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(54) Benævnelse: **TRICYKLISK P2-LIGAND INDEHOLDENDE HIV-PROTEASEHÆMMERE MOD HIV/AIDS**

(56) Fremdragne publikationer:
WO-A1-2012/031237
WO-A1-2012/092188
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JP-A- S5 524 139
A. J. BIRCH ET AL: "1027. Aucubin", JOURNAL OF THE CHEMICAL SOCIETY, 1 January 1961 (1961-01-01), page 5194, XP055677436, ISSN: 0368-1769, DOI: 10.1039/jr9610005194
GHOSH ET AL.: 'Highly Potent HIV-1 Protease Inhibitors with Novel Tricyclic P2-ligands: Design, Synthesis, and Protein-ligand X-Ray Studies' J MED CHEM. vol. 56, no. 17, 2013, pages 6792 - 6802, XP055489766
ZHANG ET AL.: 'Novel P2 tris-tetrahydrofuran group in antiviral compound 1 (GRL-0519) fills the S2 binding pocket of selected mutants of HIV-1 protease' J MED CHEM. vol. 56, no. 3, 2013, pages 1074 - 1083, XP055489769
AMANO ET AL.: 'GRL-0519, a Novel Oxatricyclic Ligand-Containing Nonpeptidic HIV-1 Protease Inhibitor (PI), Potently Suppresses Replication of a Wide Spectrum of Multi-PI-Resistant HIV-1 Variants In Vitro' ANTIMICROBIAL AGENTS AND CHEMOTHERAPY vol. 57, no. 5, pages 2036 - 2046, XP055489770
AGNISWAMY ET AL.: 'Extreme multidrug resistant HIV-1 protease with 20 mutations is resistant to novel

Fortsættes ...

protease inhibitors with P1'-pyrrolidinone or P2-tris-tetrahydrofuran' J MED CHEM. vol. 56, no. 10, pages 4017 - 4027, XP055489773

DESCRIPTION

BACKGROUND OF THE INVENTION

[0001] The AIDS epidemic is one of the most challenging problems in medicine in the 21st century. Among many strategies to combat this disease, highly active antiretroviral therapy (HAART) with HIV protease inhibitors (Pis) in combination with reverse transcriptase inhibitors (RTIs) continues to be the first line treatment for control of HIV infection. Although such combination therapy has improved quality of life, enhanced HIV management, and halted the progression of the disease, there remain many challenges to treating this devastating disease, including decreasing both the toxicity and complexity of these treatment regimens. In addition, there is a growing population of patients that is developing multi-drug resistant strains of HIV. And there is ample evidence that these strains can be further transmitted.

[0002] Even though HAART has had a major impact on the AIDS epidemic in industrially advanced nations, it has not achieved the eradication of human immunodeficiency virus type 1 (HIV 1), in part due to the viral reservoirs remaining in blood and infected tissues. The limitation of antiviral therapy of AIDS is also exacerbated by complicated regimens, the development of drug-resistant HIV-1 variants, and a number of inherent adverse effects. Further, efforts to bring about the optimal benefits of HAART have met with a number of challenges, including (i) drug-related toxicities; (ii) partial restoration of immunologic functions once individuals developed AIDS; (iii) development of various cancers as a consequence of survival prolongation; (iv) flame-up of inflammation in individuals receiving HAART or immune re-construction syndrome (IRS); and (v) increased cost of antiviral therapy. Such limitations of HAART are exacerbated by the development of drug-resistant HIV-1 variant.

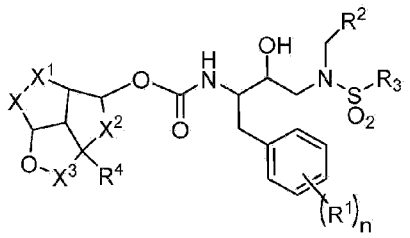
[0003] WO 2012/031237 A1 discloses tricyclic ether carbamates that inhibit HIV proteolytic enzymes and WO 2015/175994 A1 discloses compounds that are inhibitors of HIV-1 protease. Anti-HIV agents are also disclosed in GHOSH et al. ("Highly Potent HIV-1 Protease Inhibitors with Novel Tricyclic P2-ligands: Design, Synthesis, and Protein-ligand X-Ray Studies" J Med Chem., vol. 56, no. 17, 2013, pages 6792-6802), ZHANG et al. ("Novel P2 tris-tetrahydrofuran group in antiviral compound 1(GRL-0519) fills the S2 binding pocket of selected mutants of HIV-1 protease", J Med Chem., vol. 56, no. 3, 2013, pages 1074-1083), AMANO et al. ("GRL-0519, a Novel Oxatricyclic Ligand-Containing Nonpeptidic HIV-1 Protease Inhibitor (PI), Potently Suppresses Replication of a Wie Spectrum of Multi-PI-Resistant HIV-1 Variants In Vitro", Antimicrobial Agents and Chemotherapy, vol. 57, no. 5, pages 2036-2046) and AGNISWAMY et al. ("Extreme multidrug resistant HIV-1 protease with 20 mutations is resistant to novel protease inhibitors with P1'-pyrrolidinone or P2-tris-tetrahydrofuran", J Med Chem., vol. 56, no. 10, pages 4017-42027).

