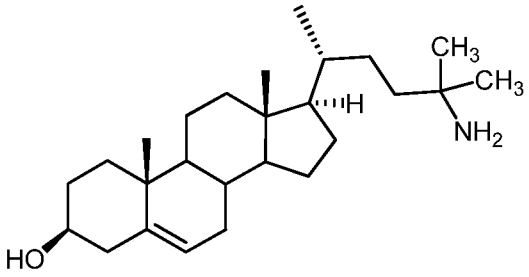
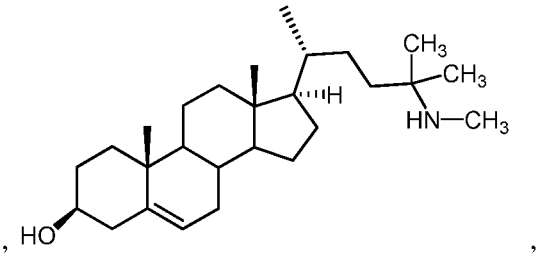
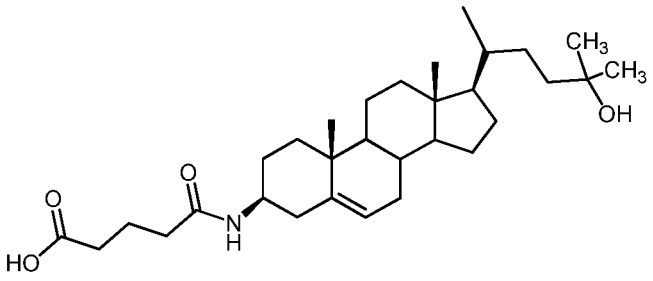
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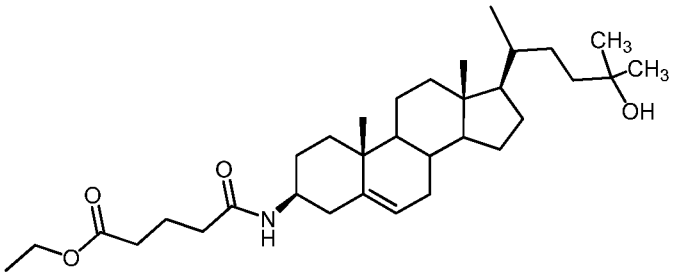
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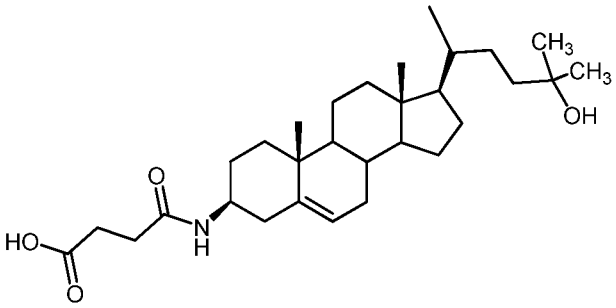
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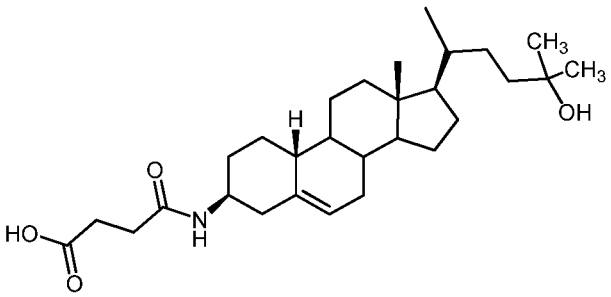
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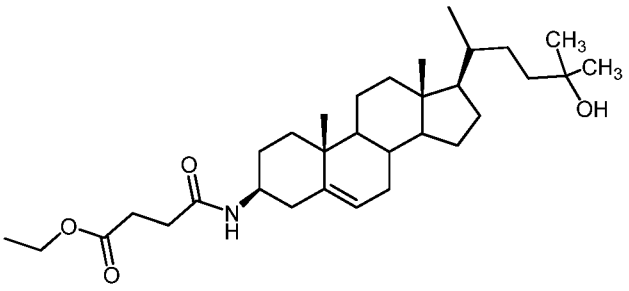
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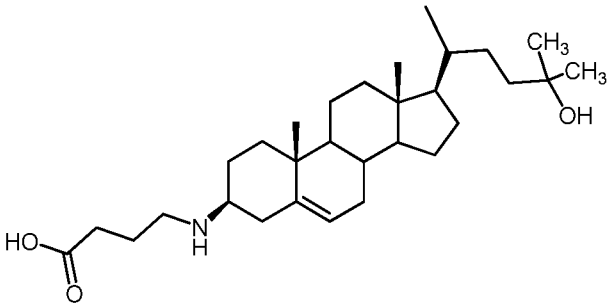

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CH3
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CH3
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CH3
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CH3
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CH3
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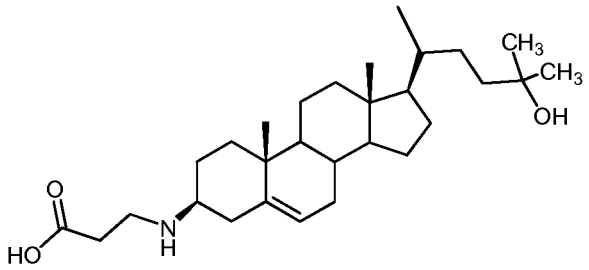

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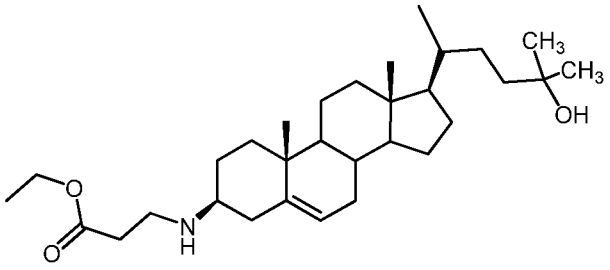

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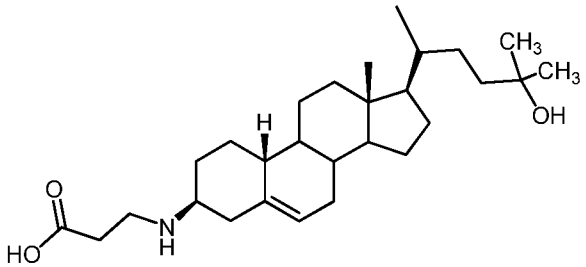

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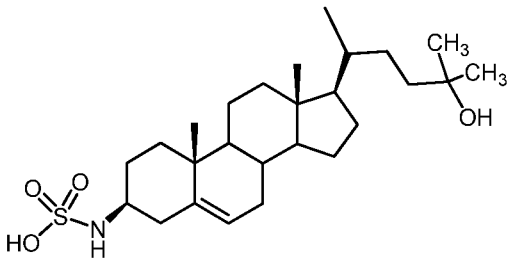

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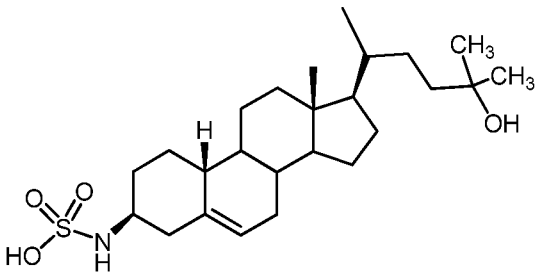

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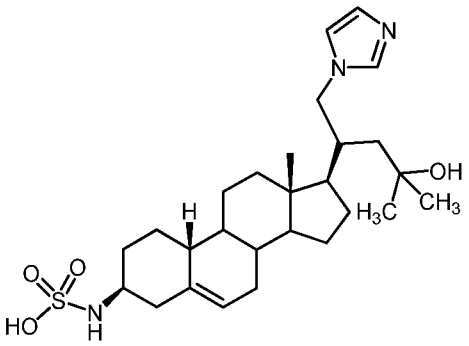

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CH3
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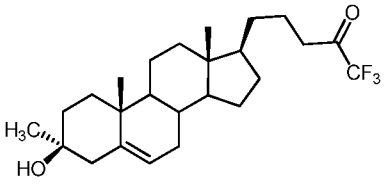

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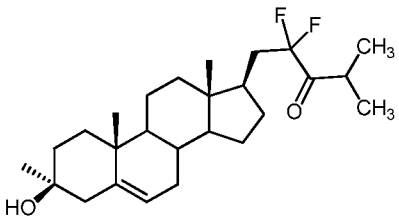


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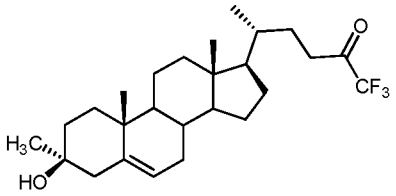
or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof.

[00163] In certain embodiments the compound is any one of the following compounds:

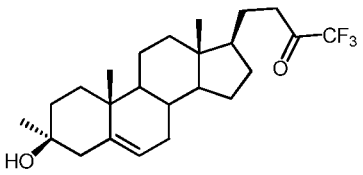




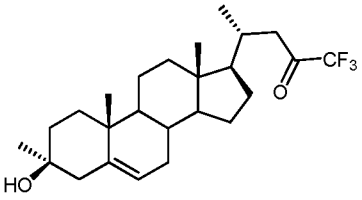
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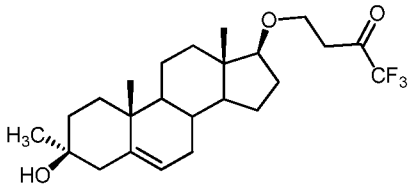
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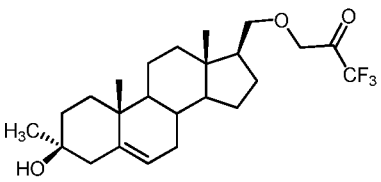
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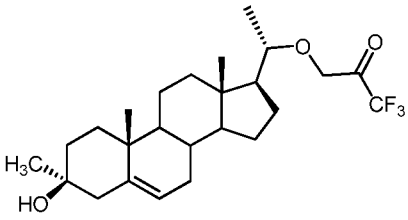
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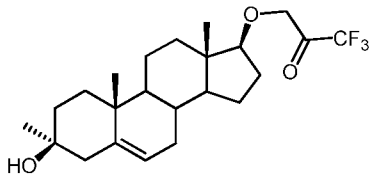
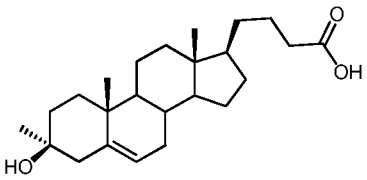
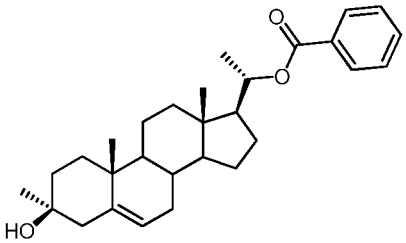
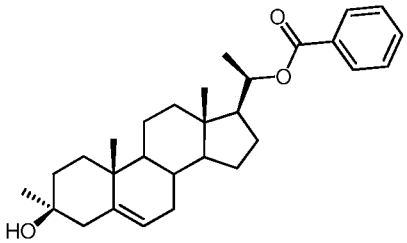
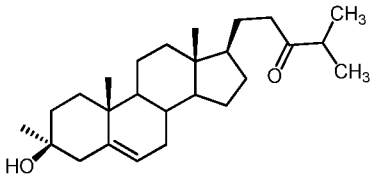
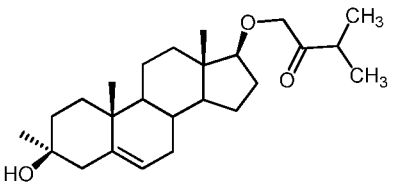
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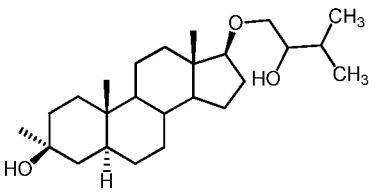
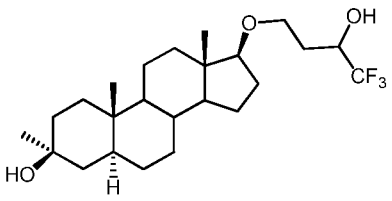
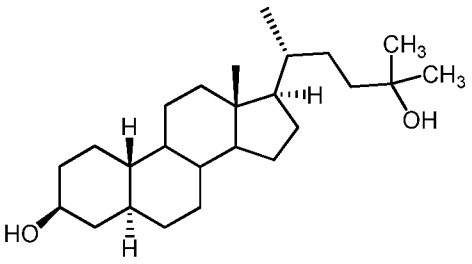
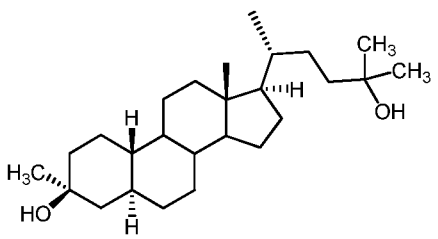


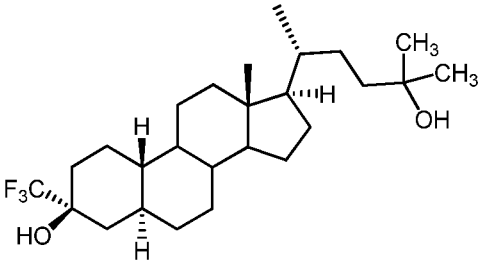
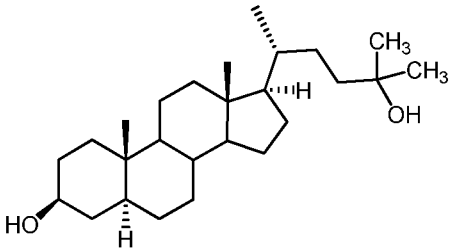
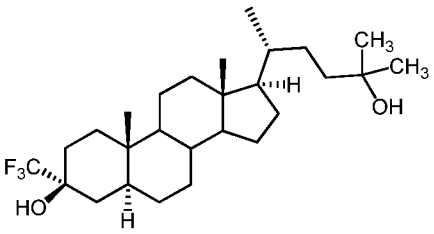
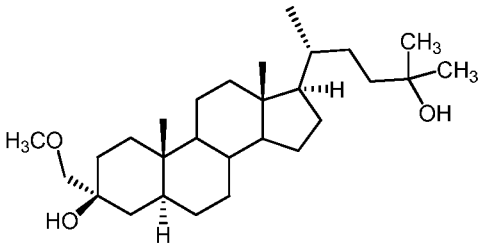
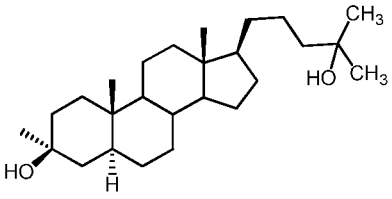
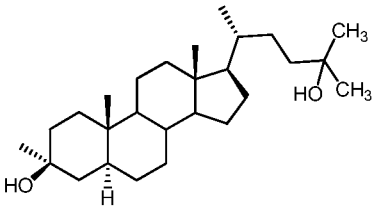
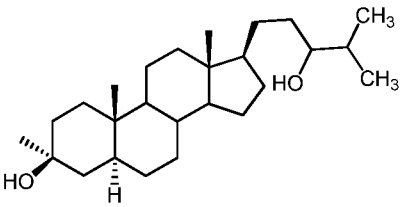
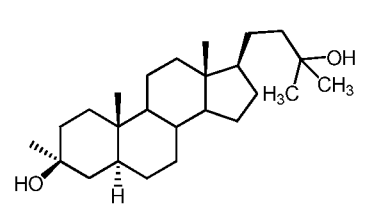
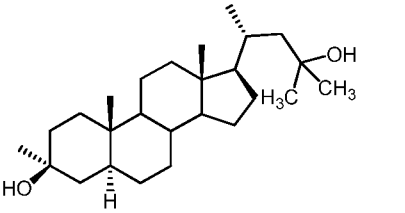
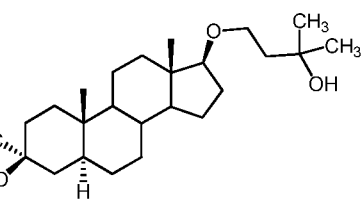
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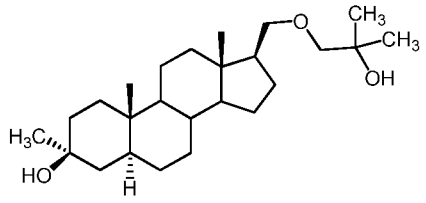
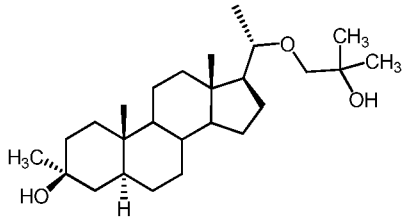
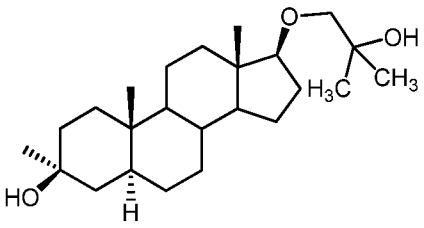
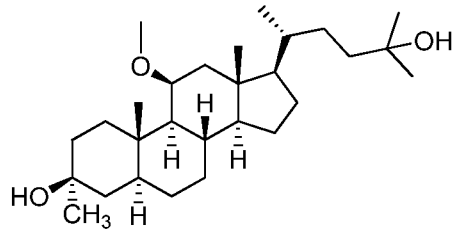
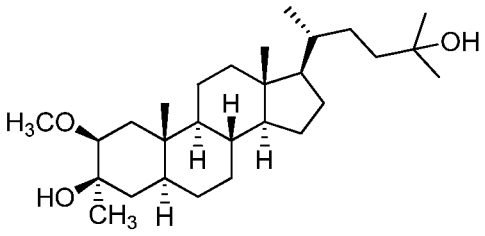
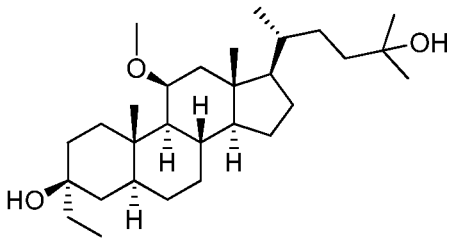
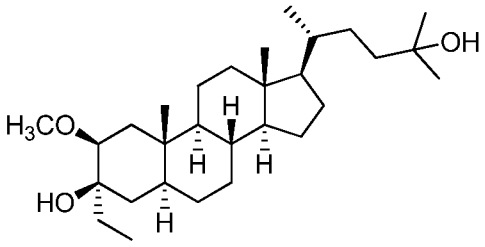
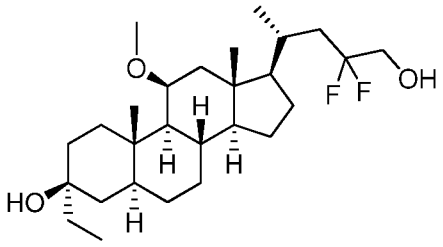
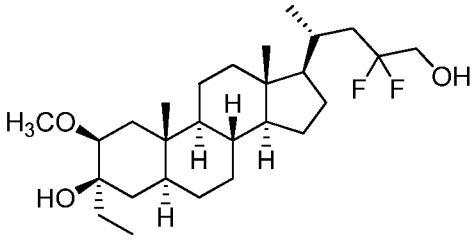






, or ,

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof.

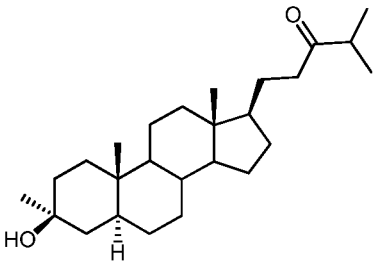
[00164] In certain embodiments the compound is any one of the following compounds:





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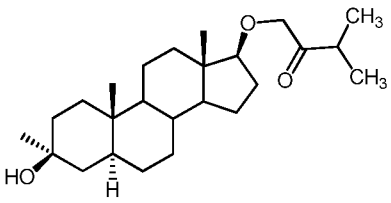




















, or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof.

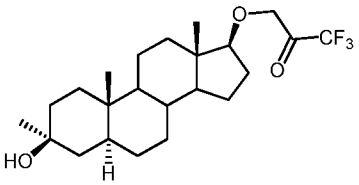
[00165] In certain embodiments the compound is any one of the following compounds:


O
HO
H

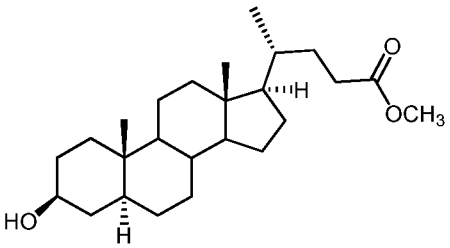
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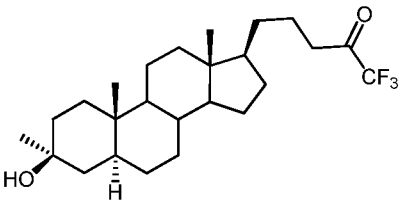
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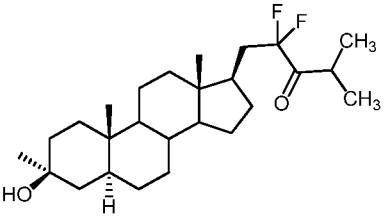
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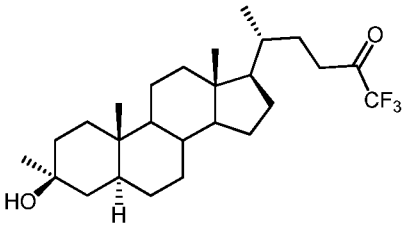
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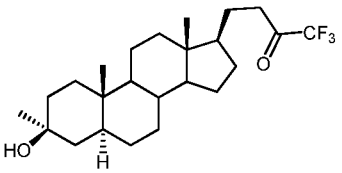
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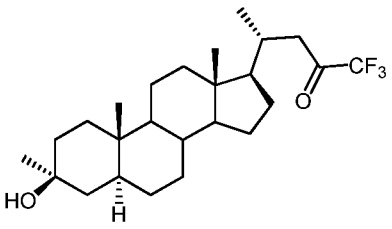
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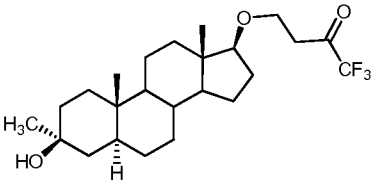
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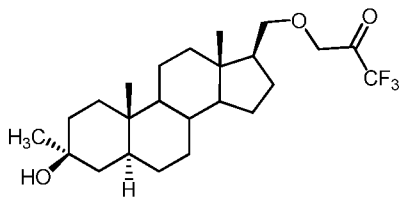
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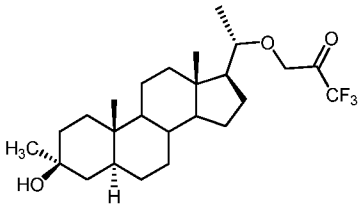

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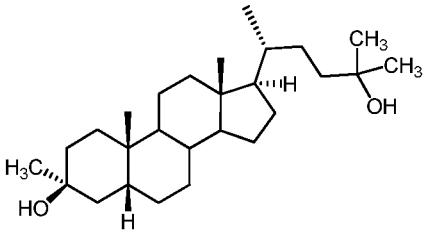


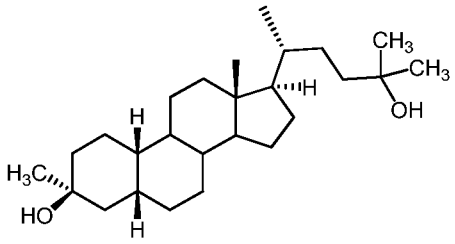
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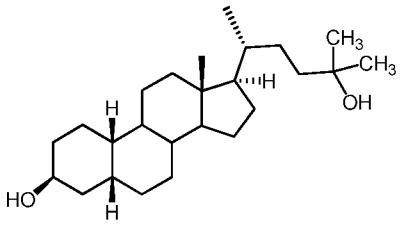
or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof.