[0004] There is presently a paucity of antiretroviral drugs or agents that are not only substantially specific for HIV-1, but also devoid of toxicity or side effects in the therapy of AIDS.

DETAILED DESCRIPTION OF THE INVENTION

[0005] While the disclosed subject matter will be described in conjunction with the enumerated claims, it will be understood that the exemplified subject matter is not intended to limit the claims to the disclosed subject matter.

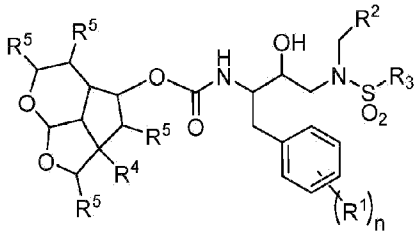
[0006] Various embodiments are directed to a compound of the formula (I):



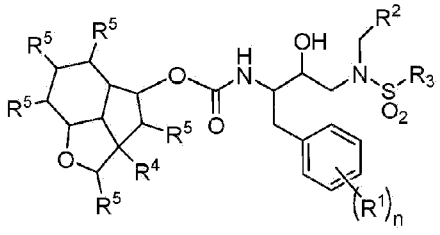
(I)

or a pharmaceutically acceptable salt, polymorph, solvate or clathrate thereof, wherein: n is an integer from 0 to 3; X is $(-CHR^5-)_m$ or -O-, wherein m is 1 or 2 and each R^5 is, independently H, alkyl or alkoxy; X^1, X^2, and X^3 are each, independently, $(-CHR^5-)_m$,; R^1 is alkyl, alkoxy, aryl, heterocyclyl, halo, hydroxy or amino; R^2 is alkyl; R^3 is aryl, benzthiazole, benzoxazole, benzofuranyl or indolyl; and R^4 is H, alkyl or alkoxy; wherein alkoxy refers to an oxygen atom connected to an alkyl group including a cycloalkyl group; and alkyl refers to substituted and unsubstituted straight chain and branched alkyl groups and cycloalkyl groups having from 1 to 40 carbon atoms. In some examples, n is 0. In addition, (i) X^1 can be $(-CHR^5-)_m$, with m being 2, and X^2 and X^3 can each be $(-CHR^5-)_m$, with m being 1 and each R^5 being the same or different and as defined herein; or (ii) X^1 and X^2 can be $(-CHR^5-)_m$, with m being 1, and X^3 can be $(-CHR^5-)_m$, with m being 2 and each R^5 being the same or different and as defined herein. In either instance (i) or (ii), X can be O. In addition, either instance (i) or (ii), X can be $(-CHR^5-)_m$, wherein m is 1 and R^5 is as defined herein (e.g., H). In any of the foregoing examples, R^4 can be H or alkoxy.

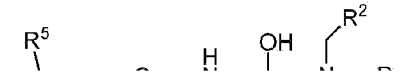
[0007] Various other embodiments are directed to a compound of the formula (Ia)-(Ic):

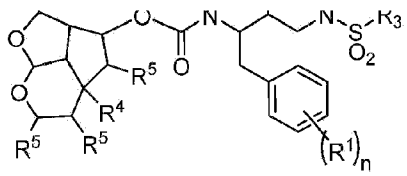


(Ia)



(Ib)

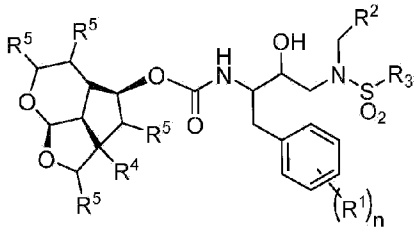


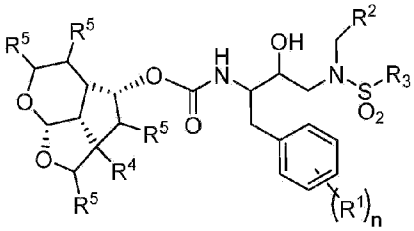


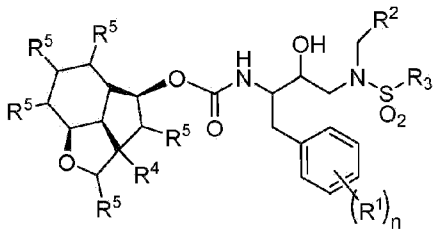
(Ic)