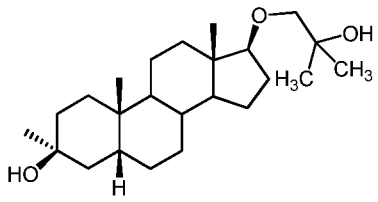
[00166] In certain embodiments the compound is any one of the following compounds:



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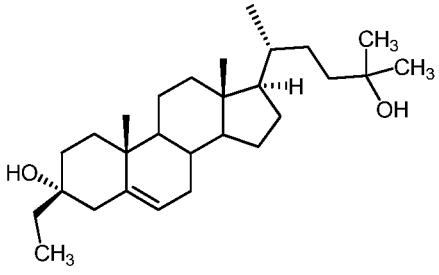


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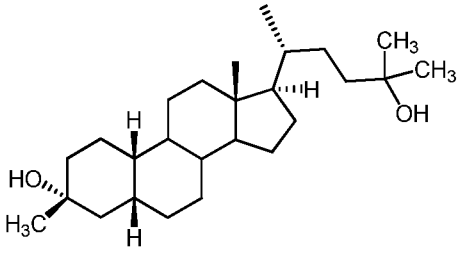
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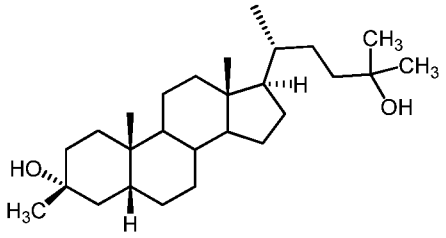
or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof.

[00167] In certain embodiments the compound is any one of the following compounds:



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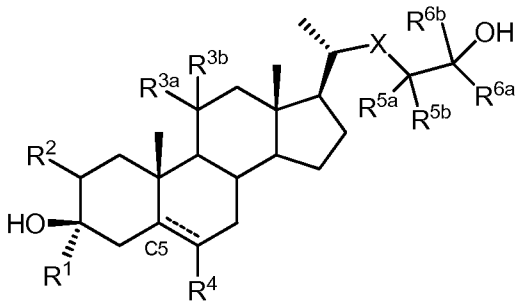


, or 

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or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer, isotopic variant, or N–oxide thereof, or a combination thereof.

[00168] In certain embodiments, the compound is a compound of Formula (**I**) is a compound of Formula (**I-q**),



(**I-q**)

and pharmaceutically acceptable salts thereof;

wherein:

R^1 is substituted or unsubstituted alphatic;

R^2 is hydrogen, halogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted cyclopropyl, or $-OR^{A2}$, wherein R^{A2} is hydrogen or substituted or unsubstituted alkyl;

R^{3a} is hydrogen or $-OR^{A3}$, wherein R^{A3} is hydrogen or substituted or unsubstituted alkyl, and R^{3b} is hydrogen; or R^{3a} and R^{3b} are joined to form an oxo (=O) group;

R^4 is hydrogen, substituted or unsubstituted alkyl, or halogen;

X is $-C(R^X)_2-$ or –O-, wherein R^X is hydrogen or fluorine, or one R^X group and R^{5b} are joined to form a double bond;

each instance of R^{5a} and R^{5b} is independently hydrogen or fluorine;

R^{6a} is a non-hydrogen group selected from the group consisting of substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted carbocyclyl, substituted and unsubstituted heterocyclyl, substituted and unsubstituted aryl,

and substituted and unsubstituted heteroaryl group, wherein the non-hydrogen group is optionally substituted with fluorine; and

R^{6b} is hydrogen or a substituted or unsubstituted alkyl group optionally substituted with fluorine;

===== represents a single or double bond, provided if a single bond is present, then the hydrogen at C5 is in the *alpha* configuration;

and further provided that:

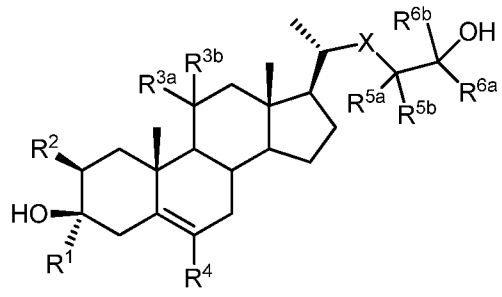
(1) at least one of R^X, R^{5a}, and R^{5b} is fluorine; or

(2) at least one of R^{6a} and R^{6b} is a non-hydrogen group substituted with a fluorine; or

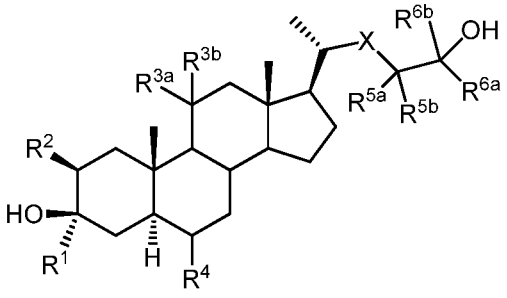
(3) R^{6a} is a non-hydrogen group comprising between two and ten carbon atoms.

[00169] In certain embodiments, the compound of the present invention is a pharmaceutically acceptable salt.

[00170] As generally described herein, compounds of formula (I-q) wherein the hydrogen at C_5 is provided in the *beta* configuration demonstrate loss of NMDA potentiation compared to compounds wherein the hydrogen at C_5 is *alpha*, or wherein a double bond is present at C_5-C_6. Thus, the compound of Formula (**I-q**) encompasses only compounds of Formula (**I-qA**) and (**I-qB**):



(I-qA)



(I-qB)

and pharmaceutically acceptable salts thereof.

Group R^1 of compounds of formula (I-q)

[00171] As generally defined herein, R^1 is substituted or unsubstituted alphatic, *i.e.*, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, or substituted or unsubstituted carbocyclyl.

[00172] In certain embodiments, R^1 is substituted or unsubstituted alkyl, *e.g.*, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or

unsubstituted C_{5-6}alkyl. Exemplary R^1 C_{1-6}alkyl groups include, but are not limited to, substituted or unsubstituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), n–hexyl (C_6), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more fluoro groups (*e.g.*, $–CF_3$, $–CH_2F$, $–CHF_2$, difluoroethyl, and 2,2,2–trifluoro–1,1–dimethyl–ethyl), C_{1-6} alkyl substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more chloro groups (*e.g.*, $–CH_2Cl$, $–CHCl_2$), and C_{1-6} alkyl substituted with alkoxy groups (*e.g.*, $–CH_2OCH_3$, $–CH_2OCH_2CH_3$, $–CH_2O$-cyclopropyl). In certain embodiments, R^1 is substituted alkyl, *e.g.*, R^1 is haloalkyl, alkoxyalkyl, or aminoalkyl. In certain embodiments, R^1 is Me, Et, n-Pr, n-Bu, i-Bu, fluoromethyl, chloromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, difluoroethyl, 2,2,2-trifluoro-1,1-dimethyl-ethyl, methoxymethyl, methoxyethyl, or ethoxymethyl.

[00173] In certain embodiments, R^1 is unsubstituted C_{1-3} alkyl, *e.g.*, R^1 is $–CH_3$, $-CH_2CH_3$, $–CH_2CH_2CH_3$ or $–CH_2CH_2CH_2CH_3$.

[00174] In certain embodiments, R^1 is alkyl substituted with one or more fluorine atoms; *e.g.*, R^1 is $–CH_2F$, $-CHF_2$, or $–CF_3$.

[00175] In certain embodiments, R^1 is alkyl substituted with one or more $–OR^{A1}$ groups, wherein R^{A1} is hydrogen or substituted or unsubstitued alkyl. In certain embodiments, R^1 is $–CH_2OR^{A1}$, *e.g.*, wherein R^{A1} is hydrogen, $–CH_3$, $-CH_2CH_3$, or $–CH_2CH_2CH_3$.

[00176] In certain embodiments, R^1 is substituted or unsubstituted alkenyl, *e.g.*, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-3}alkenyl, substituted or unsubstituted C_{3-4}alkenyl, substituted or unsubstituted C_{4-5}alkenyl, or substituted or unsubstituted C_{5-6}alkenyl. In certain embodiments, R^1 is ethenyl (C_2), propenyl (C_3), or butenyl (C_4), unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, alkoxyalkyl, or hydroxyl. In certain embodiments, R^1 is ethenyl, propenyl, or butenyl, unsubstituted or substituted with alkyl, halo, haloalkyl, alkoxyalkyl, or hydroxy. In certain embodiments, R^1 is ethenyl.

[00177] In certain embodiments, R^1 is substituted or unsubstituted alkynyl, *e.g.*, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{2-3}alkynyl, substituted or unsubstituted C_{3-4}alkynyl, substituted or unsubstituted C_{4-5}alkynyl, or substituted or unsubstituted C_{5-6}alkynyl. Exemplary substituted or unsubstituted R^1 alkynyl groups include, but are not limited to, ethynyl, propynyl, or butynyl, unsubstituted or substituted with alkyl, halo, haloalkyl (*e.g.*, CF_3), alkoxyalkyl, cycloalkyl (*e.g.*, cyclopropyl or cyclobutyl), or hydroxyl. In certain embodiments, R^1 is selected from the group consisting of trifluoroethynyl, cyclopropylethynyl, cyclobutylethynyl, and propynyl, fluoropropynyl, and chloroethynyl. In certain embodiments, R^1 is ethynyl (C_2), propynyl (C_3), or butynyl (C_4), unsubstituted or

substituted with one or more substituents selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl. In certain embodiments, R^1 is ethynyl (C_2), propynyl (C_3), or butynyl (C_4) substituted with substituted phenyl. In certain embodiments, the phenyl substitutent is further substituted with one or more substituents selected from the group consisting of halo, alkyl, trifluoroalkyl, alkoxy, acyl, amino or amido. In certain embodiments, R^1 is ethynyl (C_2), propynyl (C_3), or butynyl (C_4) substituted with substituted or unsubstituted pyrrolyl, imidazolyl, pyrazolyl, oxazoyl, thiazolyl, isoxazoyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, or tetrazolyl.

[00178] In certain embodiments, R^1 is ethynyl, propynyl, or butynyl, unsubstituted or substituted with alkyl, halo, haloalkyl, alkoxyalkyl, or hydroxyl. In certain embodiments, R^1 is ethynyl or propynyl, substituted with substituted or unsubstituted aryl. In certain embodiments, R^1 is ethynyl or propynyl, substituted with phenyl unsubstituted or substituted with halo, alkyl, alkoxy, haloalkyl, trihaloalkyl, or acyl. In certain embodiments, R^1 is ethynyl or propynyl, substituted with substituted or unsubstituted carbocyclyl. In certain embodiments, R^{3a} is ethynyl or propynyl, substituted with substituted or unsubstituted cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In certain embodiments, R^1 is ethynyl or propynyl, substituted with substituted or unsubstituted heteroaryl. In certain embodiments, R^1 is ethynyl or propynyl, substituted with substituted or unsubstituted pyridinyl, or pyrimidinyl. In certain embodiments, R^1 is ethynyl or propynyl, substituted with substituted or unsubstituted pyrrolyl, imidazolyl, pyrazolyl, oxazoyl, thiazolyl, isoxazoyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl. In certain embodiments, R^1 is ethynyl or propynyl, substituted with substituted or unsubstituted heterocyclyl. In certain embodiments, R^1 is ethynyl or propynyl, substituted with substituted or unsubstituted pyrrolidinyl, piperidinyl, piperazinyl, or mopholinyl. In certain embodiments, R^1 is propynyl or butynyl, substituted with hydroxyl or alkoxy. In certain embodiments, R^1 is propynyl or butynyl, substituted with methoxy or ethoxy. In certain embodiments, R^1 is ethynyl or propynyl, substituted with chloro. In certain embodiments, R^1 is ethynyl or propynyl, substituted with trifluoromethyl.

[00179] In certain embodiments, R^1 is substituted or unsubstituted carbocyclyl, *e.g.,* substituted or unsubstituted C_{3-6}carbocyclyl, substituted or unsubstituted C_{3-4}carbocyclyl, substituted or unsubstituted C_{4-5} carbocyclyl, or substituted or unsubstituted C_{5-6} carbocyclyl. In certain embodiments, R^1 is substituted or unsubstituted cyclopropyl or substituted or unsubstituted cyclobutyl.

Groups R^2, R^{3a}, R^{3b}, and R^4 of compounds of formula (I-q)

[00180] As generally defined herein, R^2 is hydrogen, halogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted cyclopropyl, or $-OR^{A2}$, wherein R^{A2} is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 is halogen, *e.g.,* fluoro, chloro, bromo, or iodo. In certain embodiments, R^2 is fluoro or chloro. In certain embodiments, R^2 is substituted or unsubstituted C_{1-6}alkyl, *e.g.,* substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl. In certain embodiments, R^2 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, or cyclopropyl. In certain embodiments, R^2 is $-OR^{A2}$. In certain embodiments, R^{A2} is hydrogen. In certain embodiments, R^{A2} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl. In certain embodiments, R^{A2} is hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH_2CH_2CH_3$, *i.e.,* to provide a group R^2 of formula –OH, $-OCH_3$, $-OCH_2CH_3$, or $-OCH_2CH_2CH_3$. In certain embodiments, R^2 is a non-hydrogen substitutent in the *alpha* configuration. In certain embodiments, R^2 is a non-hydrogen substituent in the *beta* configuration.

[00181] As generally defined herein, R^{3a} is hydrogen or $-OR^{A3}$, wherein R^{A3} is hydrogen or substituted or unsubstituted alkyl, and R^{3b} is hydrogen; or R^{3a} and R^{3b} are joined to form an oxo (=O) group.

[00182] In certain embodiments, both R^{3a} and R^{3b} are both hydrogen.

[00183] In certain embodiments, R^{3a} and R^{3b} are joined to form an oxo (=O) group.

[00184] In certain embodiments, R^{3a} is $-OR^{A3}$ and R^{3b} is hydrogen. In certain embodiments, wherein R^{3a} is $-OR^{A3}$, R^{3a} is in the *alpha* or *beta* configuration. In certain embodiments, wherein R^{3a} is $-OR^{A3}$, R^{3a} is in the *alpha* configuration. In certain embodiments, wherein R^{3a} is $-OR^{A3}$, R^{3a} is in the *beta* configuration. In certain embodiments, R^{A3} is hydrogen. In certain embodiments, R^{A3} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl. In certain embodiments, R^{A3} is hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH_2CH_2CH_3$, *i.e.,* to provide a group R^{3a} of formula –OH, $-OCH_3$, $-OCH_2CH_3$, or $-OCH_2CH_2CH_3$.

[00185] As generally defined herein, R^4 is hydrogen, substituted or unsubstituted alkyl, or halogen. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is halogen, *e.g.,* fluoro. In certain embodiments, R^4 is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted

C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl. In certain embodiments, R^4 is C_1 alkyl, *e.g.*, -CH_3 or -CF_3. In certain embodiments, R^4 is hydrogen, -CH_3, or –F. In certain embodiments, wherein ===== represents a single bond, R^4 is a non-hydrogen substitutent in the *alpha* configuration. In certain embodiments, wherein ===== represents a single bond, R^4 is a non-hydrogen substituent in the *beta* configuration.

Group X, R^{5a}, R^{5b}, R^{6a}, and R^{6b} of compounds of formula (I-q)

[00186] As generally defined herein, X is –$C(R^X)_2$– or –O-, wherein R^X is hydrogen or fluorine, or one R^X group and R^{5b} are joined to form a double bond; each of R^{5a} and R^{5b} is independently hydrogen or fluorine; R^{6a} is a non-hydrogen group selected from the group consisting of substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted carbocyclyl, substituted and unsubstituted heterocyclyl, substituted and unsubstituted aryl, and substituted and unsubstituted heteroaryl group, wherein the non-hydrogen group is optionally substituted with fluorine; and R^{6b} is hydrogen or a substituted or unsubstituted alkyl group optionally substituted with fluorine; provided: (1) at least one of R^X, R^{5a}, and R^{5b} is fluorine; or (2) at least one of R^{6a} and R^{6b} is a non-hydrogen group substituted with fluorine; or (3) R^{6a} is a non-hydrogen group comprising between two and ten carbon atoms.

[00187] In certain embodiments, X is –O–. In certain embodiments, X is –CH_2–. In certain embodiments, X is –CF_2–.

[00188] In certain embodiments, at least one of R^{5a} and R^{5b} is hydrogen. In certain embodiments, at least one of R^{5a} and R^{5b} is fluorine. In certain embodiments, R^{5a} and R^{5b} are both hydrogen. In certain embodiments, R^{5a} and R^{5b} are both fluorine. In certain embodiments, R^X and R^{5b} are joined to form a double bond, *e.g., cis* or *trans* double bond.

[00189] In certain embodiments, R^{6a} is a non-hydrogen group, as described herein, which is not substituted with fluorine. In certain embodiments, R^{6a} is substituted or unsubstituted alkyl (*e.g.*, –CH_3, –CH_2CH_3, –$CH(CH_3)_2$), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, or substituted or unsubstituted carbocyclyl (*e.g.*, isopropanol). In certain embodiments, R^{6a} is a non-hydrogen group, as described herein, which is substituted with fluorine.

[00190] In certain embodiments, R^{6a} is a non-hydrogen group, as described herein, and R^{6b} is hydrogen. In certain embodiments, R^{6a} is a non-hydrogen group, as described herein, and R^{6b} is a substituted or unsubstituted alkyl group optionally substituted by fluorine. In certain embodiments, R^{6b} is

an alkyl group which is not substituted with fluorine. In certain embodiments, R^{6a} is an alkyl group which is substituted with fluorine.

[00191] In certain embodiments, R^{6b} is hydrogen. In certain embodiments, R^{6b} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl, optionally substituted by fluorine. In certain embodiments, R^{6b} is C_1 alkyl optionally substituted by fluorine, *e.g.,* $–CH_3$ or $–CF_3$.

[00192] In certain embodiments, R^{6a} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, substituted or unsubstituted C_{2-3}alkyl, substituted or unsubstituted C_{3-4}alkyl, substituted or unsubstituted C_{4-5}alkyl, or substituted or unsubstituted C_{5-6}alkyl. Exemplary R^{6a} C_{1-6}alkyl groups include, but are not limited to, substituted or unsubstituted methyl (C_1), substituted or unsubstituted ethyl (C_2), substituted or unsubstituted n–propyl (C_3), substituted or unsubstituted isopropyl (C_3), substituted or unsubstituted n–butyl (C_4), substituted or unsubstituted tert–butyl (C_4), substituted or unsubstituted sec–butyl (C_4), substituted or unsubstituted iso–butyl (C_4), substituted or unsubstituted n–pentyl (C_5), substituted or unsubstituted 3–pentanyl (C_5), substituted or unsubstituted amyl (C_5), substituted or unsubstituted neopentyl (C_5), substituted or unsubstituted 3–methyl–2–butanyl (C_5), substituted or unsubstituted tertiary amyl (C_5), substituted or unsubstituted n–hexyl (C_6). In certain embodiments, R^{6a} is alkyl, as described above, substituted with one or more fluorines, *e.g.,* 1, 2, 3, 4, or more fluorines. In certain embodiments, R^{6a} is $–CF_3$, $–CH_2F$, $–CHF_2$, difluoroethyl, or 2,2,2–trifluoro–1,1–dimethyl–ethyl). In certain embodiments, R^{6a} is alkyl, as described above, substituted with one or more $–OR^{A6}$ groups, wherein R^{A6} is hydrogen or substituted or unsubstitued alkyl. In certain embodiments, R^{6a} is $–CH_2OR^{A6}$, $–CH_2CH_2OR^{A6}$, or $–CH_2CH_2CH_2OR^{A6}$, *e.g.,* $–CH_2OCH_3$, $–CH_2CH_2OCH_3$, or $–CH_2CH_2CH_2OCH_3$.

[00193] In certain embodiments, R^{6a} is substituted or unsubstituted alkenyl, *e.g.,* substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-3}alkenyl, substituted or unsubstituted C_{3-4}alkenyl, substituted or unsubstituted C_{4-5}alkenyl, or substituted or unsubstituted C_{5-6}alkenyl, optionally substituted with fluorine. In certain embodiments, R^{6a} is substituted or unsubstituted vinyl (C_2) or substituted or unsubstituted allyl (C_3).

[00194] In certain embodiments, R^{6a} is substituted or unsubstituted alkynyl, *e.g.,* substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{2-3}alkynyl, substituted or unsubstituted C_{3-4}alkynyl, substituted or unsubstituted C_{4-5}alkynyl, or substituted or unsubstituted C_{5-6}alkynyl, optionally substituted with fluorine. In certain embodiments, R^{6a} is substituted or unsubstituted ethynyl (C_2) or substituted or unsubstituted propargyl (C_3).

[00195] In certain embodiments, R^{6a} is substituted or unsubstituted carbocyclyl, *e.g.,* substituted or unsubstituted C_{3-6}carbocyclyl, substituted or unsubstituted C_{3-4}carbocyclyl, substituted or unsubstituted C_{4-5} carbocyclyl, or substituted or unsubstituted C_{5-6} carbocyclyl, optionally substituted with fluorine. In certain embodiments, R^{6a} is substituted or unsubstituted cyclopropyl.

[00196] In certain embodiments, R^{6a} is substituted or unsubstituted heterocyclyl, *e.g.,* substituted or unsubstituted C_{3-6} heterocyclyl, substituted or unsubstituted C_{3-4} heterocyclyl, substituted or unsubstituted C_{4-5} heterocyclyl, or substituted or unsubstituted C_{5-6} heterocyclyl, optionally substituted with fluorine.

[00197] In certain embodiments, R^{6a} is substituted or unsubstituted aryl, *e.g.,* substituted or unsubstituted phenyl, optionally substituted with fluorine.

[00198] In certain embodiments, R^{6a} is substituted or unsubstituted heteroaryl, *e.g.,* optionally substituted 5– to 6–membered heteroaryl, optionally substituted with fluorine.

[00199] In certain embodiments, R^{6a} is a non-hydrogen group comprising between two and ten carbon atoms, *e.g.,* between two and nine, two and eight, two and seven, two and six, two and five, two and four, or two and three carbon atoms, inclusive. For example, in certain embodiments, R^{6a} is substituted or unsubstituted C_{2-3} alkyl, substituted or unsubstituted C_{2-3} alkenyl, substituted or unsubstituted C_{2-3} alkynyl, or substituted or unsubstituted C_3 carbocyclyl.

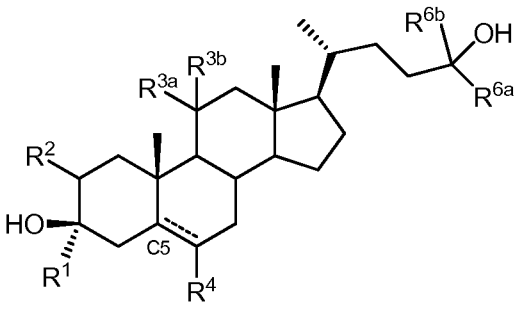
[00200] In certain embodiments, wherein at least one of R^X, R^{5a}, and R^{5b} is fluorine; or at least one of R^{6a} and R^{6b} is a non-hydrogen group substituted with fluorine; R^{6a} is substituted or unsubstituted C_{1-3} alkyl, substituted or unsubstituted C_{1-3} alkenyl, substituted or unsubstituted C_{1-3} alkynyl, or substituted or unsubstituted C_3 carbocyclyl.

[00201] In certain embodiments, R^{6a} and R^{6b} are the same group. In certain embodiments, R^{6a} and R^{6b} are different groups, and the carbon to R^{6a} is attached is in the (S) or (R) configuration. In certain embodiments, the carbon to which R^{6a} is attached is in the (S) configuration. In certain embodiments, the carbon to which R^{6a} is attached is in the (R) configuration. In certain embodiments, R^{6a} is $–CF_3$ and R^{6b} is hydrogen or C_{1-4} alkyl. In certain embodiments, R^{6a} is a non-hydrogen group substituted with fluorine, and R^{6b} is $–CH_3$. In certain embodiments, R^{6a} is substituted with one or more $–OR^{A6}$ groups, wherein R^{A6} is hydrogen or substituted or unsubstitued alkyl. In certain embodiments, R^{6a} is a substituted or unsubstituted C_{2-4} alkyl, substituted or unsubstituted C_{2-3} alkenyl, substituted or unsubstituted C_{2-3} alkynyl, or substituted or unsubstituted C_3 carbocyclyl, and R^{6b} is $–CH_3$. In certain embodiments, R^{6a} is a unsubstituted C_{2-4} alkyl, unsubstituted C_{2-3} alkenyl, or unsubstituted C_{2-3} alkynyl, or unsubstituted C_3 carbocyclyl, and R^{6b} is $–CH_3$. In certain embodiments, R^{6a} is a non-hydrogen group substituted with fluorine, and R^{6b} is $–CH_3$.

Various Combinations of Certain Embodiments

[00202] Various combinations of certain embodiments are futher contemplated herein.

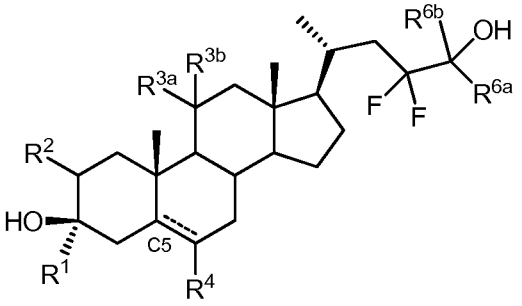
[00203] For example, in certain embodiments, wherein X is $-CH_2-$ and R^{5a} and R^{5b} are both hydrogen, provided is a compound of Formula (**I-qa**):



(**I-qa**)

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^{6a} is a non-hydrogen group comprising between two and ten carbon atoms. In certain embodiments, at least one of R^{6a} and R^{6b} is a non-hydrogen group substituted with fluorine. In certain embodiments, the carbon to which R^{6a} is attached is in the (S) configuration. In certain embodiments, the carbon to which R^{6a} is attached is in the (R) configuration. In certain embodiments, R^{6a} is methyl (C_1) optionally substituted with one or more fluorines, *e.g.*, $-CH_3$ or $-CF_3$. In certain embodiments, R^{6a} is substituted or unsubstituted ethyl (C_2), substituted or unsubstituted n–propyl (C_3), or substituted or unsubstituted isopropyl (C_3). In certain embodiments, R^{6a} is $-CH_2OR^{A6}$, $-CH_2CH_2OR^{A6}$, or $-CH_2CH_2CH_2OR^{A6}$. In certain embodiments, R^{6a} is substituted or unsubstituted vinyl (C_2) or substituted or unsubstituted allyl (C_3). In certain embodiments, R^{6a} is substituted or unsubstituted ethynyl (C_2) or substituted or unsubstituted propargyl (C_3). In certain embodiments, R^{6a} is substituted or unsubstituted cyclopropyl. In certain embodiments, R^{6b} is hydrogen. In certain embodiments, R^{6b} is $-CH_3$ or $-CF_3$. In certain embodiments, ----- represents a single bond, and the hydrogen at C5 is *alpha*. In certain embodiments, ----- represents a double bond. In certain embodiments, R^1 is $-CH_3$ or $-CH_2CH_3$. In certain embodiments, R^2 is hydrogen, –OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, cyclopropyl, fluoro, or chloro. In certain embodiments, R^2 is a non-hydrogen substitutent in the *alpha* configuration. In certain embodiments, R^2 is a non-hydrogen substituent in the *beta* configuration. In certain embodiments, R^{3a} and R^{3b} are both hydrogen. In certain embodiments, R^{3a} and R^{3b} are joined to form =O (oxo). In certain embodiments, R^4 is hydrogen.

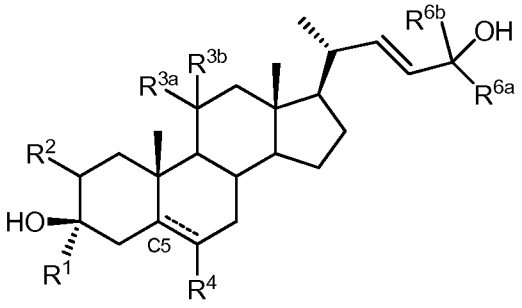
[00204] In certain embodiments, wherein X is $-CH_2-$ and R^{5a} and R^{5b} are both fluorine, provided is a compound of Formula (**I-qb**):



(I-qb)

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^{6a} is a non-hydrogen group comprising between two and ten carbon atoms. In certain embodiments, at least one of R^{6a} and R^{6b} is a non-hydrogen group substituted with fluorine. In certain embodiments, the carbon to which R^{6a} is attached is in the (S) configuration. In certain embodiments, the carbon to which R^{6a} is attached is in the (R) configuration. In certain embodiments, R^{6a} is methyl (C_1), optionally substituted with one or more fluorines, *e.g.*, $-CH_3$ or $-CF_3$. In certain embodiments, R^{6a} is substituted or unsubstituted ethyl (C_2), substituted or unsubstituted n–propyl (C_3), or substituted or unsubstituted isopropyl (C_3). In certain embodiments, R^{6a} is $-CH_2OR^{A6}$, $-CH_2CH_2OR^{A6}$, or $-CH_2CH_2CH_2OR^{A6}$. In certain embodiments, R^{6a} is substituted or unsubstituted vinyl (C_2) or substituted or unsubstituted allyl (C_3). In certain embodiments, R^{6a} is substituted or unsubstituted ethynyl (C_2) or substituted or unsubstituted propargyl (C_3). In certain embodiments, R^{6a} is substituted or unsubstituted cyclopropyl. In certain embodiments, R^{6b} is hydrogen. In certain embodiments, R^{6b} is $-CH_3$ or $-CF_3$. In certain embodiments, ===== represents a single bond, and the hydrogen at C5 is *alpha*. In certain embodiments, ===== represents a double bond. In certain embodiments, R^1 is $-CH_3$ or $-CH_2CH_3$ In certain embodiments, R^2 is hydrogen, –OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, cyclopropyl, fluoro, or chloro. In certain embodiments, R^2 is a non-hydrogen substitutent in the *alpha* configuration. In certain embodiments, R^2 is a non-hydrogen substituent in the *beta* configuration. In certain embodiments, R^{3a} and R^{3b} are both hydrogen. In certain embodiments, R^{3a} and R^{3b} are joined to form =O (oxo). In certain embodiments, R^4 is hydrogen.

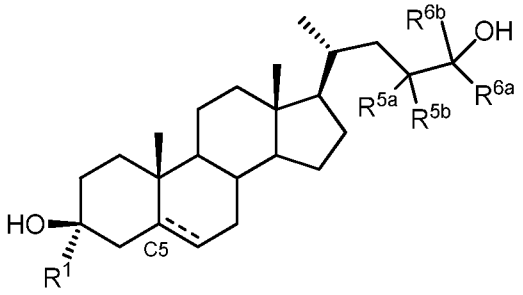
[00205] In certain embodiments, wherein X is $-C(R^X)_2-$ and one R^X group and R^{5b} are joined to form a *trans* double bond, provided is a compound of Formula (**I-qc**):



(I-qc)

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^{6a} is a non-hydrogen group comprising between two and ten carbon atoms. In certain embodiments, at least one of R^{6a} and R^{6b} is a non-hydrogen group substituted with fluorine. In certain embodiments, the carbon to which R^{6a} is attached is in the (S) configuration. In certain embodiments, the carbon to which R^{6a} is attached is in the (R) configuration. In certain embodiments, R^{6a} is methyl (C_1) optionally substituted with one or more fluorines, *e.g.*, $-CH_3$ or $-CF_3$. In certain embodiments, R^{6a} is substituted or unsubstituted ethyl (C_2), substituted or unsubstituted n–propyl (C_3), or substituted or unsubstituted isopropyl (C_3). In certain embodiments, R^{6a} is $-CH_2OR^{A6}$, $-CH_2CH_2OR^{A6}$, or $-CH_2CH_2CH_2OR^{A6}$. In certain embodiments, R^{6a} is substituted or unsubstituted vinyl (C_2) or substituted or unsubstituted allyl (C_3). In certain embodiments, R^{6a} is substituted or unsubstituted ethynyl (C_2) or substituted or unsubstituted propargyl (C_3). In certain embodiments, R^{6a} is substituted or unsubstituted cyclopropyl. In certain embodiments, R^{6b} is hydrogen. In certain embodiments, R^{6b} is $-CH_3$ or $-CF_3$. In certain embodiments, ===== represents a single bond, and the hydrogen at C5 is *alpha*. In certain embodiments, ===== represents a double bond. In certain embodiments, R^1 is $-CH_3$ or $-CH_2CH_3$. In certain embodiments, R^2 is hydrogen, –OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, cyclopropyl, fluoro, or chloro. In certain embodiments, R^2 is a non-hydrogen substitutent in the *alpha* configuration. In certain embodiments, R^2 is a non-hydrogen substituent in the *beta* configuration. In certain embodiments, R^{3a} and R^{3b} are both hydrogen. In certain embodiments, R^{3a} and R^{3b} are joined to form =O (oxo). In certain embodiments, R^4 is hydrogen.

[00206] In certain embodiments, the compound of Formula (**I-q**) is selected from a compound of Formula (**I-qd**):

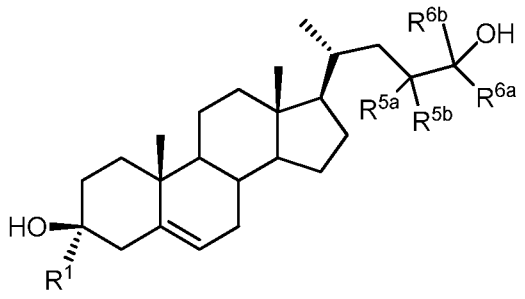


(I-qd)

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^{6a} is a non-hydrogen group comprising between two and ten carbon atoms. In certain embodiments, at least one of R^{6a} and R^{6b} is a non-hydrogen group substituted with fluorine. In certain embodiments, the carbon to which R^{6a} is attached is in the (S) configuration. In certain embodiments, the carbon to which R^{6a} is attached is in the (R) configuration. In certain embodiments, R^{6a} is methyl (C_1) optionally substituted with one or more fluorines, *e.g.*, $-CH_3$ or $-CF_3$. In certain embodiments, R^{6a} is substituted or unsubstituted ethyl (C_2),

substituted or unsubstituted n–propyl (C_3), or substituted or unsubstituted isopropyl (C_3). In certain embodiments, R^{6a} is $–CH_2OR^{A6}$, $–CH_2CH_2OR^{A6}$, or $–CH_2CH_2CH_2OR^{A6}$. In certain embodiments, R^{6a} is substituted or unsubstituted vinyl (C_2) or substituted or unsubstituted allyl (C_3). In certain embodiments, R^{6a} is substituted or unsubstituted ethynyl (C_2) or substituted or unsubstituted propargyl (C_3). In certain embodiments, R^{6a} is substituted or unsubstituted cyclopropyl. In certain embodiments, R^{6b} is hydrogen. In certain embodiments, R^{6b} is $–CH_3$ or $–CF_3$. In certain embodiments, ===== represents a single bond, and the hydrogen at C5 is *alpha*. In certain embodiments, ===== represents a double bond. In certain embodiments, R^1 is $–CH_3$ or $–CH_2CH_3$.

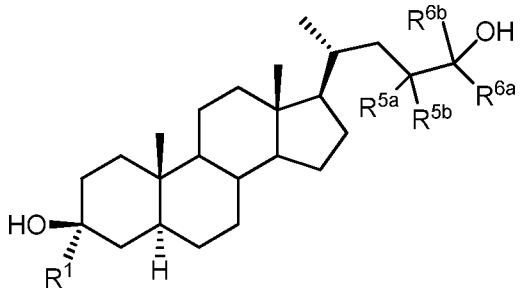
[00207] In certain embodiments, the compound of Formula (**I-q**) is selected from a compound of Formula (**I-qe**):



(**I-qe**)

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^{6a} is a non-hydrogen group comprising between two and ten carbon atoms. In certain embodiments, at least one of R^{6a} and R^{6b} is a non-hydrogen group substituted with fluorine. In certain embodiments, the carbon to which R^{6a} is attached is in the (S) configuration. In certain embodiments, the carbon to which R^{6a} is attached is in the (R) configuration. In certain embodiments, R^{6a} is methyl (C_1) optionally substituted with one or more fluorines, *e.g.*, $-CH_3$ or $-CF_3$. In certain embodiments, R^{6a} is substituted or unsubstituted ethyl (C_2), substituted or unsubstituted n–propyl (C_3), or substituted or unsubstituted isopropyl (C_3). In certain embodiments, R^{6a} is $–CH_2OR^{A6}$, $–CH_2CH_2OR^{A6}$, or $–CH_2CH_2CH_2OR^{A6}$. In certain embodiments, R^{6a} is substituted or unsubstituted vinyl (C_2) or substituted or unsubstituted allyl (C_3). In certain embodiments, R^{6a} is substituted or unsubstituted ethynyl (C_2) or substituted or unsubstituted propargyl (C_3). In certain embodiments, R^{6a} is substituted or unsubstituted cyclopropyl. In certain embodiments, R^{6b} is hydrogen. In certain embodiments, R^{6b} is $–CH_3$ or $–CF_3$. In certain embodiments, R^1 is $–CH_3$ or $–CH_2CH_3$.

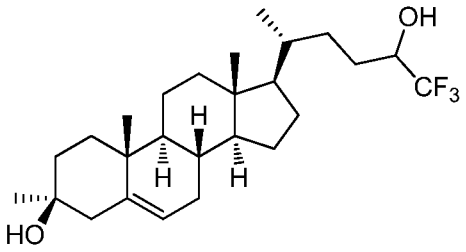
[00208] In certain embodiments, the compound of Formula (**I-q**) is selected from a compound of Formula (**I-qf**):



(I-qf)

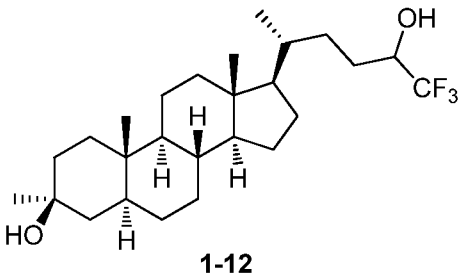
or a pharmaceutically acceptable salt thereof. In certain embodiments, R^{6a} is a non-hydrogen group comprising between two and ten carbon atoms. In certain embodiments, at least one of R^{6a} and R^{6b} is a non-hydrogen group substituted with fluorine. In certain embodiments, the carbon to which R^{6a} is attached is in the (S) configuration. In certain embodiments, the carbon to which R^{6a} is attached is in the (R) configuration. In certain embodiments, R^{6a} is methyl (C_1) optionally substituted with one or more fluorines, *e.g.*, $-CH_3$ or $-CF_3$. In certain embodiments, R^{6a} is substituted or unsubstituted ethyl (C_2), substituted or unsubstituted n–propyl (C_3), or substituted or unsubstituted isopropyl (C_3). In certain embodiments, R^{6a} is $-CH_2OR^{A6}$, $-CH_2CH_2OR^{A6}$, or $-CH_2CH_2CH_2OR^{A6}$. In certain embodiments, R^{6a} is substituted or unsubstituted vinyl (C_2) or substituted or unsubstituted allyl (C_3). In certain embodiments, R^{6a} is substituted or unsubstituted ethynyl (C_2) or substituted or unsubstituted propargyl (C_3). In certain embodiments, R^{6a} is substituted or unsubstituted cyclopropyl. In certain embodiments, R^{6b} is hydrogen. In certain embodiments, R^{6b} is $-CH_3$ or $-CF_3$. In certain embodiments, R^1 is $-CH_3$ or $-CH_2CH_3$.

[00209] In certain embodiments, a compound of Formula (**I-q**) is selected from the group consisting of:



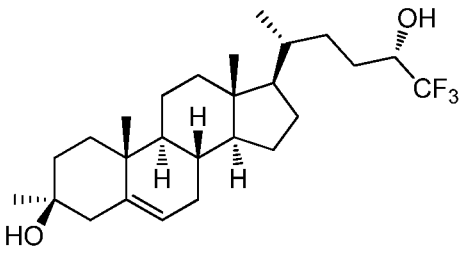
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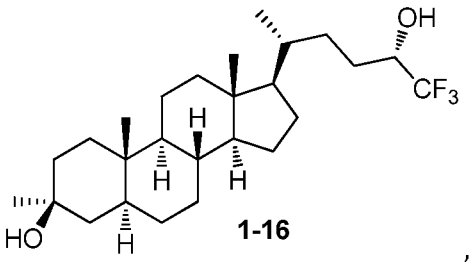


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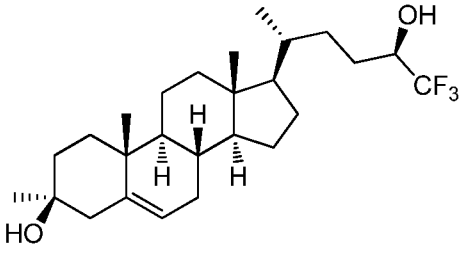
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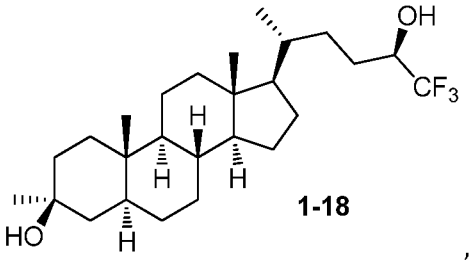
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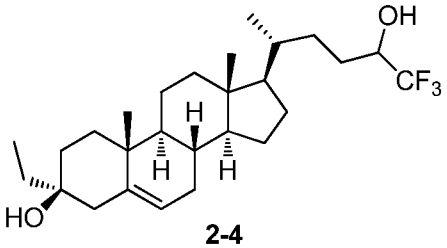
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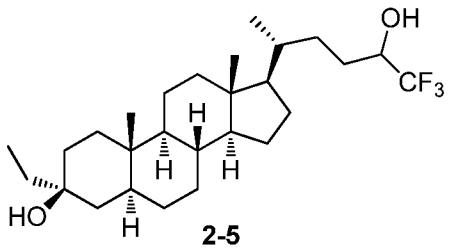
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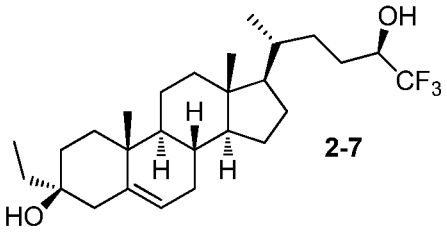
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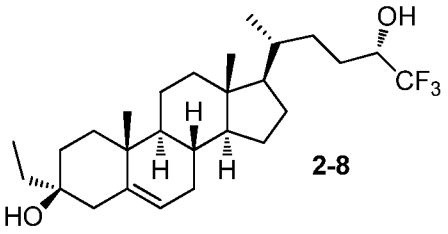
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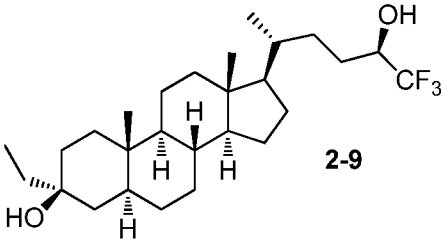
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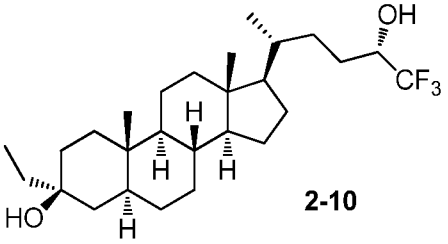
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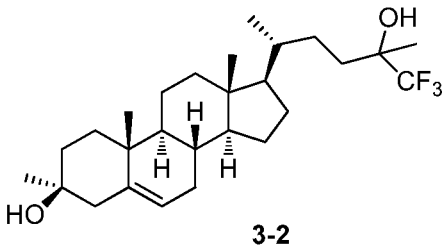
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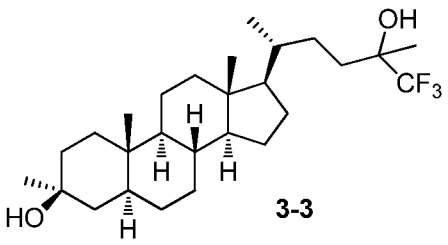