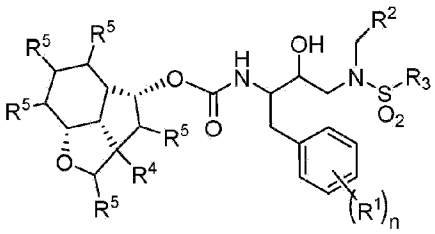
or a pharmaceutically acceptable salt, polymorph, solvate or clathrate thereof, wherein n, R^1, R^2, R^3, R^4 and R^5 are as defined herein and wherein each R^5 can be the same or different.

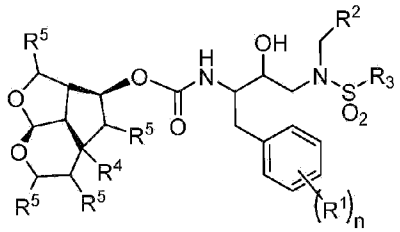
[0008] All diastereomers of the compounds of the formula (I) and (Ia)-(Ic) are contemplated herein, including:

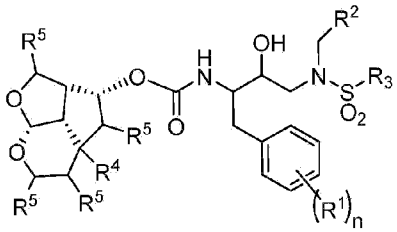


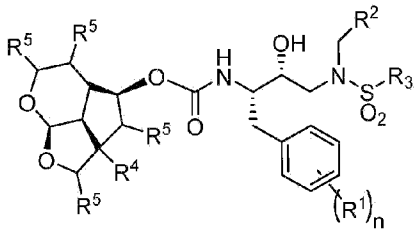


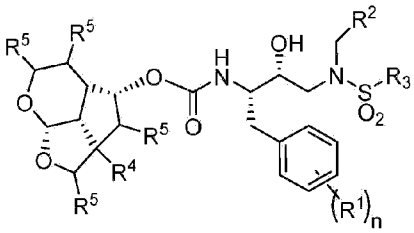


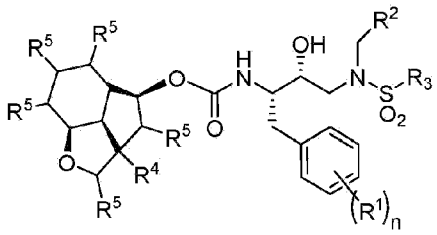


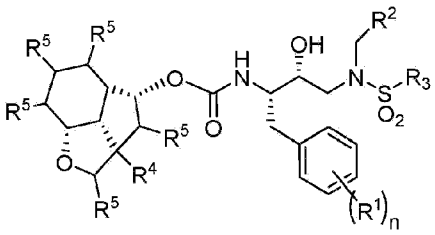


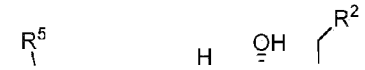


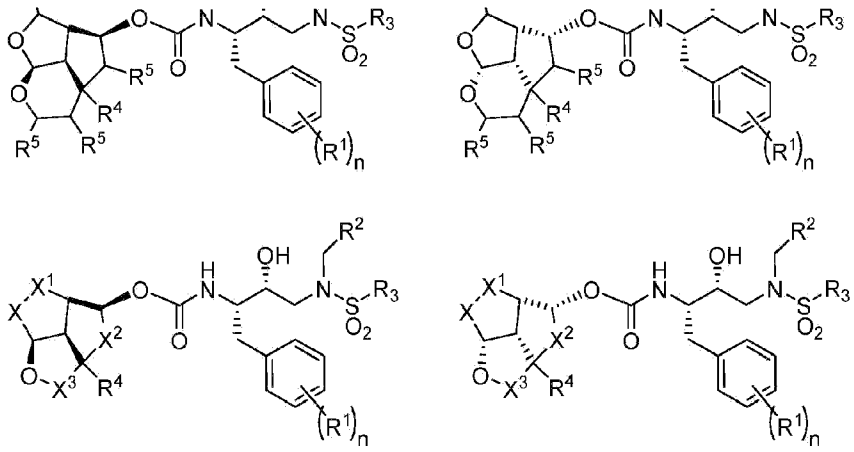






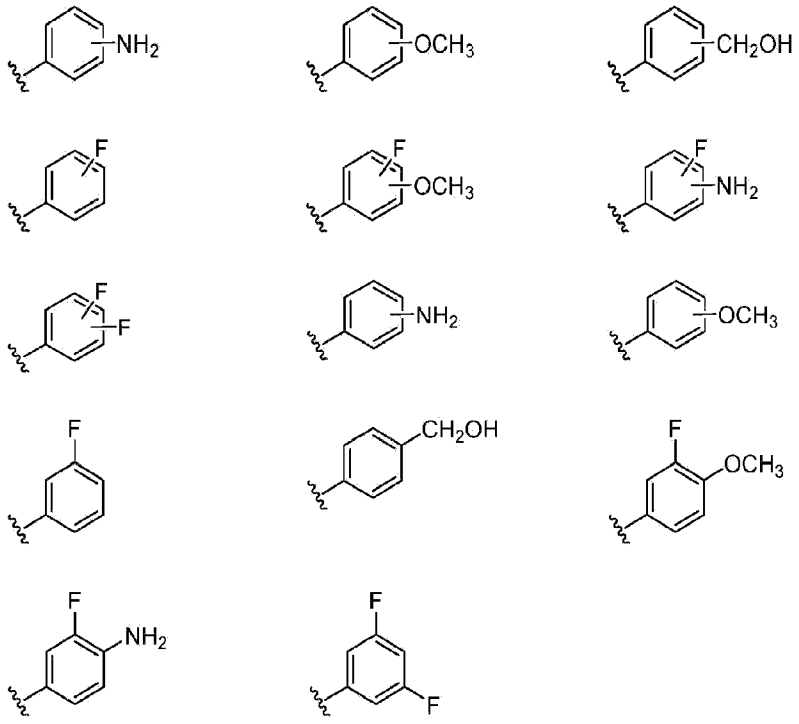




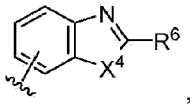


or a pharmaceutically acceptable salt, polymorph, solvate or clathrate thereof, wherein n, R^1, R^2, R^3, and R^4 are as defined herein. In addition, (i) X^1 can be $(-CHR^5-)_m$, with m being 2, and X^2 and X^3 can each be $(-CHR^5-)_m$, with m being 1 and each R^5 being the same or different and as defined herein; or (ii) X^1 and X^2 can be $(-CHR^5-)_m$, with m being 1, and X^3 can be $(-CHR^5-)_m$, with m being 2 and each R^5 being the same or different and as defined herein. In either instance (i) or (ii), X can be O. In addition, either instance (i) or (ii), X can be $(-CHR^5-)_m$, wherein m is 1 and R^5 is as defined herein (e.g., H). In any of the foregoing examples, R^4 can be H or alkoxy.

[0009] In any of the examples disclosed herein, R^3 can an unsubstituted or substituted aryl. R^3 can be, for example, phenyl. But R^3 can be substituted aryl. The substituted aryl groups represented by R^3 herein can be, for example, selected from the group consisting of:



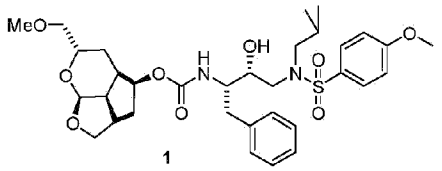
[0010] In any of the examples disclosed herein, R^3 is a benzthiazole or a benzoxazole:



,

wherein R^6 is alkyl (e.g., C_1-C_6 alkyl), alkylamino (e.g., C_1-C_6 alkylamino), cycloalkylamino (e.g., C_3-C_6 cycloalkylamino), cycloalkyl heterocycloamino (e.g., C_3-C_6 cycloalkyl-C_3-C_6 heterocycloamino), heterocyclo cycloalkylamino (e.g., C_3-C_6 heterocyclo-C_3-C_6 cycloalkylamino) or heterocycloamino (e.g., C_3-C_6 heterocycloamino); and X^4 is S, O or NR^7, wherein R^7 is H, alkyl, cycloalkyl or alkylaryl. X^4 can be S or O.

[0011] Examples of the compounds of the formula (I) and (Ia)-(Ic) include, but are not limited to the compounds of formula 1-24:



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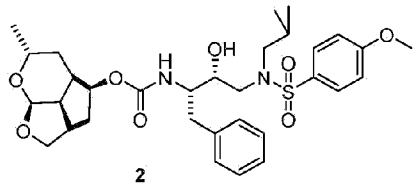

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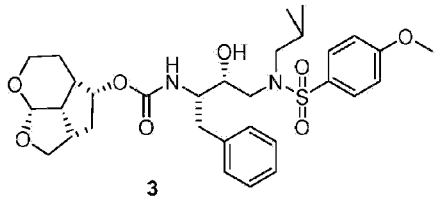

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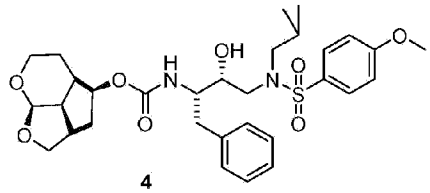

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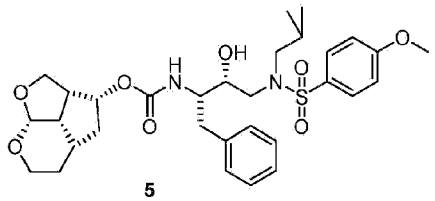

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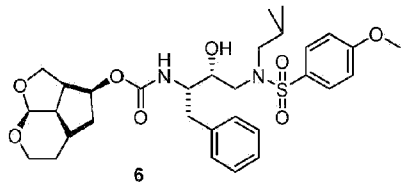

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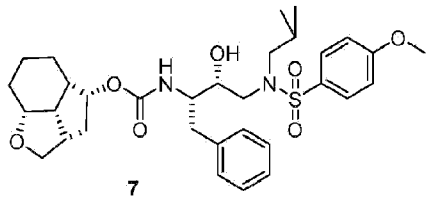

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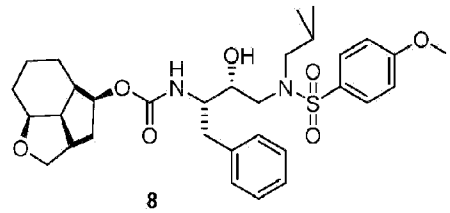

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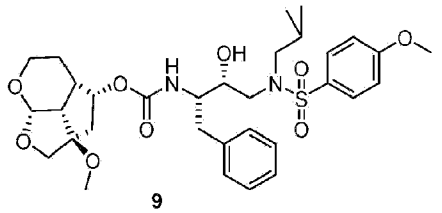

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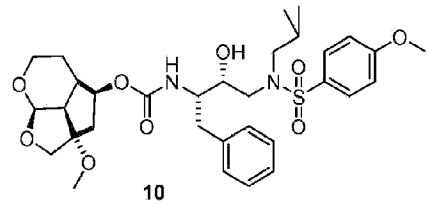

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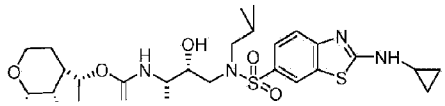

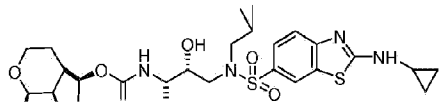

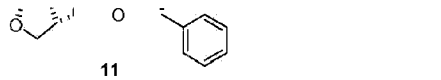

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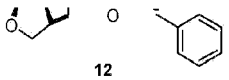

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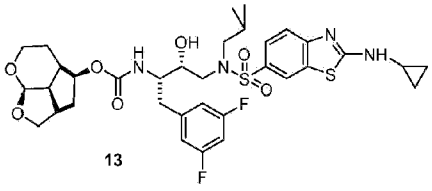

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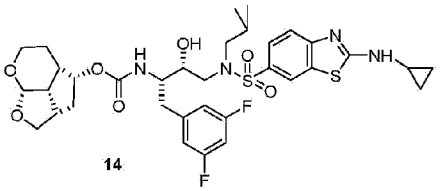

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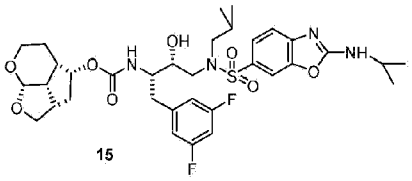

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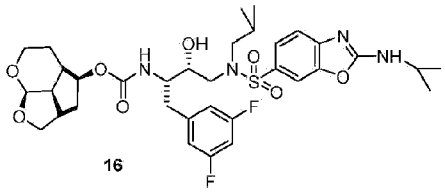

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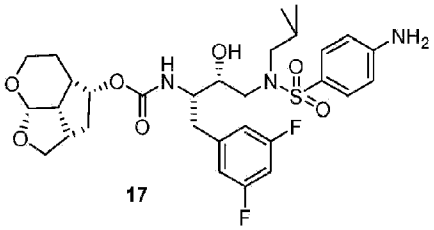