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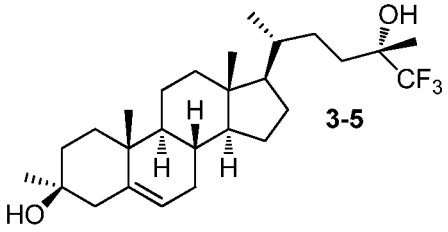
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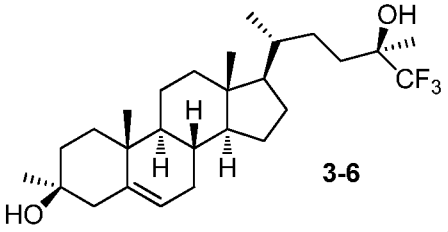
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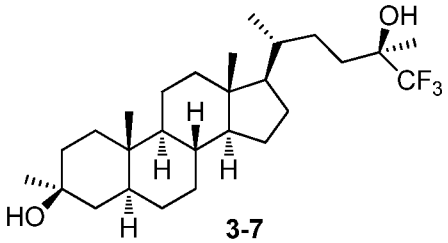
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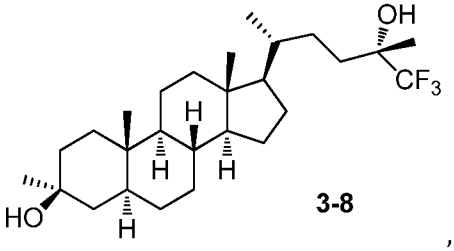
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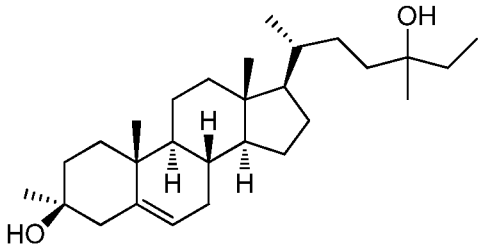
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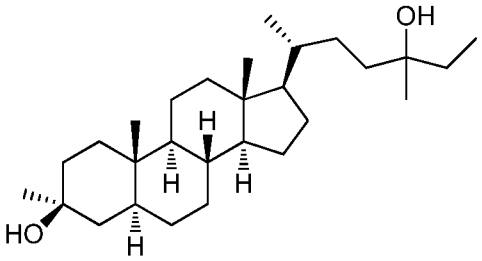
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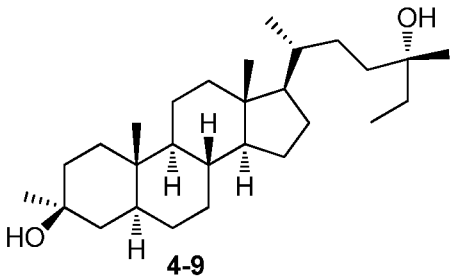
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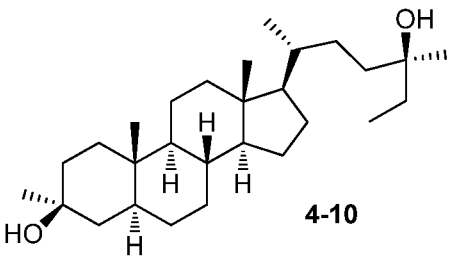
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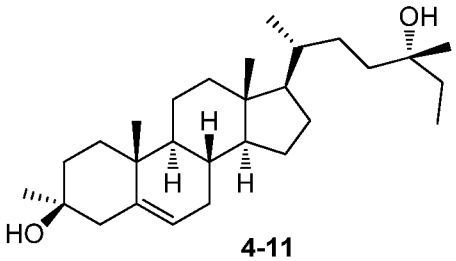
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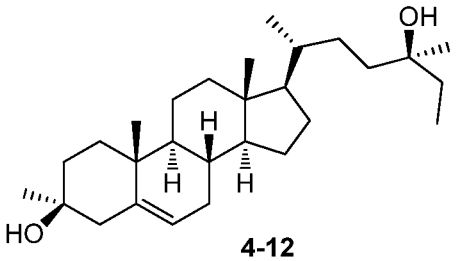


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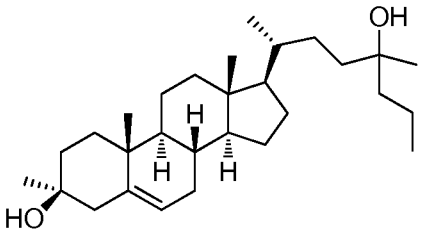
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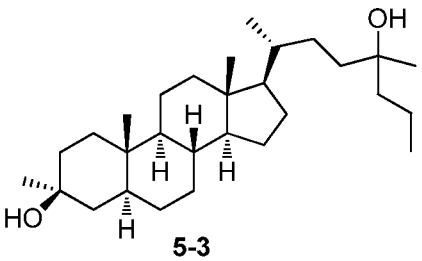
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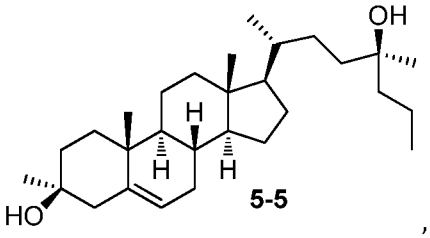
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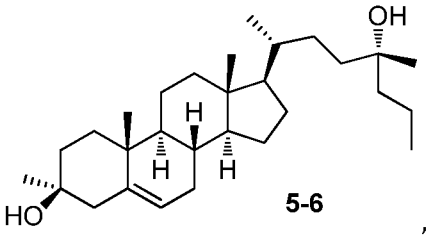
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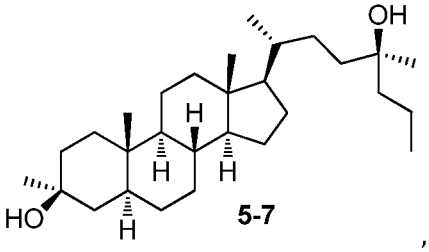
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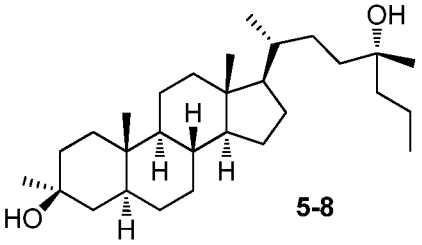
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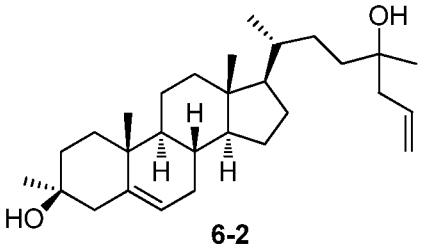
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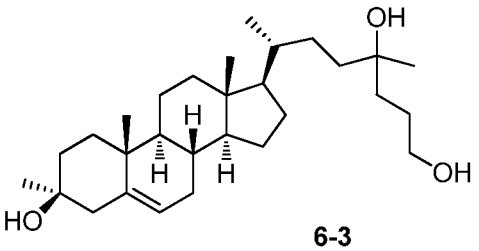
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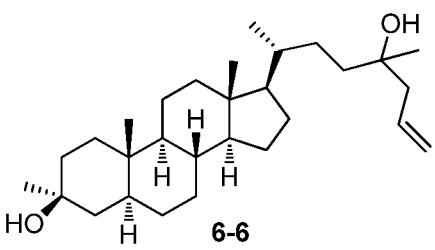
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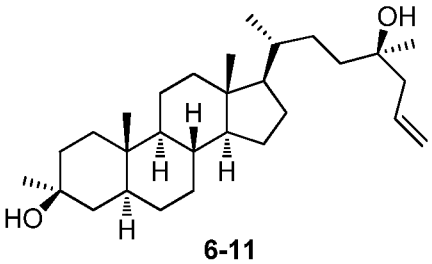
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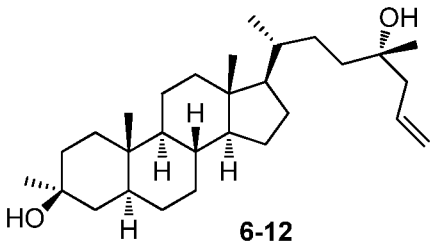
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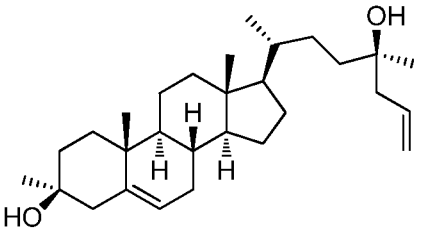
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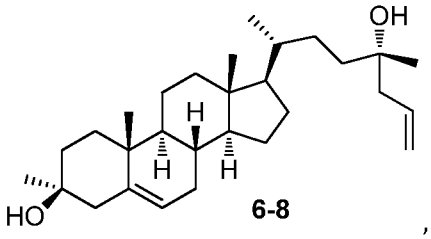
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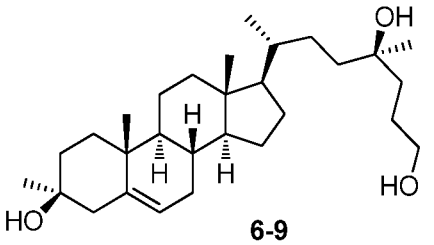
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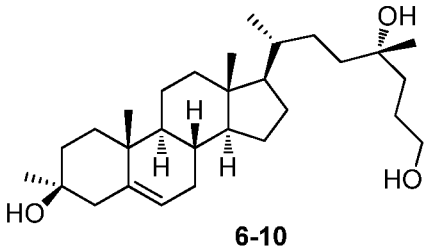
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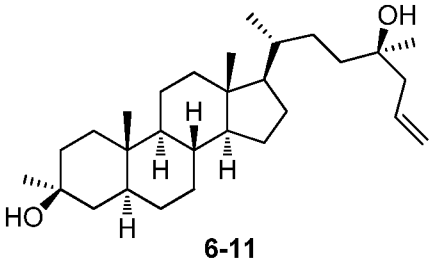
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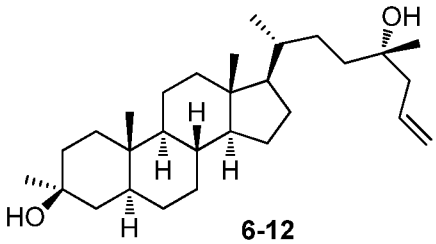
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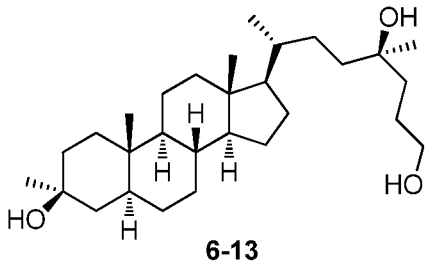
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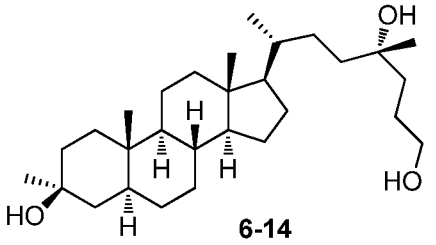
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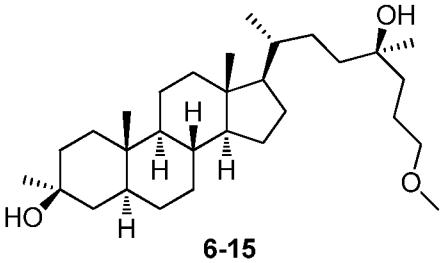
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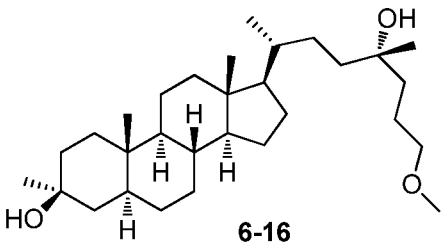
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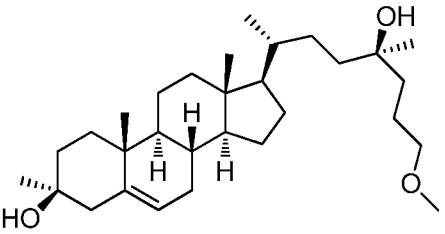


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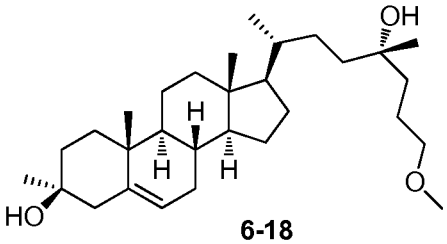
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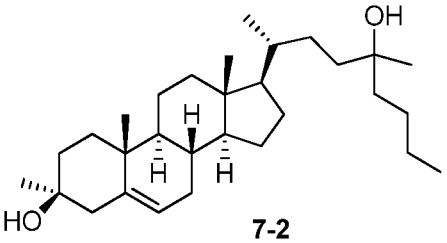
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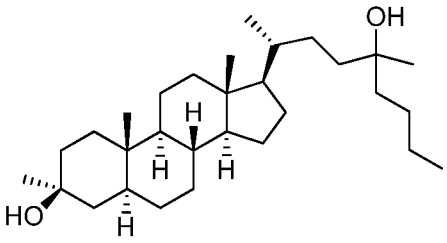
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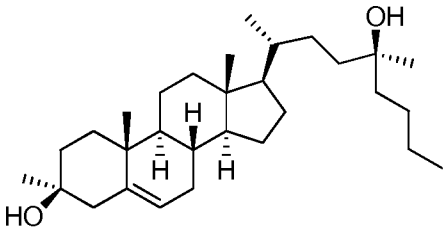
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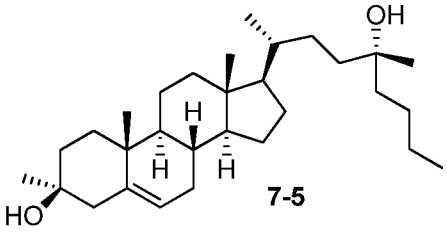
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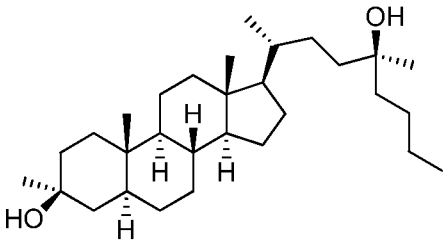
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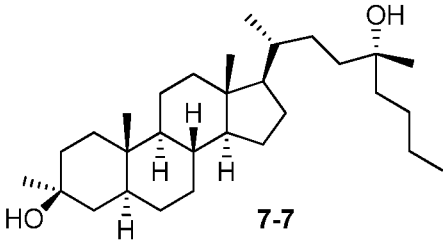
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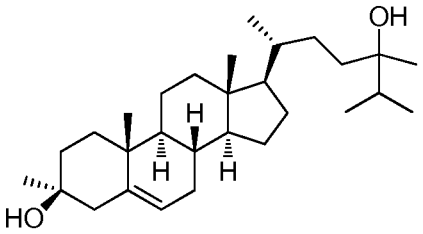
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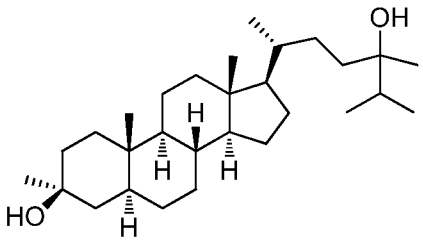
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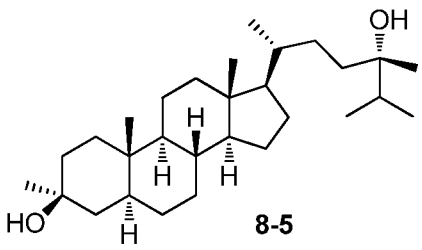
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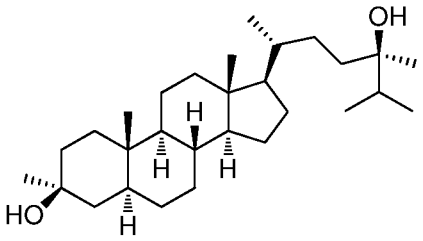
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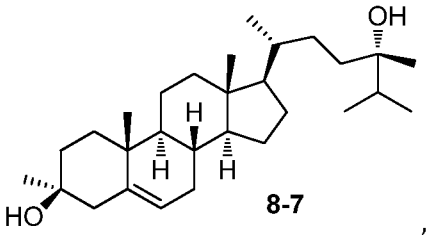
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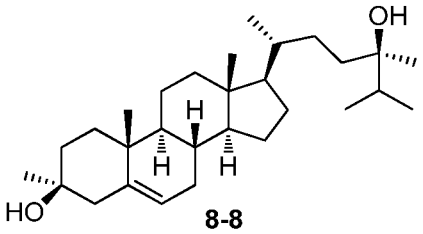
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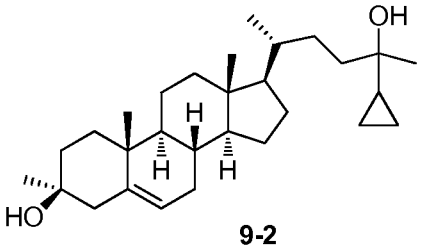
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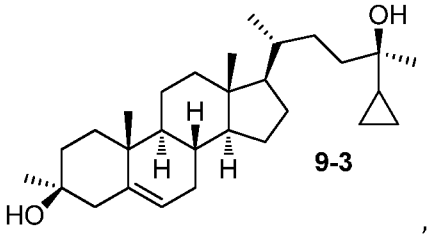
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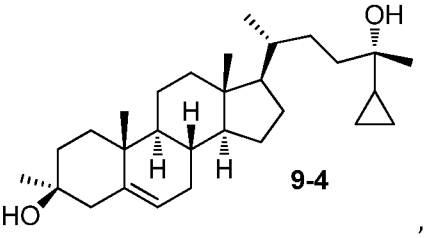
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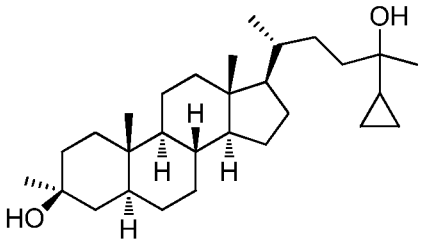
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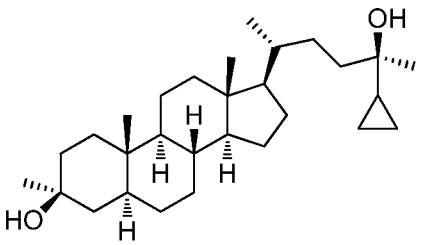


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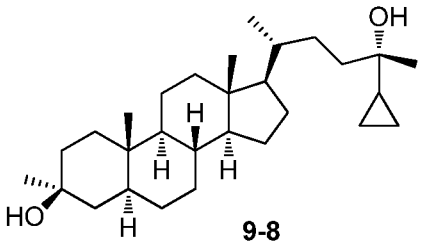
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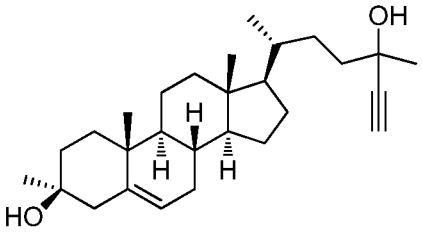
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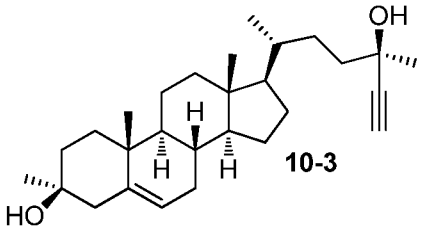
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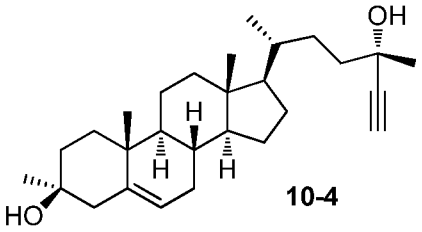
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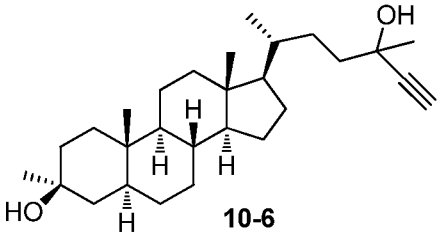
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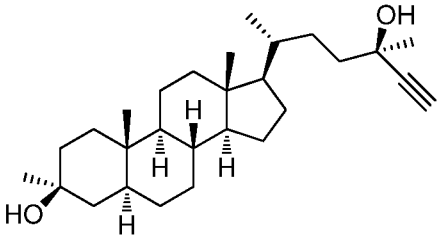
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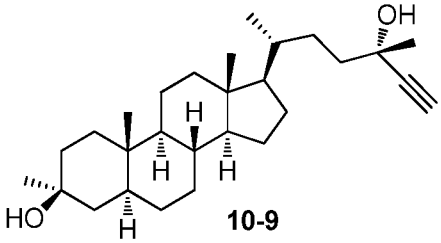
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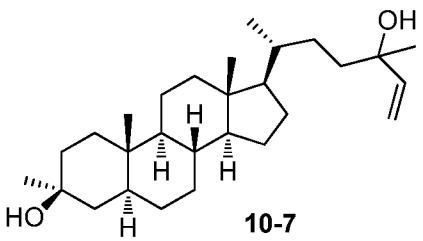
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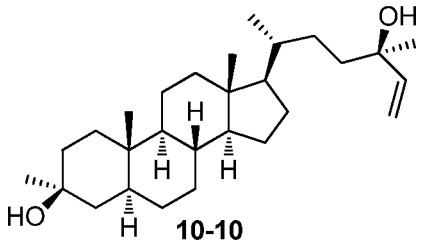
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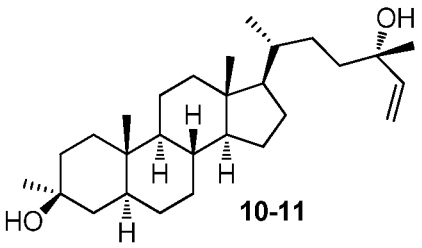
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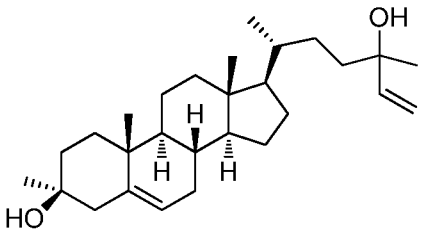
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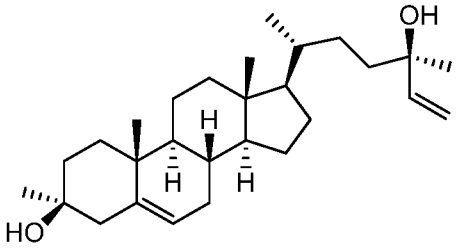
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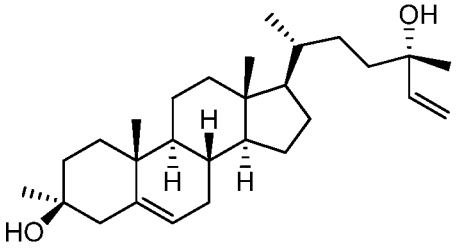
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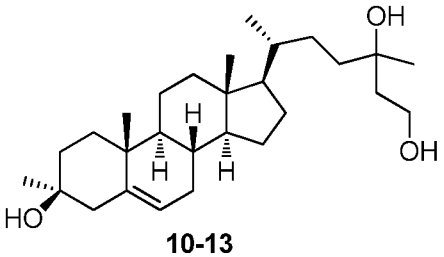
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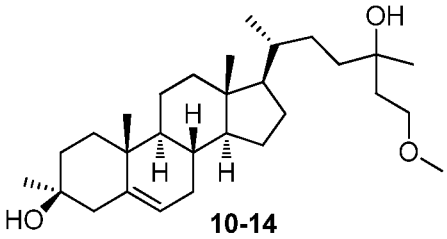
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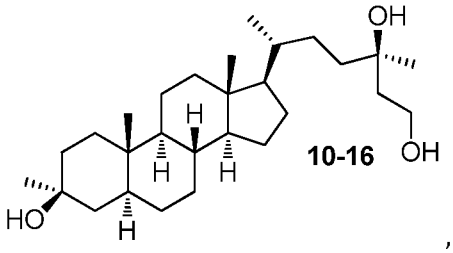
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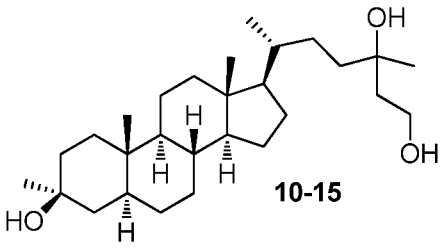
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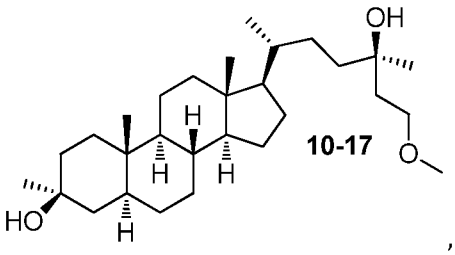
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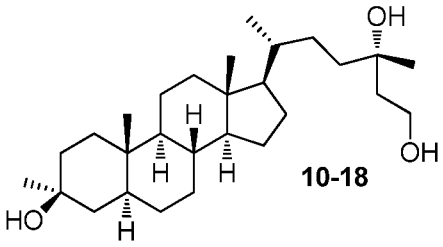
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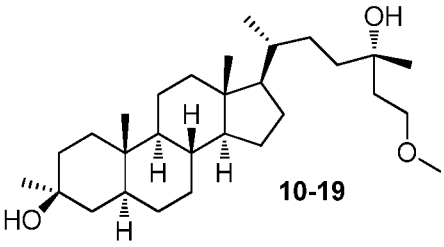
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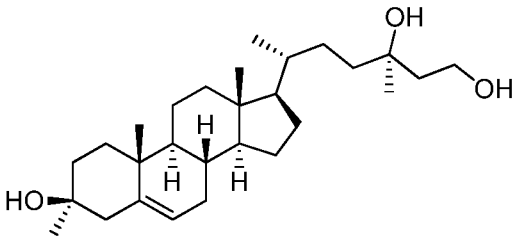
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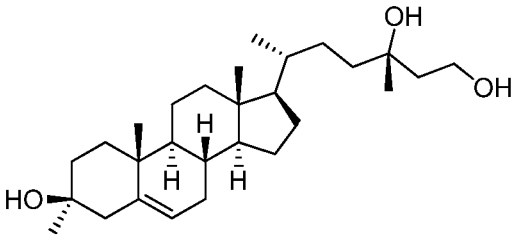
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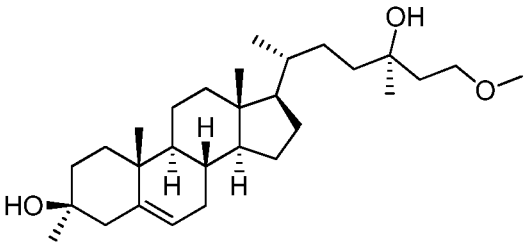
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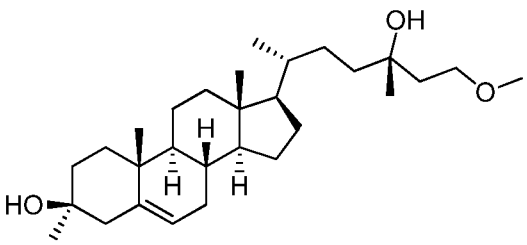
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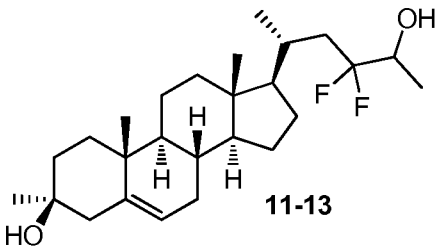
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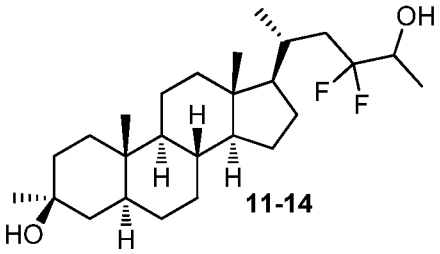
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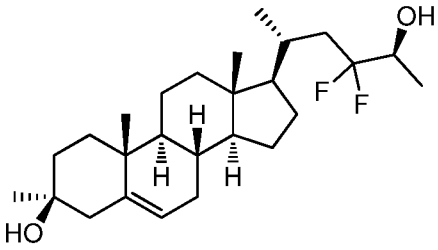
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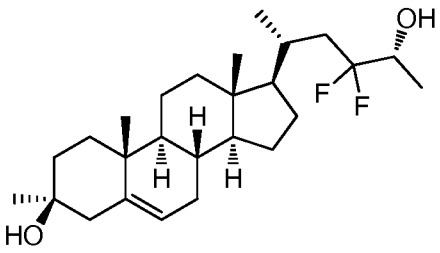
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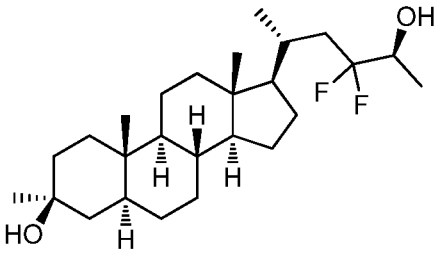
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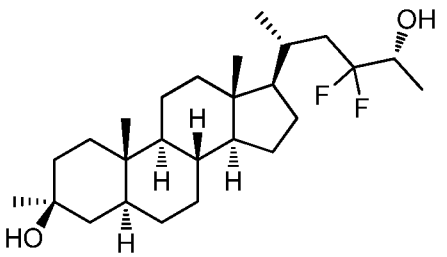
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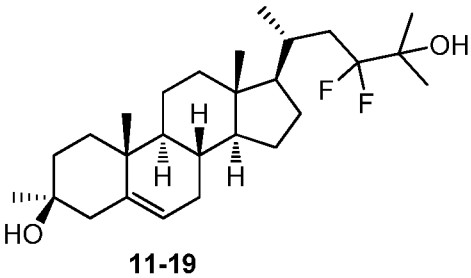
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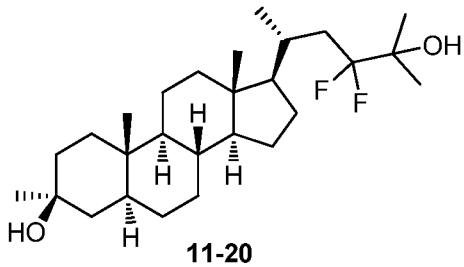
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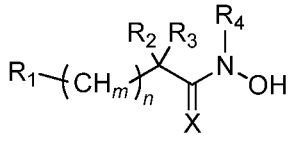


11-20

and pharmaceutically acceptable salts thereof.

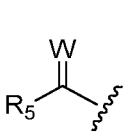
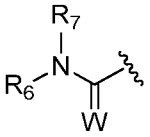
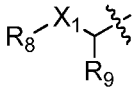
[00210] Compounds of the Formula (**I**), and related compounds are described in WO2013/036835, WO2014/160480, and WO2014/160441, the contents of which are incorporated in their entirety.

[00211] Exemplary compounds of the invention also include compounds of the Formula (**II-a**):



(**II-a**),

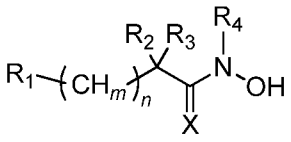
or a pharmaceutically acceptable salt thereof, where m may be an integer with a value ranging from zero to two; n may be an integer with a value ranging from one to six; R_2 and R_3 may include an amino group, a small alkyl, or a halide. One of either R_2 or R_3 may include an amino group and the other a small alkyl such as methyl, ethyl propyl, or halogen group such as fluoro, chloro and bromo. R_4 may include a hydrogen, small alkyl, substituted alkyl; X may include an oxygen or sulfur; R_1 and R_2 may include a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, phenyl, substituted phenyl, heterocyclic, halide, nitrate, nitrite, nitrile, hydroxyl, thiol, sulfonamide, amine, guanidine, isoguanidine, cyanate,

isocyanate, and carboxylate, or one of the following structural formulae: , , and ;

where X may be oxygen, sulfur, —S(O)— or —$S(O)_2$—, =NH, =NCN, X_1 is O, S, —S(O)— or —$S(O)_2$—;

W may be oxygen, sulfur, or pharmaceutically-acceptable salts thereof; R_5 may include an alkoxy, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl; R_6 and R_7 may include a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl and substituted cycloalkenyl; or R_6 and R_7 may be joined to form an alkylene or substituted alkylene group having from two to ten carbon atoms; R_8 may include an alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl and substituted cycloalkenyl; and R_9 may include a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl and substituted cycloalkenyl; or R_8 and R_9 may be joined to form an alkylene or substituted alkylene group having from two to ten carbon atoms; or R_1 and R_2 may be selected from the group consisting of CH_3O—, C_5H_9O—, $C_6H_5SO_2O$—, CH_3CO—, $C_6H_5SO_2NH$—, $(C_6H_5SO_2)_2N$—, C_4H_8N—, $C_5H_{10}N$—, and $C_5H_{11}NN$—.

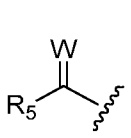
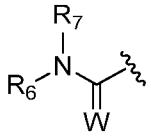
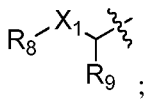
[00212] Exemplary compounds of the invention also include compounds of the Formula (**II-b**):



(**II-b**)

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from the group consisting of $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$substituted alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$substituted alkenyl, $C_{2\text{-}6}$alkynyl, $C_{2\text{-}6}$substituted alkynyl, $C_{3\text{-}6}$cycloalkyl, $C_{3\text{-}6}$substituted cycloalkyl, phenyl, cyano, hydroxyl, thiol, sulfonamide, amine, or:

, , and ;

X is oxygen or sulfur;

X_1 is O, S, —S(O)— or —$S(O)_2$—;

W is oxygen or sulfur;

R_5 is selected from the group consisting of alkoxy, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl and substituted cycloalkenyl;

R_6 and R_7 are each independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}substituted alkyl, C_{2-6}alkenyl, C_{2-6}substituted alkenyl, C_{2-6}alkynyl, C_{2-6}substituted alkynyl, C_{3-6}cycloalkyl, C_{3-6}6substituted cycloalkyl; or R_6 and R_7 are joined to form an C_{3-10}-cycloalkyl;

R_8 is $_{\text{selected}}$ from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}substituted alkyl, C_2-6alkenyl, C_{2-6}substituted alkenyl, C_{2-6}alkynyl, C_{2-6}substituted alkynyl, C_{3-6}cycloalkyl, C_{3-6}6substituted cycloalkyl; and

R_9 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}substituted alkyl, C_{2-6}alkenyl, C_{2-6}substituted alkenyl, C_{2-6}alkynyl, C_{2-6}substituted alkynyl, C_{3-6}cycloalkyl, C_{3-6}6substituted cycloalkyl;

R_2 is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R_3 is selected from the group consisting of C_{1-6}alkyl-NH—, NH_2—, -alkyl-C(O)—NH—, $C_6H_5SO_2NH$—, $(C_6H_5SO_2)_2N$—, C_4H_8N—, and $C_5H_{11}NN$—;

R_4 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}substituted alkyl.

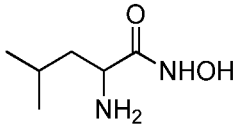
[00213] In some embodiments, R_2 may be hydrogen. In another embodiment, R_4 may be H, or R_4 may be a lower alkyl group, *e.g.,* methyl, ethyl, propyl, isobutyl, t-butyl, n-butyl, isopropyl, etc.

[00214] In certain embodiments, X is oxygen. In another embodiment, R_3 may be NH_2 or CH_3—C(O)—NH—.

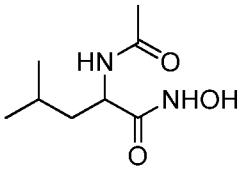
[00215] R_1 may be an alkyl group, e.g. a straight or branched alkyl, such as iso-butyl, propyl, ethyl, methyl, t-butyl, n-butyl, etc. In some embodiments, R_2 and R_3 are connected to a chiral center.

[00216] In some embodiments, the 3,4,5,-trisubstituted aryl amino hydroxamic acid may include one or more chiral centers. Such compounds may be prepared as a racemic mixture. If desired, however, such compounds may be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers and enriched mixtures of the alkyl amino hydroxamic acid of Formula (**II-a**) and (**II-b**) are included within the scope of the present disclosure. Pure stereoisomers or enriched mixtures may be prepared using, for example, optically active starting materials or stereoselective reagents well known in the art. Alternatively, racemic mixtures of such compounds may be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

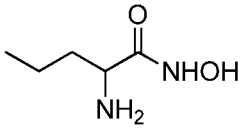
[00217] In some embodiments, the compound is selected from:



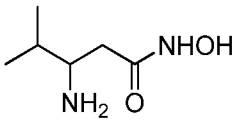
(AK-10), or 2-amino-N-hydroxy-4-methylpentamide (Salt TFA);



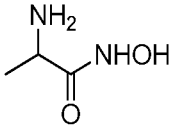
(AK-12), or 2-acetoamido-N-hydroxy-4-methylpentamide;



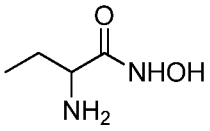
(AK-25), or 2-amino-N-hydroxypentamide (Salt TFA);



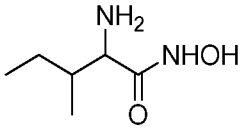
(AK-26), or 3-amino-N-hydroxy-4-methylpentamide (Salt TFA);



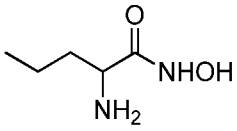
(AK-27), or 2-amino-N-hydroxypropanamide (Salt TFA);



(AK-28), or 2-amino-N-hydroxybutanamide (Salt TFA);



(AK-29), or 2-amino-N-hydroxy-3-methylpentamide (Salt TFA);

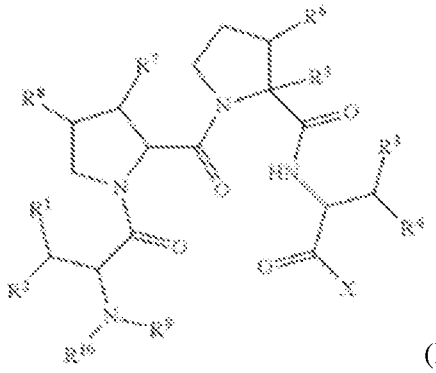


(AK-30), or 2-amino-N-hydroxy-4-methylpentamide (Salt TFA),

and pharmaceutically acceptable salts thereof.

[00218] Compounds of the Formula (**II-a**) and (**II-b**), and related compounds are described in US20140045943, the contents of which are incorporated in its entirety.

[00219] Exemplary compounds of the invention also include a compound of the Formula (**III**):



(III)

and pharmaceutically acceptable salts, stereoisomers, metabolites, and hydrates thereof, wherein:

R^1, R^2, R^3, and R^4 may be independently selected from the group consisting of hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted aryl; substituted or unsubstituted heteroaryl; —OR^x; —NO_2; —N_3; —CN; —SCN; —SR^x; —$C(O)R^x$; —$CO_2(R^x)$; —$C(O)N(R^x)_2$; —$C(NR^x)N(R^x)_2$; —$OC(O)R^x$; —OCO_2R^x; —$OC(O)N(R^x)_2$; —$N(R^x)_2$; —SOR^x; —$S(O)_2R^x$; —$NR^xC(O)R^x$; —$NR^xC(O)N(R^x)_2$; —$NR^xC(O)OR^x$; —$NR^xC(NR^x)N(R^x)_2$; and —$C(R^x)_3$; wherein each occurrence of R^x is independently selected from the group consisting of hydrogen; halogen; acyl; optionally substituted aliphatic; optionally substituted heteroaliphatic; optionally substituted aryl; and optionally substituted heteroaryl;

R^5 and R^6 may be independently selected from the group consisting of -Q-Ar and hydrogen, provided that at least one of R^5 and R^6 is -Q-Ar; wherein Q is independently selected from the group consisting of cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; and a bond; and wherein Ar is selected from the group consisting substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; or R^5 and R^6, together with the atoms to which they are attached, form a substituted or unsubstituted 4-6 membered heterocyclic or cycloalkyl ring;

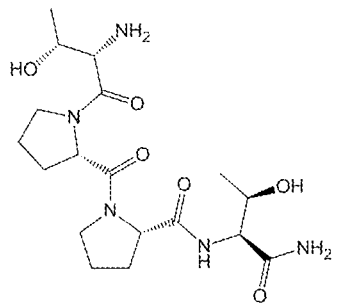
R^7 and R^8 may be independently selected from the group consisting of hydrogen; halogen; hydroxyl; substituted or unsubstituted C_1-C_6 alkyl; substituted or unsubstituted C_1-C_6 alkoxy; and substituted or unsubstituted aryl; or R^7 and R^8, together with the atoms to which they are attached, form a substituted or unsubstituted 4-6 membered heterocyclic or cycloalkyl ring;

R^9 and R^{10} may be independently selected from the group consisting of hydrogen; C_1-C_6 alkyl, optionally substituted by one or more substituents each independently selected from the group

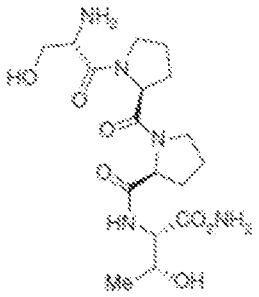
consisting of halogen, oxo, and hydroxyl; C_{2-6}alkenyl, optionally substituted by one or more substituents each independently selected from the group consisting of halogen, oxo, and hydroxyl; C_{2-6}alkynyl, optionally substituted by one or more substituents each independently selected from the group consisting of halogen, oxo, and hydroxyl; C_{3-6}cycloalkyl, optionally substituted by one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, oxo, and hydroxyl; phenyl, optionally substituted by one or more substituents each independently selected from the group consisting of C_{1-6}alkyl; C_{1-6}alkoxy; halogen; hydroxyl; —$C(O)R^x$; —$CO_2(R^x)$; —$C(O)N(R^x)_2$; —$C(NR^x)N(R^x)_2$; and —$C(R^x)_3$;

X is selected from the group consisting of OR^x or NR^xR^x; wherein each occurrence of R^x is independently selected from the group consisting of hydrogen; halogen; C_{1-6}alkyl; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{3-6}cycloalkyl; and phenyl; or R^9 and R^{10}, together with N, form a 4-6 membered heterocyclic ring, optionally substituted by one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, oxo, and hydroxyl.

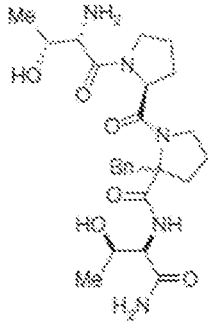
[00220] In some embodiments, the compound of the Formula (**III**) is a compound of the Formula (**III-A**) (**III-B**), and (**III-C**):



(**III-A**)



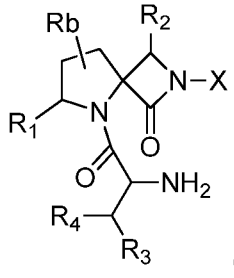
(**III-B**)



(**III-C**)

[00221] The compound of the Formula (**III-A**) is also referred to as Glyx-13. Compounds of the Formula (**III**) are described in US 8,673,843, the contents of which are incorporated in its entirety.

[00222] Exemplary compounds of the present invention also include compounds of the Formula (**IV**):



(**IV**)

and pharmaceutically acceptable salts, stereoisomers, and N-oxides thereof, wherein

Rb is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6 alkyl;

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_3 is selected from the group consisting of H, C_1-C_6 alkyl, -OH, C_1-C_6 alkoxy, -OC(O)-C_1-C_6 alkyl and -OC(O)-phenyl (optionally substituted by one, two or three substituents selected from the group consisting of halogen, hydroxyl, C_1-C_6 alkyl, and C_1-C_6 alkoxy);

R_4 is H or C_1-C_6 alkyl; and

X is selected from the group consisting of hydrogen, - C_1-C_6 alkylene- C_1-C_3 cycloalkyl; C_1-C_6 alkylene- heterocycle (optionally substituted by one, two or three substituents selected from the group consisting of halogen, hydroxyl, C_1-C_6 alkyl, and C_1-C_6 alkoxy), and - C_1-C_6 alkylene- heteroaryl (optionally substituted by one, two or three substituents selected from the group consisting of halogen, hydroxyl, C_1-C_6 alkyl, and C_1-C_6 alkoxy);

or in other embodiments, the variables set forth in formula (**III**) are as defined as follows:

Rb is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6 alkyl (*e.g.*, H);

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_3 is selected from the group consisting of H, C_1-C_6 alkyl, -OH, C_1-C_6 alkoxy, -OC(O)-C_1-C_6 alkyl and -OC(O)-phenyl (optionally substituted by one, two or three substituents independently selected from the group consisting of halogen, hydroxyl, C_1-C_6 alkyl, and C_1-C_6 alkoxy);

R_4 is H or C_1-C_6 alkyl;

X is selected from the group consisting of:

(i) hydrogen;

(ii) - C_1-C_6 alkylene- C_3-C_6 cycloalkyl;

(iii) - C_1-C_6 alkylene- heterocyclyl including from 3 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, (C_1-C_3 alkyl), O, and S; wherein the heterocyclyl is optionally substituted by one, two or three substituents independently selected from the group consisting of halogen, hydroxyl, C_1-C_6 alkyl, and C_1-C_6 alkoxy);

(iv) - C_1-C_6 alkylene- C(O)-heterocyclyl including from 3 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S; wherein the heterocyclyl is optionally substituted by one, two or three substituents independently selected from the group consisting of halogen, hydroxyl, C_1-C_6 alkyl, and C_1-C_6 alkoxy);

(v) - C_1-C_6 alkylene- heteroaryl including from 5 to 6 ring atoms wherein 1 , 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S; wherein the heteroaryl is optionally substituted by one, two or three substituents independently selected from the group consisting of halogen, hydroxyl, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

(vi) branched unsubstituted C_3-C_6 alkyl; and

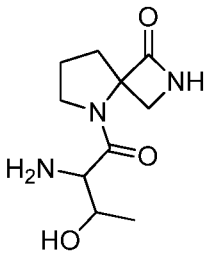
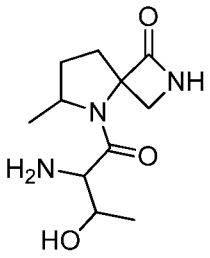
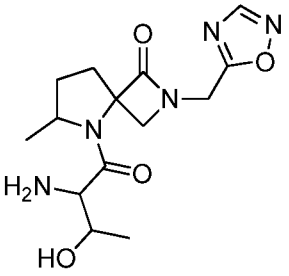
(vii) branched C_3-C_6 alkyl substituted with -C(O)NH2 on one carbon and -OH on another carbon;

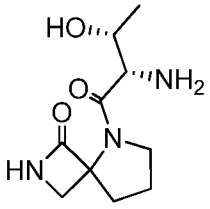
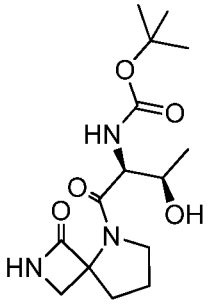
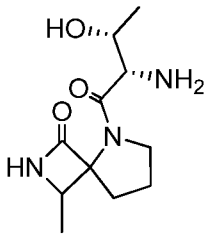
and wherein the -N¾ group attached to the carbon adjacent to -CH(R_3)(R_4) is optionally substituted with a substituent selected from -C(O)OR_{31} and -C(O) R_{32}, wherein:

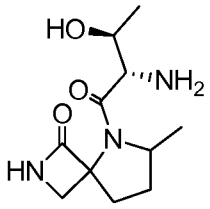
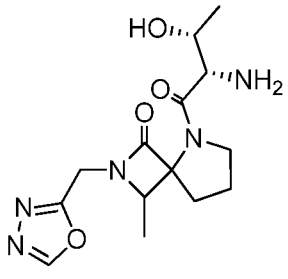
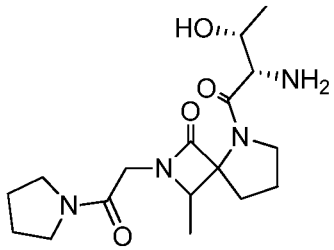
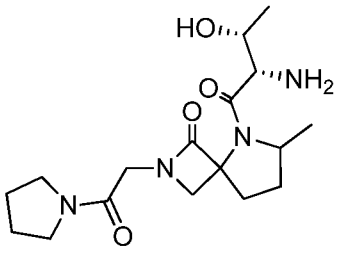
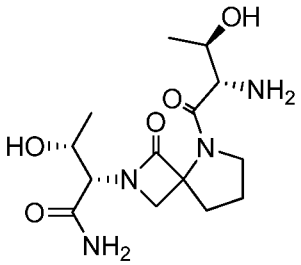
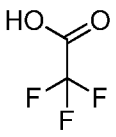
R_{31} is selected from the group consisting of: C_1-C_6 alkyl; C_1-C_6 haloalkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_{10} cycloalkyl, wherein the C_3-C_{10} cycloalkyl is optionally substituted with from 1-3 independently selected C_1-C_3 alkyl; -CH_2- C_3-C_{10} cycloalkyl wherein the C_3-C_{10} cycloalkyl is optionally substituted with from 1-3 independently selected C_1-C_3 alkyl; -CH2-phenyl, wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from C_1-C_3alkyl; C_1-C_3 haloalkyl; C_1-C_3alkoxy; C_1-C_3 haloalkoxy; nitro; halo; SO_2Me, cyano; and -OC(O)CH_3; and -CH_2- pyridyl; and

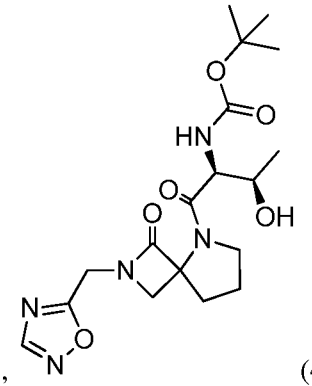
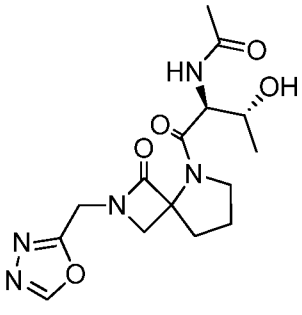
R_{32} is selected from the group consisting of: H; C_1-C_6 alkyl; C_1-C_6 haloalkyl; phenyl, wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from C_1-C_3 alkyl; C_1-C_3 haloalkyl; C_1-C_3 alkoxy; C_1-C_3 haloalkoxy; nitro; halo; SO_2Me, cyano; and -$OC(O)CH_3$; and pyridyl.