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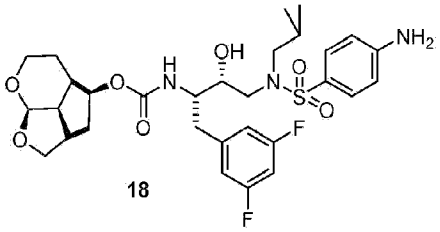

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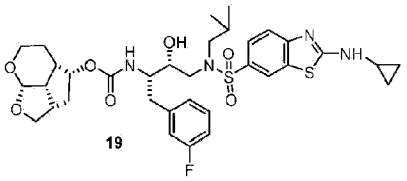

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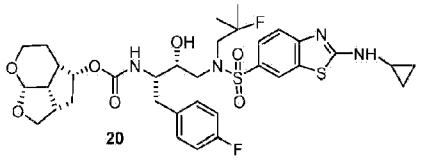

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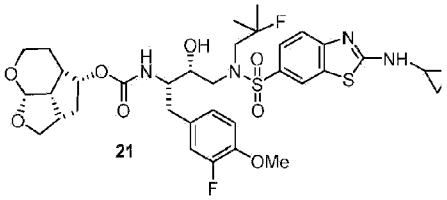

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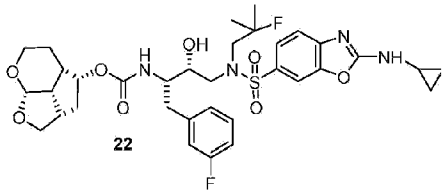

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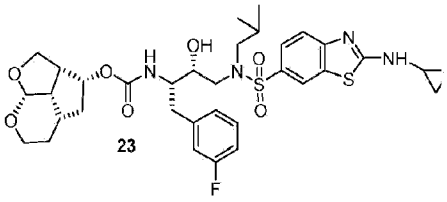

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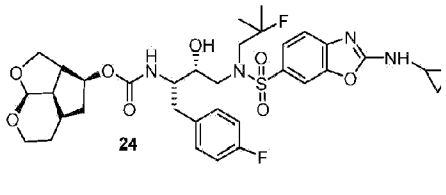

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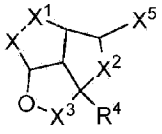
or a pharmaceutically acceptable salt, polymorph, solvate or clathrate thereof.

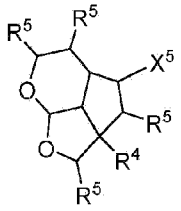
[0012] Compounds of the formula (II), which are disclosed herein but not claimed, can serve as, among other things, building blocks for the various compounds described herein:



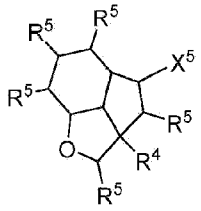
(II)

or a pharmaceutically acceptable salt, polymorph, solvate or clathrate thereof, wherein X, X^1-X^3, and R^4 are defined herein and wherein X^5 is selected from the group consisting of hydroxy, alkoxy, amino, C(O)R, C(O)OR, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}O(R)C(O)R$, $(CH_2)_{0-2}N(R)C(O)R$, $(CH_2)_{0-2}O(R)C(O)OR$, $(CH_2)_{0-2}O(R)C(O)OR$ or $(CH_2)_{0-2}N(R)N(R)_2$, wherein each R can be, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl or two R groups bonded to a nitrogen atom or to adjacent nitrogen atoms can together with the nitrogen atom or atoms form a heterocyclyl. In addition, (i) X^1 can be $(-CHR^5-)_m$, with m being 2, and X^2 and X^3 can each be $(-CHR^5-)_m$, with m being 1 and each R^5 being the same or different and as defined herein; or (ii) X^1 and X^2 can be $(-CHR^5-)_m$, with m being 1, and X^3 can be $(-CHR^5-)_m$, with m being 2 and each R^5 being the same or different and as defined herein. In either instance (i) or (ii), X can be O. In addition, either instance (i) or (ii), X can be $(-CHR^5-)_m$, wherein m is 1 and R^5 is as defined herein (e.g., H). In any of the foregoing examples, R^4 can be H or alkoxy.