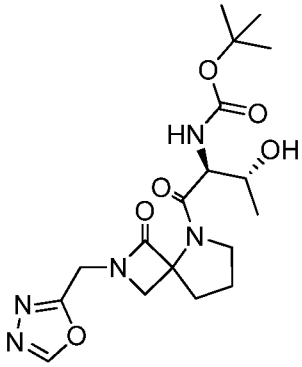
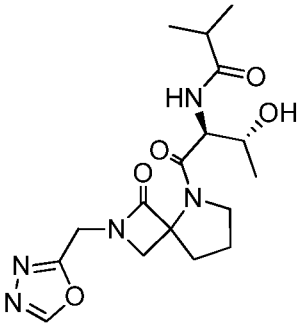
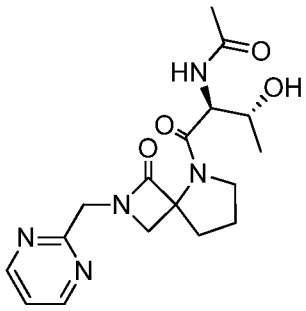
[00223] In some embodiments, the compound of the Formula (**IV**) is a compound of the formula:

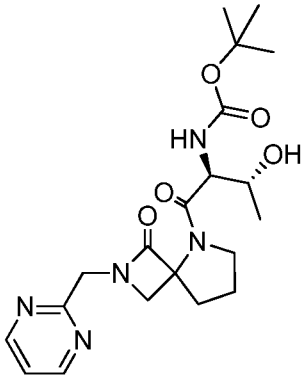
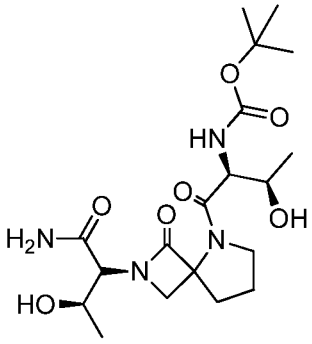
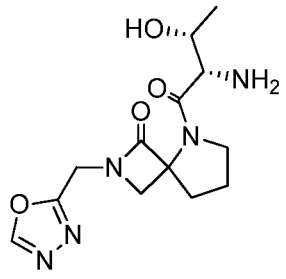

, 
(Compound Z), 
(Compound Y),

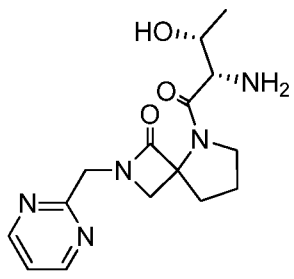

(4S-FNL-1), 
(4S-FNL-2), 
(4S-FNL-16),

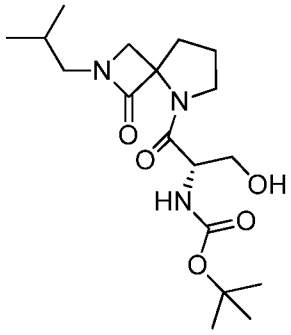

(4S-FNL-14), 
(4S-FNL-20), 
(4S-FNL-18), 
(4S-FNL-15), 

(4S-FNL-

3),  (4S-FNL-19),  (4S-FNL-10),

 (4S-FNL-7),  (4S-FNL-9), 

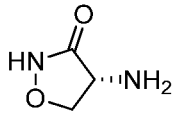
 (4S-FNL-13),  (4S-FNL-12),  (4S-7),

 (4S-40), (4S-17),

or  (4S-FNL-4).

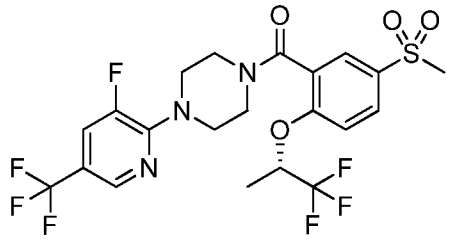
[00224] Compounds of the Formula (**IV**) are described in WO2014/120786, the contents of which are incorporated in its entirety.

[00225] Exemplary compounds of the present invention also include a compound of the Formula (**V**):

 (**V**).

The compound of the Formula (**V**) is also referred to as 4-amino-3-isoxazolidinone, (R)-4-amino-1,2-oxazolidin-3-one, cycloserine, and seromycin.

[00226] Exemplary compounds of the present invention also include a compound of the Formula (**VI**):

 (**VI**),

or a pharmaceutically acceptable salt thereof.

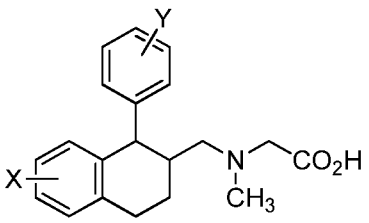
[00227] The compound of the Formula (**VI**) is also referred to as [4-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}(5-methylsulfonyl)-2-[(1S)-2,2,2-trifluoro-1-methylethoxy]phenyl}methanone, RG1678, RO-4917838, and bitopertin. In some embodiments, the compounds of the invention (*e.g.*, the compound of Formula (**VI**)) are glycine reuptake inhibitors. In

some embodiments, the compounds of the invention (*e.g.,* the compound of Formula (**VI**)) are glycine transporter 1 (GlyT1) inhibitors. In some embodiments, the compounds of the invention (e.g, GlyT1) inhibitors are described in US 8524909 and US 20130158050, the contents of which are incorporated in its entirety.

[00228]

[00229] In some embodiments, the compounds of the invention (*e.g.,* the compound of Formula (**VI**)) are glycine reuptake inhibitors.

[00230] Exemplary compounds of the present invention also include compounds of the Formula (**VII**):



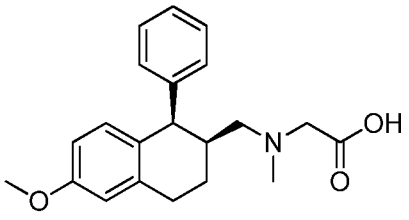
(**VII**),

wherein:

X is 1-3 substituents selected from hydrogen, halogen, methyl, methoxy, trifluoromethyl, and trifluoromethoxy; and

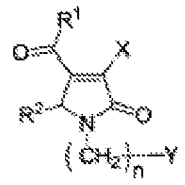
Y is 1-3 substituents selected from hydrogen, methyl, and halogen; or a pharmaceutically acceptable salt thereof.

[00231] In some embodiments, the compounds (*e.g.,* compounds of the Formula (**VII**)) are glycine transporter-1 inhibitors. In some embodiments, the compound of the Formula (**VII**) is 2-([(1R,2S)-6-methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl]methyl-methylamino)acetic acid. In some embodiments, the compound is Org 25935. In some embodiments, the compound of the Formula (**VII**) is a compound of the Formula (**VII-a**):



(**VII-a**). Compounds of the Formula (**VII**) are described in WO2009/059961, the contents of which are incorporated in its entirety.

[00232] Exemplary compounds of the present invention also include a compound of the Formula (**VIII**):



Formula (**VIII**)

or salts thereof, wherein

X is OH or NH_2, wherein X optionally substituted with J;

Y is a bicyclic carbocyclyl or Ar^1 is aryl, heterocyclyl, bicyclic heterocyclyl, bicyclic heterocycle comprising one five-membered ring and one six-membered ring, bicyclic heterocycle comprising one five-membered heterocyclic ring and one six-membered aryl ring, bicyclic heterocycle comprising one five-membered heterocyclic ring and one six-membered heterocyclic ring, a bicyclic heterocycle comprising two six-membered rings; a bicyclic heterocycle comprising two six-membered aryl rings, a bicyclic heterocycle comprising two six-membered hetercyclic rings, a bicyclic heterocycle comprising one heterocyclic six-membered ring and one aromatic six-membered ring, or an bicyclic aryl, wheren Y or Ar^1 is optionally substituted with one or more, the same or different, J;

n is 0, 1, 2, 3, 4, or 5;

R^1 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfmyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^1 is optionally substituted with one or more, the same or different, J;

R is hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino,

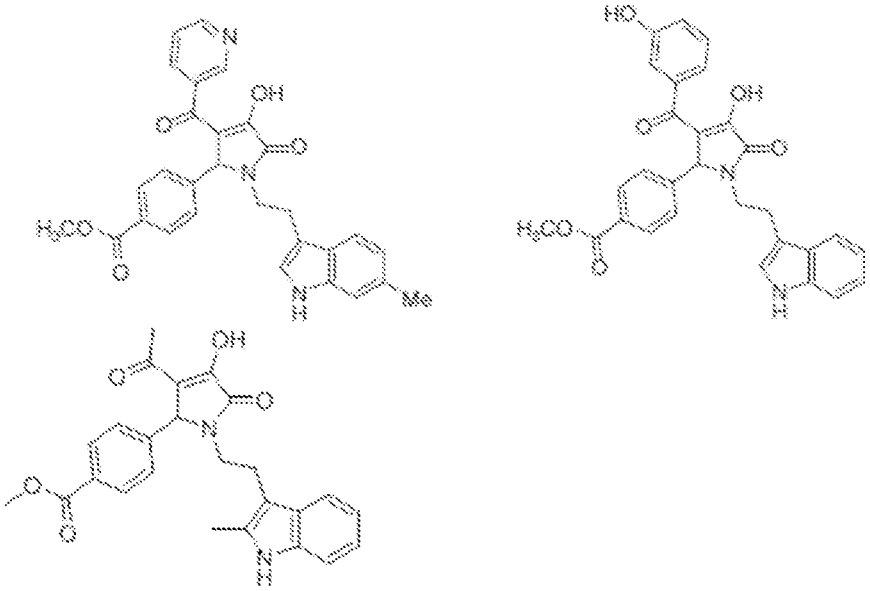
alkylsulfmyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R is optionally substituted with one or more, the same or different, J; and

J is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfmyl,

alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein J is optionally substituted with one or more, the same or different, K;

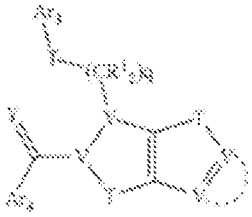
K is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfmyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

[00233] In some embodiments, the compound of the Formula (**VIII**) is of the formula:

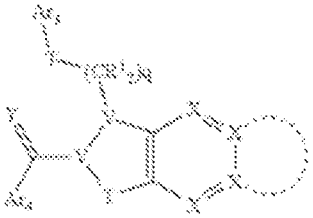


[00234] Compounds of the Formula (**VIII**) are described in WO2014/025942, the contents of which are incorporated in its entirety.

[00235] Exemplary compounds of the present invention also include a compound of the Formulas (**IX-A**) and (**IX-B**) provided below:

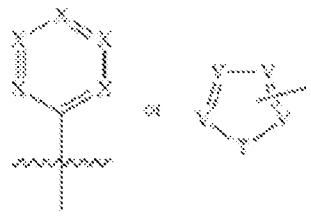


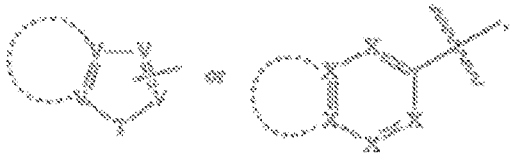
(**IX-A**)



(**IX-B**)

wherein for Formulas (**IX-A**) and (**IX-B**),

Ar_3= 

Ar_4= 

X is, independently, N or C bonded to H or a substituent, J, with the proviso that no more than three of X are N;

Y is independently selected from O, S, NR^1, CH_2, and CR^1_2;

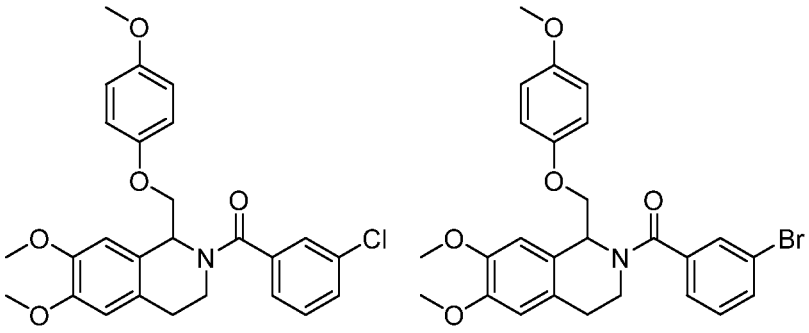
R^1 and R^2 are, independently, selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and hydroxy, and, when R^1 is attached to a carbon atom, it can be halo or cyano,

T is, independently, CHR^1, CR^1_2, O, S, or NR^1,

V is, independently, N, or C bonded to H or a substituent J,

J is a non-hydrogen substituent selected from the group consisting of halo (—F, —Cl, —Br, —I), nitro, amino (NR^1R^2), OR^1, SR^1, —R^1, —CF_3, —CN, —C_2R^1, —SO_2CH_3, —C(=O)NR^1R^2—NR′ C(=O)R^1, —C(=O)R^1, —C(=O)OR^1, —$(CH_2)_qOR^1$, —OC(=O)R^1, —OC(=O)NR^1R^2, —NR^1(C=Y)—NR^1R^2, —NR^1(C=Y)—OH, —NR^1(C=Y)—SH, sulfonyl, sulfinyl, phosphoryl, and azo, and q is 0-5.

[00237] In some embodiments, the compound of the Formula (**IX-A**) and (**IX-B**) is of the formula:



[00238] Compounds of the Formula (**IX-A**) and (**IX-B**) are described in WO2010/088414 and US 2014/0275529, the contents of which are incorporated in its entirety.

[00239] Exemplary compounds of the present invention also include a compound of the Formula (**X**):

 (**X**)

wherein:

each L is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)—(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, alkaryl, hydroxy, —O-alkyl, —O-aryl, —SH, —S-alkyl, —S-aryl, fluoro, chloro, bromo, iodo, nitro, or cyano; or two L groups may be taken together with Ar^1 to form: a dioxolane ring or a cyclobutane

ring;

k=0, 1, 2, 3, 4 or 5;

each Ar^1 and Ar^2 is independently aryl or heteroaryl;

W is a bond, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

X is a bond, NR^1 or O;

each R^1 and R^2 is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_6-C_{12} aralkyl; or

R^1 and R^2 can be taken together to form a 5-8 membered ring;

each R^3 and R^4 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)—(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^3R^4 is C=O;

n and p are each independently 1, 2, 3 or 4;

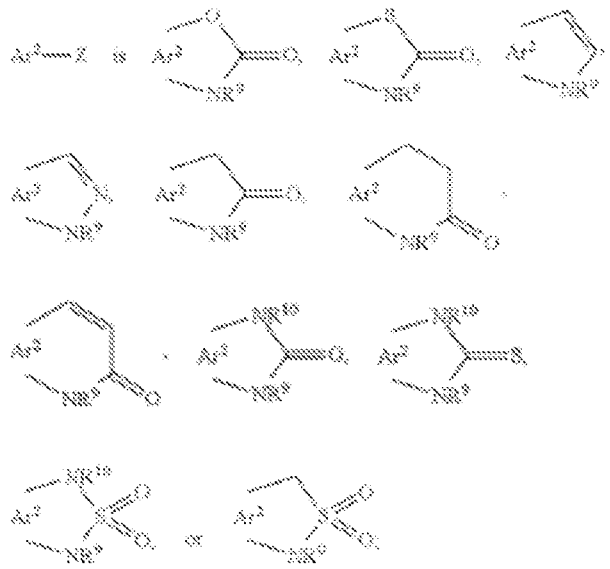
each R^5 and R^6 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C(=O)—(C_1-C_6)-alkyl, C_1-C_6 haloalkyl, hydroxy, fluoro, chloro, bromo, iodo, nitro, or cyano; or CR^5R^6 is C=O or $C=CH_2$;

or wherein —NR^2—$(CR^5R^6)_p$— can be



Y is a bond, O, S, SO, SO_2, CH_2, NH, N(C_1-C_6 alkyl), or NHC(=O);

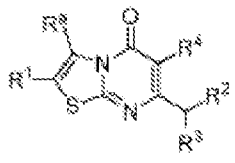
Z is OH, NR^6R^7, NR^8SO_2(C_1-C_6 alkyl), $NR^8C(O)NR^6R^7$, $NR^8C(S)NR^6R^7$, $NR^8C(O)O$(C_1-C_6 alkyl), NR^8-dihydrothiazole, or NR^8-dihydroimidazole; wherein each R^6, R^7 and R^8 is independently H, C_1-C_6 alkyl or C_6-C_{12} aralkyl; or



wherein R^9 and R^{10} are each independently H, C_1-C_6 alkyl, aralkyl.

[00241] Compounds of the Formula (**X**) are described in US 2011/0160223 and US 2014/0031363, the contents of which are incorporated in its entirety.

[00242] Exemplary compounds of the present invention also include a compound of the Formula (**XI-A**) or (**XI-B**):



(**XI-A**)

wherein

R^a is Ci-$_6$alkyl or C_2-$_6$alkenyl, each optionally substituted with one or more R^b substituents; C_2-$_6$alkynyl; halo; -C(0)R^c; -NR^dR^e; -C(0)NR^dR^e; -C(S)NR^dR^e; -C(=N-OH)-C_{1-4}alkyl; -OC_{1-4}alkyl; -OC_{1-4}haloalkyl; -SC_{1-4}alkyl; -$S0_2C_{1-4}$alkyl; cyano; C_{3_6}cycloalkyl optionally substituted with one or more R^f substituents; or a phenyl, monocyclic heteroaryl, or heterocycloalkyl ring, each ring optionally substituted with one or more R^g substituents;

wherein each R^b substituent is independently selected from the group consisting of -OH, -Ci$_{_4}$alkoxy, -NR^dR^e, -C(0)NR^dR^e, -SC_{1-4}alkyl, -$S0_2C_{1-4}$alkyl, cyano, halo, C_{3-6}cycloalkyl, and monocyclic heteroaryl;

R^c is C_{1-4}alkyl, -C_{1-4}haloalkyl, C_3-$_6$cycloalkyl, or a monocyclic, carbon-linked heterocycloalkyl;

R^d is H or C_{1-4}alkyl;

R^e is H; C_{1-4}alkyl optionally substituted with -CN, $-CF_3$, -OH, or a monocyclic heterocycloalkyl; C_{3-6}cycloalkyl; -OH; or $-OC_{1-4}$alkoxy;

or R^d and R^e taken together with the nitrogen to which they are attached form a heterocycloalkyl, optionally substituted with C_{1-4}alkyl or -OH;

each R^f substituent is independently selected from the group consisting of: C_{1-4}alkyl optionally substituted with -OH, cyano, or C_{1-4}alkoxy; -OH; halo; C_{1-4}haloalkyl; $-CONH_2$; and cyano; and each R^g substituent is independently selected from the group consisting of C_{1-4}alkyl, $-CF_3$, halo, $-NH_2$, $-OCH_3$, cyano, and -OH;

R^1 is selected from the group consisting of H, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{3-6}cycloalkyl, halo, $-OC_{1-4}$alkyl, $-OC_{1-4}$haloalkyl, cyano, and $-C(0)C_{1-4}$alkyl; or R^a and R^1 taken together with the carbons to which they are attached form a 5- to 7-membered ring, optionally containing an O or NH, and optionally substituted with one or more R^h substituents;

wherein each R^h substituent is independently -C(0)NR¾^j, cyano, or is C_{1-4}alkyl optionally substituted with -OH, $-OCH_3$, cyano, or -C(0)NR¾^j; or two R^h groups attached to the same carbon and taken together with the carbon to which they are attached form a carbonyl or a C_{3-6}cycloalkyl;

wherein R^1 and R^J are each independently H or C_{1-4}alkyl;

R^2 is $-R^m$, $-OR^m$, or $-NR^mR^n$;

wherein R^m is aryl or heteroaryl, each optionally substituted with one or more R^s substituents;

wherein each R^s substituent is independently selected from the group consisting of C_{1-4}alkyl, C_2.

$_4$alkenyl (optionally substituted with halo), C_{2-4}alkynyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}alkyl- OH, C_{1-4}haloalkoxy, halo, cyano, C_{3_6}cycloalkyl (optionally substituted with -OH or halo), monocyclic heteroaryl, $-NH_2$, $-N0_2$, $-NHS0_2C_{1-4}$alkyl, and $-S0_2C_{1-4}$alkyl;

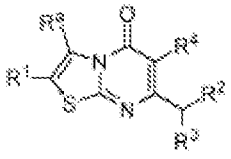
R^n is H, C_{1-4}haloalkyl, or C_{1-4}alkyl optionally substituted with -OH or C_{1-4}alkoxy;

or R^m and R^n taken together with the nitrogen to which they are attached form a pyrrolidine or piperidine ring, optionally substituted with C_{1-4}alkyl and optionally fused to phenyl, wherein said phenyl is optionally substituted with halo;

R^3 is H or methyl; and

R^4 is H or fluoro; or a pharmaceutically acceptable salt thereof.