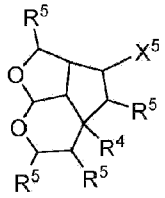
[0013] Also disclosed but not claimed are compounds of the formula (IIa-IIc):



(IIa)



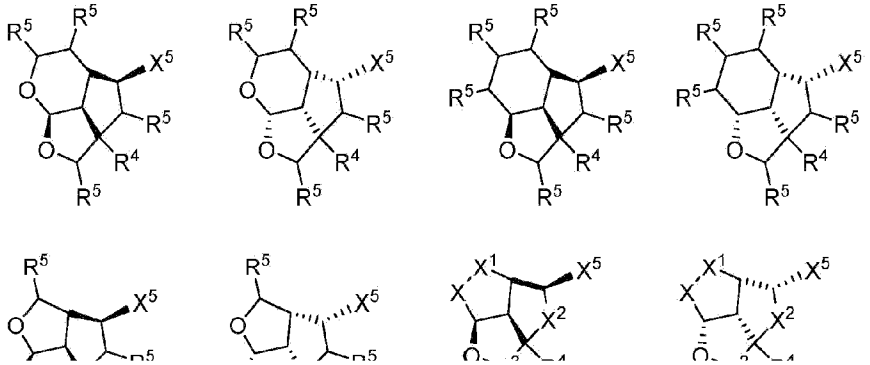
(IIb)

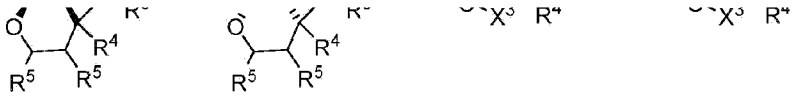


(IIc)

wherein R^4, R^5 and X^5 are defined herein.

[0014] All diastereomers of the compounds of the formula (II) and (IIa)-(IIc) are contemplated herein but not claimed, including compounds of the formula:





wherein X, X^1-X^3, R^4, and X^5 are as defined herein. In addition, (i) X^1 can be $(-CHR^5-)_m$, with m being 2, and X^2 and X^3 can each be $(-CHR^5-)_m$, with m being 1 and each R^5 being the same or different and as defined herein; or (ii) X^1 and X^2 can be $(-CHR^5-)_m$, with m being 1, and X^3 can be $(-CHR^5-)_m$, with m being 2 and each R^5 being the same or different and as defined herein. In either instance (i) or (ii), X can be O. In addition, either instance (i) or (ii), X can be $(-CHR^5-)_m$, wherein m is 1 and R^5 is as defined herein (e.g., H). In any of the foregoing examples, R^4 can be H or alkoxy.

[0015] Various embodiments also contemplate pharmaceutical compositions comprising one or more compounds of the various embodiments described herein (e.g. a compound of the formula (I), (Ia)-(Ic) and 1-24) and one or more pharmaceutically acceptable carriers, diluents, excipients or combinations thereof. A "pharmaceutical composition" refers to a chemical or biological composition suitable for administration to a subject (e.g., mammal). Such compositions may be specifically formulated for administration via one or more of a number of routes, including but not limited to buccal, cutaneous, epicutaneous, epidural, infusion, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, pulmonary, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. In addition, administration can by means of capsule, drops, foams, gel, gum, injection, liquid, patch, pill, porous pouch, powder, tablet, or other suitable means of administration.

[0016] A "pharmaceutical excipient" or a "pharmaceutically acceptable excipient" comprises a carrier, sometimes a liquid, in which an active therapeutic agent is formulated. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Examples of suitable formulations can be found, for example, in Remington, The Science And Practice of Pharmacy, 20th Edition, (Gennaro, A. R., Chief Editor), Philadelphia College of Pharmacy and Science, 2000.

[0017] As used herein "pharmaceutically acceptable carrier" or "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, sublingual, or oral administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary

active compounds can also be incorporated into the compositions.

[0018] Pharmaceutical compositions may be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

[0019] In some cases isotonic agents can be included in the pharmaceutical compositions, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the compounds described herein can be formulated in a time release formulation, for example in a composition that includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers may be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

[0020] Oral forms of administration are also contemplated herein. The pharmaceutical compositions may be orally administered as a capsule (hard or soft), tablet (film coated, enteric coated or uncoated), powder or granules (coated or uncoated) or liquid (solution or suspension). The formulations may be conveniently prepared by any of the methods well-known in the art. The pharmaceutical compositions may include one or more suitable production aids or excipients including fillers, binders, disintegrants, lubricants, diluents, flow agents, buffering agents, moistening agents, preservatives, colorants, sweeteners, flavors, and pharmaceutically compatible carriers.

[0021] For each of the recited embodiments, the compounds can be administered by a variety of dosage forms as known in the art. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, chewable tablets, quick dissolve tablets, effervescent tablets, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, tablets, multi-layer tablets, bi-layer tablets, capsules, soft gelatin capsules, hard gelatin capsules, caplets, lozenges, chewable lozenges, beads, powders, gum, granules, particles, microparticles, dispersible granules, cachets, douches, suppositories, creams, topicals, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, ingestibles, injectables (including subcutaneous, intramuscular, intravenous, and intradermal), infusions, and combinations thereof.