In one aspect, the invention is directed to a compound of Formula (**XI-B**):



(XI-B)

wherein

R^a is C_{1-6}alkyl optionally substituted with one or more R^b substituents; C_{2-6}alkenyl; C_{2-6}alkynyl; halo; -C(0)R^c; -NR^dR^e; -C(0)NR^dR^e; -C(S)NR^dR^e; -C(=N-OH)-C_{1-4}alkyl; -$S0_2C_{1-4}$alkyl; cyano; C_{3-6}cycloalkyl optionally substituted with one or more R^f substituents; or a phenyl, monocyclic heteroaryl, or heterocycloalkyl ring, each ring optionally substituted with one or more R^g substituents;

wherein each R^b substituent is independently selected from the group consisting of -OH, -C_{1-4}alkoxy, -NR^dR^e, -C(0)NR^dR^e, -SC_{1-4}alkyl, -$S0_2C_{1-4}$alkyl, cyano, halo, and monocyclic heteroaryl;

R^c is C_{1-4}alkyl, -C_{1-4}haloalkyl, $C_{3.6}$cycloalkyl, or a monocyclic, carbon-linked heterocycloalkyl;

R^d is H or C_{1-4}alkyl;

R^e is H; C_{1-4}alkyl optionally substituted with -CN, -CF_3, -OH, or a monocyclic heterocycloalkyl; C_{3-6}cycloalkyl; -OH; or -OC_{1-4}alkoxy;

or R^d and R^e taken together with the nitrogen to which they are attached form a heterocycloalkyl, optionally substituted with C_{1-4}alkyl or -OH;

each R^f substituent is independently selected from the group consisting of: C_{1-4}alkyl optionally substituted with -OH, cyano, or C_{1-4}alkoxy; C_{1-4}haloalkyl; -$CONH_2$; and cyano; and

each R^g substituent is independently selected from the group consisting of C_{1-4}alkyl, -CF_3, halo, -NH_2, -OCH_3, cyano, and -OH;

R^1 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-4}haloalkyl, and C_{3_6}cycloalkyl; or R^a and R^1 taken together with the carbons to which they are attached form a 5- to 7-membered ring, optionally containing an O or NH, and optionally substituted with one or more R^h substituents; wherein each R^h substituent is independently -C(0)NR¾^j, cyano, or is C_{1-4}alkyl optionally substituted with -OH, -OCH_3, cyano, or -C(0)NR¾^j; or two R^h groups attached to the same carbon and taken together with the carbon to which they are attached form a carbonyl or a $C_{3.\ 6}$cycloalkyl;

wherein R^1 and R^J are each independently H or C_{1-4}alkyl; R^2 is -R^m, -OR^m, or -NR^mR^n;

wherein R^m is aryl or heteroaryl, each optionally substituted with one or more R^s substituents;

wherein each R^s substituent is independently selected from the group consisting of C_{1-4}alkyl, Q.

$_4$haloalkyl, C_{1-4}alkoxy, C_{1-4}alkyl-OH, C_{1-4}haloalkoxy, halo, cyano, C_{3-6}cycloalkyl, -$NHSO_2C_{1-4}$alkyl, and -SO_2C_{1-4}alkyl;

R^n is H, C_{1-4}haloalkyl, or C_{1-4}alkyl optionally substituted with -OH or C_{1-4}alkoxy;

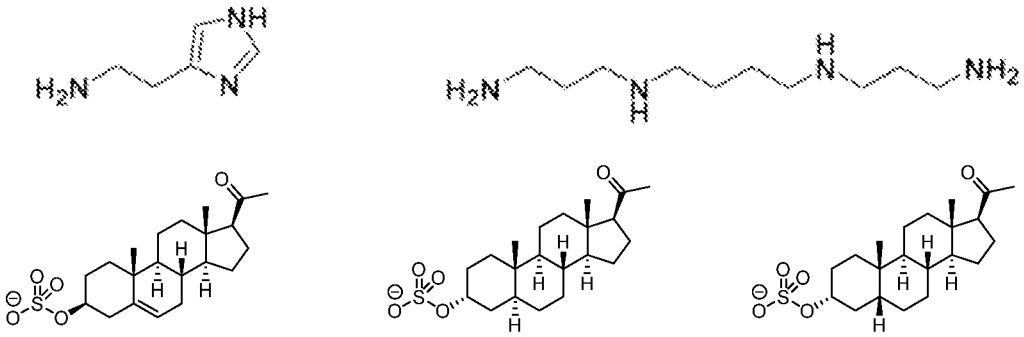
or R^m and R^n taken together with the nitrogen to which they are attached form a pyrrolidine or piperidine ring, optionally substituted with C_{1-4}alkyl and optionally fused to phenyl, wherein said phenyl is optionally substituted with halo;

R^3 is H or methyl; and

R^4 is H or fluoro; or a pharmaceutically acceptable salt thereof.

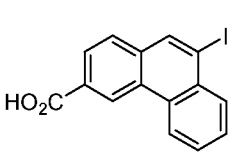
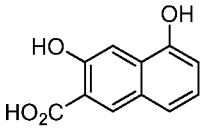
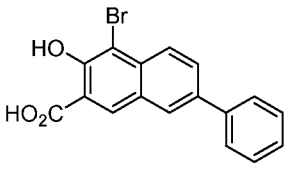
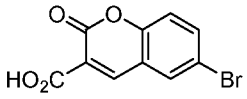
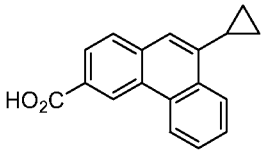
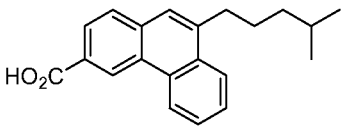
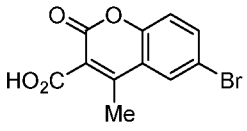
Compounds of the Formula (**XI-A**) and (**XI-B**) are described in WO 2015/052226, the contents of which are incorporated in its entirety.

[00243] Exemplary compounds of the present invention also include a compound selected from:



In some embodiments, the compound described herein is histamine, spermine, pregnenlone sulfate, allopregnanolone sulfate, or pregnanolone sulfate.

[00244] Exemplary compounds of the present invention also include a compound selected from:

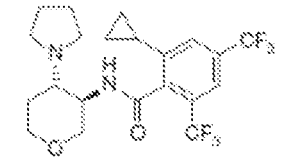








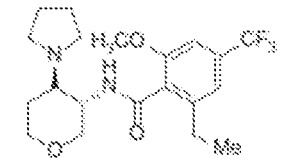
and

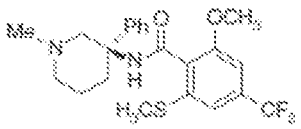
[00245] In some embodiments, the compounds of the present invesntion are described in Costa BM, Irvine MW, Fang G, et al. A novel family of negative and positive allosteric modulators of NMDA receptors. J Pharmacol Exp Ther 2010;335(3):614-21, the contents of which are incorporated in its entirety.

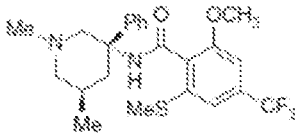
[00246] In some embodiments, the compounds of the present invesntion are described in WO2015065891, WO2014120800, WO2014120789, WO2014120783, WO2014120786, WO2014120784, US20130035292, WO2011003064, WO2010033757, and WO2009039390, the contents of which are incorporated in its entirety.

[00247] Exemplary compounds of the present invention also include a compound selected from:









Chemical Definitions

[00248] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[00249] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.,* enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et*

al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[00250] Compound described herein may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D or deuterium), and ^{3}H (T or tritium); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

[00251] When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[00252] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention. When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term "substituted" is to be defined as set out below. It should be further understood that the terms "groups" and "radicals" can be considered interchangeable when used herein. The articles "a" and "an" may be used herein to refer to one or to more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example "an analogue" means one analogue or more than one analogue.

[00253] "Aliphatic" refers to an alkyl, alkenyl, alkynyl, or carbocyclyl group, as defined herein.

[00254] "Alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C_{1-20} alkyl"). In some embodiments, an alkyl group has 1 to 12 carbon atoms ("C_{1-12} alkyl"). In some embodiments, an alkyl group has 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some

embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl", also referred to herein as "lower alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (C_8) and the like. Unless otherwise specified, each instance of an alkyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents; *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkyl group is unsubstituted C_{1-10} alkyl (*e.g.,* $–CH_3$). In certain embodiments, the alkyl group is substituted C_{1-10} alkyl. Common alkyl abbreviations include Me ($-CH_3$), Et ($-CH_2CH_3$), iPr ($-CH(CH_3)_2$), nPr ($-CH_2CH_2CH_3$), n-Bu ($-CH_2CH_2CH_2CH_3$), or i-Bu ($-CH_2CH(CH_3)_2$).

[00255] As used herein, "alkylene," "alkenylene," and "alkynylene," refer to a divalent radical of an alkyl, alkenyl, and alkynyl group, respectively. When a range or number of carbons is provided for a particular "alkylene," "alkenylene," and "alkynylene" group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. "Alkylene," "alkenylene," and "alkynylene" groups may be substituted or unsubstituted with one or more substituents as described herein.

[00256] "Alkylene" refers to an alkyl group wherein two hydrogens are removed to provide a divalent radical, and which may be substituted or unsubstituted. Unsubstituted alkylene groups include, but are not limited to, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), butylene ($-CH_2CH_2CH_2CH_2-$), pentylene ($-CH_2CH_2CH_2CH_2CH_2-$), hexylene ($-CH_2CH_2CH_2CH_2CH_2CH_2-$), and the like. Exemplary substituted alkylene groups, *e.g.,* substituted with one or more alkyl (methyl) groups, include but are not limited to, substituted methylene ($-CH(CH_3)-$, ($-C(CH_3)_2-$), substituted ethylene ($-CH(CH_3)CH_2-$,$-CH_2CH(CH_3)-$, $-C(CH_3)_2CH_2-$,$-CH_2C(CH_3)_2-$), substituted propylene ($-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH(CH_3)-$, $-C(CH_3)_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-CH_2CH_2C(CH_3)_2-$), and the like.

[00257] "Alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon double bonds (*e.g.,* 1, 2, 3, or 4 carbon–carbon double bonds), and optionally one or more carbon–carbon triple bonds (*e.g.,* 1, 2, 3, or 4 carbon–carbon triple bonds) ("C_{2-20} alkenyl"). In certain embodiments, alkenyl does not contain any triple bonds. In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C_{2-10} alkenyl"). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkenyl group is unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is substituted C_{2-10} alkenyl.

[00258] "Alkenylene" refers to an alkenyl group wherein two hydrogens are removed to provide a divalent radical, and which may be substituted or unsubstituted. Exemplary unsubstituted divalent alkenylene groups include, but are not limited to, ethenylene (-CH=CH-) and propenylene (*e.g.,* -CH=CHCH$_2$-, -CH$_2$-CH=CH-). Exemplary substituted alkenylene groups, *e.g.,* substituted with one or more alkyl (methyl) groups, include but are not limited to, substituted ethylene (-C(CH$_3$)=CH-, -CH=C(CH$_3$)-), substituted propylene (*e.g.,* -C(CH$_3$)=CHCH$_2$-, -CH=C(CH$_3$)CH$_2$-, -CH=CHCH(CH$_3$)-, -CH=CHC(CH$_3$)$_2$-, -CH(CH$_3$)-CH=CH-,-C(CH$_3$)$_2$-CH=CH-, -CH$_2$-C(CH$_3$)=CH-, -CH$_2$-CH=C(CH$_3$)-), and the like.

[00259] "Alkynyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon triple bonds (*e.g.,* 1, 2, 3, or 4 carbon–carbon triple bonds), and optionally one or more carbon–carbon double bonds (*e.g.,* 1, 2, 3, or 4 carbon–carbon

double bonds) ("C_{2-20} alkynyl"). In certain embodiments, alkynyl does not contain any double bonds. In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1–propynyl (C_3), 2–propynyl (C_3), 1–butynyl (C_4), 2–butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents; *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkynyl group is unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is substituted C_{2-10} alkynyl.

[00260] "Alkynylene" refers to a linear alkynyl group wherein two hydrogens are removed to provide a divalent radical, and which may be substituted or unsubstituted. Exemplary divalent alkynylene groups include, but are not limited to, substituted or unsubstituted ethynylene, substituted or unsubstituted propynylene, and the like.

[00261] The term "heteroalkyl," as used herein, refers to an alkyl group, as defined herein, which further comprises 1 or more (*e.g.,* 1, 2, 3, or 4) heteroatoms (*e.g.,* oxygen, sulfur, nitrogen, boron, silicon, phosphorus) within the parent chain, wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms is inserted between a carbon atom and the parent molecule, *i.e.,* between the point of attachment. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 10 carbon atoms and 1, 2, 3, or 4 heteroatoms ("heteroC_{1-10} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1, 2, 3, or 4 heteroatoms ("heteroC_{1-9} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1, 2, 3, or 4 heteroatoms ("heteroC_{1-8} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon

atoms and 1, 2, 3, or 4 heteroatoms ("heteroC_{1-7} alkyl"). In some embodiments, a heteroalkyl group is a group having 1 to 6 carbon atoms and 1, 2, or 3 heteroatoms ("heteroC_{1-6} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms ("heteroC_{1-5} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1or 2 heteroatoms ("heteroC_{1-4} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom ("heteroC_{1-3} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom ("heteroC_{1-2} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms ("heteroC_{2-6} alkyl"). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-10} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-10} alkyl.

[00262] The term "heteroalkenyl," as used herein, refers to an alkenyl group, as defined herein, which further comprises one or more (*e.g.,* 1, 2, 3, or 4) heteroatoms (*e.g.,* oxygen, sulfur, nitrogen, boron, silicon, phosphorus) wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms is inserted between a carbon atom and the parent molecule, *i.e.,* between the point of attachment. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms ("heteroC_{2-10} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1, 2, 3, or 4 heteroatoms ("heteroC_{2-9} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms ("heteroC_{2-8} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms ("heteroC_{2-7} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1, 2, or 3 heteroatoms ("heteroC_{2-6} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms ("heteroC_{2-5} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1or 2 heteroatoms ("heteroC_{2-4} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom ("heteroC_{2-3} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms ("heteroC_{2-6} alkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain

embodiments, the heteroalkenyl group is an unsubstituted heteroC_{2-10} alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC_{2-10} alkenyl.

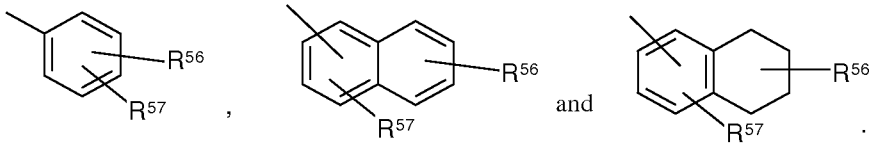
[00263] The term "heteroalkynyl," as used herein, refers to an alkynyl group, as defined herein, which further comprises one or more (*e.g.,* 1, 2, 3, or 4) heteroatoms (*e.g.,* oxygen, sulfur, nitrogen, boron, silicon, phosphorus) wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms is inserted between a carbon atom and the parent molecule, *i.e.,* between the point of attachment. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms ("heteroC_{2-10} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms ("heteroC_{2-9} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms ("heteroC_{2-8} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms ("heteroC_{2-7} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1, 2, or 3 heteroatoms ("heteroC_{2-6} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms ("heteroC_{2-5} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1or 2 heteroatoms ("heteroC_{2-4} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom ("heteroC_{2-3} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms ("heteroC_{2-6} alkynyl"). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an "unsubstituted heteroalkynyl") or substituted (a "substituted heteroalkynyl") with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted heteroC_{2-10} alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC_{2-10} alkynyl.

[00264] As used herein, "alkylene," "alkenylene," "alkynylene," "heteroalkylene," "heteroalkenylene," and "heteroalkynylene," refer to a divalent radical of an alkyl, alkenyl, alkynyl group, heteroalkyl, heteroalkenyl, and heteroalkynyl group respectively. When a range or number of carbons is provided for a particular "alkylene," "alkenylene," "alkynylene," "heteroalkylene," "heteroalkenylene," or "heteroalkynylene," group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. "Alkylene," "alkenylene," "alkynylene," "heteroalkylene," "heteroalkenylene," and "heteroalkynylene" groups may be substituted or unsubstituted with one or more substituents as described herein.

[00265] "'Aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.*, naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; *e.g.*, anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, and trinaphthalene. Particularly aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl. Unless otherwise specified, each instance of an aryl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is substituted C_{6-14} aryl.

[00266] In certain embodiments, an aryl group substituted with one or more of groups selected from halo, C_1-C_8 alkyl, C_1-C_8 haloalkyl, cyano, hydroxy, C_1-C_8 alkoxy, and amino.

[00267] Examples of representative substituted aryls include the following



wherein one of R^{56} and R^{57} may be hydrogen and at least one of R^{56} and R^{57} is each independently selected from C_1-C_8 alkyl, C_1-C_8 haloalkyl, 4-10 membered heterocyclyl, alkanoyl, C_1-C_8 alkoxy, heteroaryloxy, alkylamino, arylamino, heteroarylamino, $NR^{58}COR^{59}$, $NR^{58}SOR^{59}$ $NR^{58}SO_2R^{59}$, COOalkyl, COOaryl, $CONR^{58}R^{59}$, $CONR^{58}OR^{59}$, $NR^{58}R^{59}$, $SO_2NR^{58}R^{59}$, S-alkyl, SOalkyl, SO_2alkyl, Saryl, SOaryl, SO_2aryl; or R^{56} and R^{57} may be joined to form a cyclic ring (saturated or unsaturated) from 5 to 8 atoms, optionally containing one or more heteroatoms selected from the group N, O, or S. R^{60} and R^{61} are

independently hydrogen, C_1-C_8 alkyl, C_1-C_4 haloalkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, 5-10 membered heteroaryl, or substituted 5-10 membered heteroaryl .

[00268] "Fused aryl" refers to an aryl having two of its ring carbon in common with a second aryl or heteroaryl ring or with a carbocyclyl or heterocyclyl ring.

[00269] "Aralkyl" is a subset of alkyl and aryl, as defined herein, and refers to an optionally substituted alkyl group substituted by an optionally substituted aryl group.

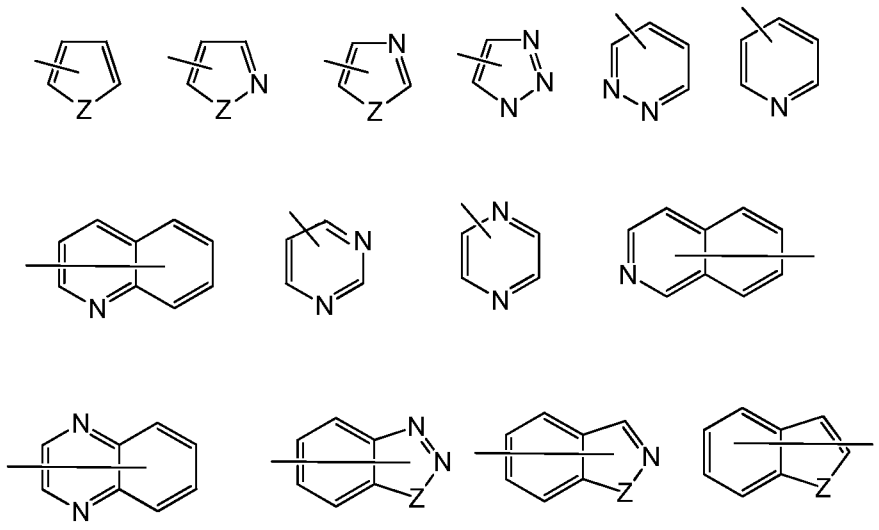
[00270] "Heteroaryl" refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system (*e.g.,* having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5–10 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.,* indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.,* either the ring bearing a heteroatom (*e.g.,* 2–indolyl) or the ring that does not contain a heteroatom (*e.g.,* 5–indolyl).

[00271] In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6

membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5–14 membered heteroaryl.

[00272] Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[00273] Examples of representative heteroaryls include the following:



wherein each Z is selected from carbonyl, N, NR^{65}, O, and S; and R^{65} is independently hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, and 5-10 membered heteroaryl.

[00274] "Heteroaralkyl" is a subset of alkyl and heteroaryl, as defined herein, and refers to an optionally substituted alkyl group substituted by an optionally substituted heteroaryl group.

[00275] "Carbocyclyl" or "carbocyclic" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") and can be

saturated or can be partially unsaturated. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C_{3-10} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-10} carbocyclyl.

[00276] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C_{3-10} cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C_{3-10} cycloalkyl.

[00277] "Heterocyclyl" or "heterocyclic" refers to a radical of a 3– to 10–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("3–10 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point

of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3–10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3–10 membered heterocyclyl.

[00278] In some embodiments, a heterocyclyl group is a 5–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("5–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

[00279] Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–

membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[00280] "Hetero" when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbyl groups described above such as alkyl, *e.g.,* heteroalkyl, cycloalkyl, *e.g.,* heterocyclyl, aryl, *e.g,.* heteroaryl, cycloalkenyl, *e.g,.* cycloheteroalkenyl, and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

[00281] "Acyl" refers to a radical $-C(O)R^{20}$, where R^{20} is hydrogen, substituted or unsubstitued alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstitued heteroaryl, as defined herein. "Alkanoyl" is an acyl group wherein R^{20} is a group other than hydrogen. Representative acyl groups include, but are not limited to, formyl (-CHO), acetyl ($-C(=O)CH_3$), cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl ($-C(=O)Ph$), benzylcarbonyl ($-C(=O)CH_2Ph$), —$C(O)$-C_1-C_8 alkyl, $-C(O)$-$(CH_2)_t$(C_6-C_{10} aryl), $-C(O)$-$(CH_2)_t$(5-10 membered heteroaryl), $-C(O)$-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and $-C(O)$-$(CH_2)_t$(4-10 membered heterocyclyl), wherein t is an integer from 0 to 4. In certain embodiments, R^{21} is C_1-C_8 alkyl, substituted with halo or hydroxy; or C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00282] "Acylamino" refers to a radical $-NR^{22}C(O)R^{23}$, where each instance of R^{22} and R23 is independently hydrogen, substituted or unsubstitued alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstitued heteroaryl,, as defined herein, or R^{22} is an amino protecting group. Exemplary "acylamino" groups include, but are not limited to, formylamino, acetylamino, cyclohexylcarbonylamino, cyclohexylmethyl-carbonylamino, benzoylamino and benzylcarbonylamino. Particular exemplary "acylamino" groups are $-NR^{24}C(O)$-C_1-C_8 alkyl, $-NR^{24}C(O)$-$(CH_2)_t$(C_6-C_{10} aryl), $-NR^{24}C(O)$-$(CH_2)_t$(5-10 membered heteroaryl), $-NR^{24}C(O)$-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and $-NR^{24}C(O)$-$(CH_2)_t$(4-10 membered heterocyclyl), wherein t is an integer from 0 to 4, and

each R^{24} independently represents H or C_1-C_8 alkyl.In certain embodiments, R^{25} is H, C_1-C_8 alkyl, substituted with halo or hydroxy; C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy; and R^{26} is H, C_1-C_8 alkyl, substituted with halo or hydroxy; C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxyl; provided at least one of R^{25} and R^{26} is other than H.

[00283] "Acyloxy" refers to a radical -OC(O)R^{27}, where R^{27} is hydrogen, substituted or unsubstitued alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstitued heteroaryl, as defined herein. Representative examples include, but are not limited to, formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl and benzylcarbonyl. In certain embodiments, R^{28} is C_1-C_8 alkyl, substituted with halo or hydroxy; C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00284] "Alkoxy" refers to the group –OR^{29} where R^{29} is substituted or unsubstituted alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstitued heteroaryl. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, *i.e.* with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

[00285] In certain embodiments, R^{29} is a group that has 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent, selected from the group consisting of amino, substituted amino, C_6-C_{10} aryl, aryloxy, carboxyl, cyano, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, halogen, 5-10 membered heteroaryl, hydroxyl, nitro, thioalkoxy, thioaryloxy, thiol, alkyl-S(O)-, aryl–S(O)-, alkyl–$S(O)_2$- and aryl-$S(O)_2$-. Exemplary 'substituted alkoxy' groups include, but are not limited to, –O-$(CH_2)_t$(C_6-C_{10} aryl), –O-$(CH_2)_t$(5-10 membered heteroaryl), –O-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and –O-$(CH_2)_t$(4-10 membered heterocyclyl), wherein t is an integer from 0 to

4 and any aryl, heteroaryl, cycloalkyl or heterocyclyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy. Particular exemplary 'substituted alkoxy' groups are $-OCF_3$, $-OCH_2CF_3$, $-OCH_2Ph$, $-OCH_2$-cyclopropyl, $-OCH_2CH_2OH$, and $-OCH_2CH_2NMe_2$.

[00286] "Amino" refers to the radical $-NH_2$.

[00287] "Substituted amino" refers to an amino group of the formula $-N(R^{38})_2$ wherein R^{38} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstitued heteroaryl, or an amino protecting group, wherein at least one of R^{38} is not a hydrogen. In certain embodiments, each R^{38} is independently selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 alkenyl, C_3-C_8 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocyclyl, or C_3-C_{10} cycloalkyl; or C_1-C_8 alkyl, substituted with halo or hydroxy; C_3-C_8 alkenyl, substituted with halo or hydroxy; C_3-C_8 alkynyl, substituted with halo or hydroxy, or $-(CH_2)_t$(C_6-C_{10} aryl), $-(CH_2)_t$(5-10 membered heteroaryl), $-(CH_2)_t$(C_3-C_{10} cycloalkyl), or $-(CH_2)_t$(4-10 membered heterocyclyl), wherein t is an integer between 0 and 8, each of which is substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy; or both R^{38} groups are joined to form an alkylene group.

[00288] Exemplary "substituted amino" groups include, but are not limited to, $-NR^{39}$-C_1-C_8 alkyl, $-NR^{39}$-$(CH_2)_t$(C_6-C_{10} aryl), $-NR^{39}$-$(CH_2)_t$(5-10 membered heteroaryl), $-NR^{39}$-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and $-NR^{39}$-$(CH_2)_t$(4-10 membered heterocyclyl), wherein t is an integer from 0 to 4, for instance 1 or 2, each R^{39} independently represents H or C_1-C_8 alkyl; and any alkyl groups present, may themselves be substituted by halo, substituted or unsubstituted amino, or hydroxy; and any aryl, heteroaryl, cycloalkyl, or heterocyclyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy. For the avoidance of doubt the term 'substituted amino' includes the groups alkylamino, substituted alkylamino, alkylarylamino, substituted alkylarylamino, arylamino, substituted arylamino, dialkylamino, and substituted dialkylamino as defined below. Substituted amino encompasses both monosubstituted amino and disubstituted amino groups.

[00289] "Azido" refers to the radical $-N_3$.

[00290] "Carbamoyl" or "amido" refers to the radical -C(O)NH_2.

[00291] "Substituted carbamoyl" or "substituted amido" refers to the radical -C(O)N(R^{62})$_2$ wherein each R^{62} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstitued heteroaryl, or an amino protecting group, wherein at least one of R^{62} is not a hydrogen. In certain embodiments, R^{62} is selected from H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or C_1-C_8 alkyl substituted with halo or hydroxy; or C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy; provided that at least one R^{62} is other than H.

[00292] Exemplary "substituted carbamoyl" groups include, but are not limited to, –C(O) NR^{64}-C_1-C_8 alkyl, –C(O)NR^{64}-$(CH_2)_t$(C_6-C_{10} aryl), –C(O)N^{64}-$(CH_2)_t$(5-10 membered heteroaryl), –C(O)NR^{64}-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and –C(O)NR^{64}-$(CH_2)_t$(4-10 membered heterocyclyl), wherein t is an integer from 0 to 4, each R^{64} independently represents H or C_1-C_8 alkyl and any aryl, heteroaryl, cycloalkyl or heterocyclyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00293] "Carboxy" refers to the radical -C(O)OH.

[00294] "Cyano" refers to the radical -CN.

[00295] "Halo" or "halogen" refers to fluoro (F), chloro (Cl), bromo (Br), and iodo (I). In certain embodiments, the halo group is either fluoro or chloro.

[00296] "Hydroxy" refers to the radical -OH.

[00297] "Nitro" refers to the radical –NO_2.

[00298] "Cycloalkylalkyl" refers to an alkyl radical in which the alkyl group is substituted with a cycloalkyl group. Typical cycloalkylalkyl groups include, but are not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclooctylmethyl,

cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, cycloheptylethyl, and cyclooctylethyl, and the like.

[00299] "Heterocyclylalkyl" refers to an alkyl radical in which the alkyl group is substituted with a heterocyclyl group. Typical heterocyclylalkyl groups include, but are not limited to, pyrrolidinylmethyl, piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyrrolidinylethyl, piperidinylethyl, piperazinylethyl, morpholinylethyl, and the like.

[00300] "Cycloalkenyl" refers to substituted or unsubstituted carbocyclyl group having from 3 to 10 carbon atoms and having a single cyclic ring or multiple condensed rings, including fused and bridged ring systems and having at least one and particularly from 1 to 2 sites of olefinic unsaturation. Such cycloalkenyl groups include, by way of example, single ring structures such as cyclohexenyl, cyclopentenyl, cyclopropenyl, and the like.

[00301] "Fused cycloalkenyl" refers to a cycloalkenyl having two of its ring carbon atoms in common with a second aliphatic or aromatic ring and having its olefinic unsaturation located to impart aromaticity to the cycloalkenyl ring.

[00302] "Ethenyl" refers to substituted or unsubstituted –(C=C)-.

[00303] "Ethylene" refers to substituted or unsubstituted –(C-C)-.

[00304] "Ethynyl" refers to –(C≡C)-.

[00305] "Nitrogen-containing heterocyclyl" group means a 4- to 7- membered non-aromatic cyclic group containing at least one nitrogen atom, for example, but without limitation, morpholine, piperidine (*e.g.* 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (*e.g.* 2-pyrrolidinyl and 3-pyrrolidinyl), azetidine, pyrrolidone, imidazoline, imidazolidinone, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Particular examples include azetidine, piperidone and piperazone.

[00306] "Thioketo" refers to the group =S.

[00307] Alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted (*e.g.*, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or

"substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[00308] Exemplary carbon atom substituents include, but are not limited to, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3{}^+X^-$, $-N(OR^{cc})R^{bb}$, $-SH$, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_2$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)_2R^{aa}$, $-OP(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, $-OP(=O)_2N(R^{bb})_2$, $-P(=O)(NR^{bb})_2$, $-OP(=O)(NR^{bb})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(NR^{bb})_2$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{aa} groups are joined to form a 3–14 membered heterocyclyl or 5–

14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{cc} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{ee}$, $–ON(R^{ff})_2$, $–N(R^{ff})_2$, $–N(R^{ff})_3{}^+X^–$, $–N(OR^{ee})R^{ff}$, –SH, $–SR^{ee}$, $–SSR^{ee}$, $–C(=O)R^{ee}$, $–CO_2H$, $–CO_2R^{ee}$, $–OC(=O)R^{ee}$, $–OCO_2R^{ee}$, $–C(=O)N(R^{ff})_2$, $–OC(=O)N(R^{ff})_2$, $–NR^{ff}C(=O)R^{ee}$, $–NR^{ff}CO_2R^{ee}$, $–NR^{ff}C(=O)N(R^{ff})_2$, $–C(=NR^{ff})OR^{ee}$, $–OC(=NR^{ff})R^{ee}$, $–OC(=NR^{ff})OR^{ee}$, $–C(=NR^{ff})N(R^{ff})_2$, $–OC(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}C(=NR^{ff})N(R^{ff})_2$,$–NR^{ff}SO_2R^{ee}$, $–SO_2N(R^{ff})_2$, $–SO_2R^{ee}$, $–SO_2OR^{ee}$, $–OSO_2R^{ee}$, $–S(=O)R^{ee}$, $–Si(R^{ee})_3$, $–OSi(R^{ee})_3$, $–C(=S)N(R^{ff})_2$, $–C(=O)SR^{ee}$, $–C(=S)SR^{ee}$, $–SC(=S)SR^{ee}$, $–P(=O)_2R^{ee}$, $–P(=O)(R^{ee})_2$, $–OP(=O)(R^{ee})_2$, $–OP(=O)(OR^{ee})_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

each instance of R^{ee} is, independently, selected from $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, $C_{6–10}$ aryl, 3–10 membered heterocyclyl, and 3–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl and 5–10 membered

heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OC_{1–6}$ alkyl, $–ON(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_3^+X^–$, $–NH(C_{1–6}$ alkyl$)_2^+X^–$, $–NH_2(C_{1–6}$ alkyl$)^+X^–$, $–NH_3^+X^–$, $–N(OC_{1–6}$ alkyl$)(C_{1–6}$ alkyl), $–N(OH)(C_{1–6}$ alkyl), –NH(OH), –SH, $–SC_{1–6}$ alkyl, $–SS(C_{1–6}$ alkyl), $–C(=O)(C_{1–6}$ alkyl), $–CO_2H$, $–CO_2(C_{1–6}$ alkyl), $–OC(=O)(C_{1–6}$ alkyl), $–OCO_2(C_{1–6}$ alkyl), $–C(=O)NH_2$, $–C(=O)N(C_{1–6}$ alkyl$)_2$, $–OC(=O)NH(C_{1–6}$ alkyl), $–NHC(=O)(\ C_{1–6}$ alkyl), $–N(C_{1–6}$ alkyl$)C(=O)(\ C_{1–6}$ alkyl), $–NHCO_2(C_{1–6}$ alkyl), $–NHC(=O)N(C_{1–6}$ alkyl$)_2$, $–NHC(=O)NH(C_{1–6}$ alkyl), $–NHC(=O)NH_2$, $–C(=NH)O(C_{1–6}$ alkyl),$–OC(=NH)(C_{1–6}$ alkyl), $–OC(=NH)OC_{1–6}$ alkyl, $–C(=NH)N(C_{1–6}$ alkyl$)_2$, $–C(=NH)NH(C_{1–6}$ alkyl), $–C(=NH)NH_2$, $–OC(=NH)N(C_{1–6}$ alkyl$)_2$, $–OC(NH)NH(C_{1–6}$ alkyl), $–OC(NH)NH_2$, $–NHC(NH)N(C_{1–6}$ alkyl$)_2$, $–NHC(=NH)NH_2$, $–NHSO_2(C_{1–6}$ alkyl), $–SO_2N(C_{1–6}$ alkyl$)_2$, $–SO_2NH(C_{1–6}$ alkyl), $–SO_2NH_2$,– $SO_2C_{1–6}$ alkyl, $–SO_2OC_{1–6}$ alkyl, $–OSO_2C_{1–6}$ alkyl, $–SOC_{1–6}$ alkyl, $–Si(C_{1–6}$ alkyl$)_3$, $–OSi(C_{1–6}$ alkyl$)_3$ $–C(=S)N(C_{1–6}$ alkyl$)_2$, $C(=S)NH(C_{1–6}$ alkyl), $C(=S)NH_2$, $–C(=O)S(C_{1–6}$ alkyl), $–C(=S)SC_{1–6}$ alkyl, $–SC(=S)SC_{1–6}$ alkyl, $–P(=O)_2(C_{1–6}$ alkyl), $–P(=O)(C_{1–6}$ alkyl$)_2$, $–OP(=O)(C_{1–6}$ alkyl$)_2$, $–OP(=O)(OC_{1–6}$ alkyl$)_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, $C_{6–10}$ aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein $X^–$ is a counterion.

[00309] A "counterion" or "anionic counterion" is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.,* $F^–$, $Cl^–$, $Br^–$, $I^–$), $NO_3^–$, $ClO_4^–$, $OH^–$, $H_2PO_4^–$, $HSO_4^–$, SO_4^{-2}sulfonate ions (*e.g.,* methansulfonate, trifluoromethanesulfonate, p–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), and carboxylate ions (*e.g.,* acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

[00310] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substitutents include, but are not limited to, hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14

membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[00311] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other definitions

[00312] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using

counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[00313] A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.,* a male or female of any age group, *e.g.,* a pediatric subject (*e.g,* infant, child, adolescent) or adult subject (*e.g.,* young adult, middle–aged adult or senior adult)) and/or a non-human animal, *e.g.,* a mammal such as primates (*e.g.,* cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal. The terms "human," "patient," and "subject" are used interchangeably herein.

[00314] Disease, disorder, and condition are used interchangeably herein.

[00315] As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a subject is suffering from the specified disease, disorder or condition, which reduces the severity of the disease, disorder or condition, or retards or slows the progression of the disease, disorder or condition ("therapeutic treatment"), and also contemplates an action that occurs before a subject begins to suffer from the specified disease, disorder or condition ("prophylactic treatment").

[00316] In general, the "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of the invention may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the age, health, and condition of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

[00317] As used herein, and unless otherwise specified, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a disease, disorder or condition, or to delay or minimize one or more symptoms associated with the disease, disorder or condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the disease, disorder or condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

[00318] As used herein, and unless otherwise specified, a "prophylactically effective amount" of a compound is an amount sufficient to prevent a disease, disorder or condition, or one or more symptoms associated with the disease, disorder or condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the disease, disorder or condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

Pharmaceutical Compositions

[00319] In another aspect, the invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a effective amount of a compound of Formulaes (**I**), (**II-a**), (**II-b**), (**III**), (**IV**), (**V**), (**VI**), or (**VII**).

[00320] When employed as pharmaceuticals, the compounds provided herein are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

[00321] In one embodiment, with respect to the pharmaceutical composition, the carrier is a parenteral carrier, oral or topical carrier.

[00322] The present invention also relates to a compound of the present invention or pharmaceutical composition thereof for use as a pharmaceutical or a medicament.

[00323] Generally, the compounds provided herein are administered in a therapeutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[00324] The pharmaceutical compositions provided herein can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, the compounds provided herein are preferably formulated as either injectable or oral compositions or as salves, as lotions or as patches all for transdermal administration.

[00325] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units

suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[00326] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00327] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the active compound in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

[00328] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s), generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight. When formulated as a ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or the formulation. All such known transdermal formulations and ingredients are included within the scope provided herein.

[00329] The compounds provided herein can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[00330] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques

and the like are set forth in Part 8 of *Remington's Pharmaceutical Sciences*, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

[00331] The above-described components for orally administrable, injectable, or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of *Remington's The Science and Practice of Pharmacy*, 21st edition, 2005, Publisher: Lippincott Williams & Wilkins, which is incorporated herein by reference.

[00332] The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in *Remington's Pharmaceutical Sciences*.

[00333] The present invention also relates to the pharmaceutically acceptable formulations of a compound of the present invention. In one embodiment, the formulation comprises water. In another embodiment, the formulation comprises a cyclodextrin derivative. The most common cyclodextrins are α–, β– and γ– cyclodextrins consisting of 6, 7 and 8 α–1 ,4–linked glucose units, respectively, optionally comprising one or more substituents on the linked sugar moieties, which include, but are not limited to, methylated, hydroxyalkylated, acylated, and sulfoalkylether substitution. In certain embodiments, the cyclodextrin is a sulfoalkyl ether β–cyclodextrin, *e.g.,* for example, sulfobutyl ether β–cyclodextrin, also known as Captisol®. See, *e.g.,* U.S. 5,376,645. In certain embodiments, the formulation comprises hexapropyl-β-cyclodextrin. In a more particular embodiment, the formulation comprises hexapropyl-β-cyclodextrin (10-50% in water).

[00334] The present invention also relates to the pharmaceutically acceptable acid addition salt of a compound of the present invention. The acid which may be used to prepare the pharmaceutically acceptable salt is that which forms a non-toxic acid addition salt, *i.e.,* a salt containing pharmacologically acceptable anions such as the hydrochloride, hydroiodide, hydrobromide, nitrate, sulfate, bisulfate, phosphate, acetate, lactate, citrate, tartrate, succinate, maleate, fumarate, benzoate, para-toluenesulfonate, and the like.

[00335] Injection dose levels range from about 0.1 mg/kg/hour to at least 10 mg/kg/hour, all for from about 1 to about 120 hours and especially 24 to 96 hours. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 2 g/day for a 40 to 80 kg human patient.

[00336] For the prevention and/or treatment of long-term conditions the regimen for treatment usually stretches over many months or years so oral dosing is preferred for patient convenience and tolerance. With oral dosing, one to five and especially two to four and typically three oral doses per day are representative regimens. Using these dosing patterns, each dose provides from about 0.01 to about 20

mg/kg of the compound provided herein, with preferred doses each providing from about 0.1 to about 10 mg/kg, and especially about 1 to about 5 mg/kg.

[00337] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses.

[00338] When used to prevent the onset of a CNS-disorder, the compounds provided herein will be administered to a subject at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Subjects at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

Combination treatment

In some embodiments, the methods described herein is used in combination with another method, such as a method of treatment comprising administering to a subject an additional therapeutic agent. Additional therapeutic agents are described herein. Administered "in combination", as used herein, means that two (or more) different treatments are delivered to the subject during the course of the subject's affliction with the disorder, *e.g.,* the two or more treatments are delivered after the subject has been diagnosed with the disorder and before the disorder has been cured or eliminated or treatment has ceased for other reasons. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as "simultaneous" or "concurrent delivery". In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, *e.g.,* an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

Additional therapies

Additional therapies include, but are not limited to dietary cholesterol therapy (*e.g.,* cholesterol supplementation), statin treatment (*e.g.,* 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (*e.g.,* HMG CoA reductase inhibitiors), bile acid supplementation or downstream hormone supplementation, medical therapies, and surgical interventions, antioxidants, and gene therapy.

Statins

Statins are hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors that inhibit the enzyme HMG-CoA reductase (the cholesterol pathway proximal to the enzymatic defect in SLOS). Exemplary statins include, but are not limited to, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

Claims

1. A method of treating a subject suffering from a sterol synthesis disorder (*e.g.,* disorder of cholesterol biosynthesis; disorder characterized by a significant disruption of sterol biosynthesis) or a sterol deficiency disorder (*e.g.,* abnormal levels (e.g., abnormally low) of a sterol described herein; *e.g.,* 2 standard deviations below normal sterol levels as described herein), comprising administering to the subject an effective amount of an NMDA receptor modulating compound or pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein the subject suffers from a sterol synthesis disorder and a 24(S)-hydroxycholesterol deficiency disorder.

3. The method of claim 1, wherein the sterol deficiency disorder is characterized by the presence of 24(S)-hydroxycholesterol in the plasma of the subject at significantly reduced levels (*e.g.,* at least 1 or 2 standard deviations below) compared with the plasma of a subject not suffering from a sterol deficiency disorder).

4. The method of claim 1, wherein the metabolic processing of 24(S)-hydroxycholesterol is low as compared with a subject not suffering from the disorder.

5. The method of claim 1, wherein the compound is 24(S)-hydroxycholesterol.

6. The method of claim 1, wherein the compound is 24(S)-hydroxycholesterol 3-sulfate.

7. The method of claim 1, wherein the sterol is 24(S)-hydroxycholesterol, 25-hydroxycholesterol, or 27(S)-hydroxycholesterol.

8. The method of claim 1, wherein the sterol disorder is selected from: Smith-Lemli-Opitz syndrome; Conradi-Hunermann syndrome; Greenberg dysplasia; Desmosterolosis; Cerebrotendinous Xanthomatosis (CTX); Mevalonate Kinase Deficiency Syndromes (MKD); SC4MOL gene mutation (SMO Deficiency); lathosterolosis; X-linked dominant chondrodysplasia puncata; CHILD syndrome or CK-syndrome; autism spectrum disorder; Niemann-Pick disease; and disorders of dolichol synthesis or metabolism.

9. The method of claim 8, wherein the sterol disorder is selected from: Smith-Lemli-Opitz syndrome.

10. The method of claim 1, wherein the compound has an EC_{50} of 10 μM or less (*e.g.,* 5 μM, 1 μM, 500 nM, 350 nM, 250 nM, 100 nM, 50 nM, 10 nM or less).

11. The method of claim 1, wherein the compound is present at an effective plasma concentration of 10 to 800 ng/mL of plasma (*e.g.,* 10 to 600 ng/mL, 10 to 500 ng/mL, 25 to 500 ng/mL, 40 to 500 ng/mL, 25 to 350 ng/mL).

12. The method of claim 1, wherein the compound is present at an effective plasma concentration of at least 10 ng/mL of plasma (*e.g.,* at least 15 ng/mL, 20 ng/mL, 25 ng/mL, 30 ng/mL, 30 ng/mL, 35 ng/mL, 40 ng/mL, 45 ng/mL, 50 ng/mL, 55 ng/mL).

13. The method of claim 1, wherein the compound is a NMDA receptor modulator (*e.g.,* positive modulator, negative modulator).

14. The method of claim 1, wherein the compound is a compound of Formula (**I**), (**II-a**), (**II-b**), (**III**), (**IV**), (**V**), (**VI**), (**VII**), (**VIII**), (**IX-A**), (**IX-B**), (**X**), (**XI-A**), or (**XI-B**).

15. The method of claim 1, wherein the compound is a compound of Formula (**I**).

16. The method of claim 1, wherein the administration to the subject normalizes concentrations of oxysterols in circulation relative to a subject not administered with the compound or administered with a placebo.

17. The method of claim 1, wherein the administration to the subject elevates levels of cholesterol in tissues and plasma relative to a subject not administered with the compound or administered with a placebo.

18. The method of claim 1, wherein the subject is an infant.

19. The method of claim 1, wherein the subject is less than 21, 18, 15, 13, 12, 10, 8, 6, 4, 3, 2, 1 year old.

20. The method of claim 1, further comprising administration of an additional therapy.

21. The method of claim 1, within the additional therapy is dietary cholesterol therapy (*e.g.,* cholesterol supplementation, statin treatment (*e.g.,* 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (*e.g.,* HMG CoA reductase inhibitors), *e.g.,* simvastatin), bile acid supplementation or downstream hormone supplementation, medical therapies, or surgical interventions; antioxidants; gene therapy.

22. A dosage form comprising a compound of Formula (**I**), (**II-a**), (**II-b**), (**III**), (**IV**), (**V**), (**VI**), (**VII**), (**VIII**), (**IX-A**), (**IX-B**), (**X**), (**XI-A**), or (**XI-B**) configured for administration in a subject, wherein the subject is a child.

23. The dosage form of claim 22, wherein the dosage form is a liquid suspension, sprinkle, meltaway, sublingual, or injectable.

24. The dosage form of claim 23, wherein the dosage form is a solid dosage form.

25. The dosage form of claim 24, wherein the solid dosage form is a tablet, capsule, or pill.