[0022] Other compounds which can be included by admixture are, for example, medically inert ingredients (e.g., solid and liquid diluent), such as lactose, dextrosesaccharose, cellulose, starch or calcium phosphate for tablets or capsules, olive oil or ethyl oleate for soft capsules and water or vegetable oil for suspensions or emulsions; lubricating agents such as silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; gelling agents such as colloidal clays; thickening agents such as gum tragacanth or sodium alginate, binding agents such as starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinylpyrrolidone; disintegrating agents such as starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuff; sweeteners; wetting agents such as lecithin, polysorbates or laurylsulphates; and other therapeutically acceptable accessory ingredients, such as humectants, preservatives, buffers and antioxidants, which are known additives for such formulations.

[0023] Liquid dispersions for oral administration can be syrups, emulsions, solutions, or suspensions. The syrups can contain as a carrier, for example, saccharose or saccharose with glycerol and/or mannitol and/or sorbitol. The suspensions and the emulsions can contain a carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

[0024] The amount of active compound in a therapeutic composition according to various embodiments may vary according to factors such as the disease state, age, gender, weight, patient history, risk factors, predisposition to disease, administration route, pre-existing treatment regime (e.g., possible interactions with other medications), and weight of the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time, or the dose may be proportionally reduced or increased as indicated by the exigencies of therapeutic situation.

[0025] "Dosage unit form," as used herein, refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals. In therapeutic use for treatment of conditions in mammals (e.g., humans) for which the compounds of the various embodiments described herein or an appropriate pharmaceutical composition thereof are effective, the compounds of the various embodiments described herein may be administered in an effective amount. The dosages as suitable for this invention may be a composition, a pharmaceutical composition or any other compositions described herein.

[0026] The dosage can be administered once, twice, or thrice a day, although more frequent

dosing intervals are possible. The dosage may be administered every day, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, and/or every 7 days (once a week). In one embodiment, the dosage may be administered daily for up to and including 30 days, preferably between 7-10 days. In another embodiment, the dosage may be administered twice a day for 10 days. If the patient requires treatment for a chronic disease or condition, the dosage may be administered for as long as signs and/or symptoms persist. The patient may require "maintenance treatment" where the patient is receiving dosages every day for months, years, or the remainder of their lives. In addition, the composition of this invention may be to effect prophylaxis of recurring symptoms. For example, the dosage may be administered once or twice a day to prevent the onset of symptoms in patients at risk, especially for asymptomatic patients.

[0027] The compositions described herein may be administered in any of the following routes: buccal, epicutaneous, epidural, infusion, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, pulmonary, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. The preferred routes of administration are buccal and oral. The administration can be local, where the composition is administered directly, close to, in the locality, near, at, about, or in the vicinity of, the site(s) of disease, e.g., inflammation, or systemic, wherein the composition is given to the patient and passes through the body widely, thereby reaching the site(s) of disease. Local administration can be administration to the cell, tissue, organ, and/or organ system, which encompasses and/or is affected by the disease, and/or where the disease signs and/or symptoms are active or are likely to occur. Administration can be topical with a local effect, composition is applied directly where its action is desired. Administration can be enteral wherein the desired effect is systemic (non-local), composition is given via the digestive tract. Administration can be parenteral, where the desired effect is systemic, composition is given by other routes than the digestive tract.

[0028] Various embodiments contemplate compositions comprising a therapeutically effective amount of one or more compounds of the various embodiments described herein (e.g. a compound of the formula (I), (Ia)-(Ic) and compounds 1-24). The compositions are useful in a method for treating an HIV (e.g., HIV-1) infection or AIDS, the method comprising administering a therapeutically effective amount of one or more compounds of any preceding claim to a patient in need thereof. Various embodiments contemplate a compound of the formula (I), (Ia)-(Ic) and compounds 1-24 for use as a medicament for treating a patient in need of relief from an HIV infection or AIDS.

[0029] The term "therapeutically effective amount" as used herein, refers to that amount of one or more compounds of the various embodiments described herein (e.g. a compound of the formula (I), (Ia)-(Ic) and compounds 1-24) that elicits a biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. In some embodiments, the therapeutically effective amount is that which may

treat or alleviate the disease or symptoms of the disease at a reasonable benefit/risk ratio applicable to any medical treatment. However, it is to be understood that the total daily usage of the compounds and compositions described herein may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically-effective dose level for any particular patient will depend upon a variety of factors, including the condition being treated and the severity of the condition; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, gender and diet of the patient: the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidentally with the specific compound employed; and like factors well known to the researcher, veterinarian, medical doctor or other clinician. It is also appreciated that the therapeutically effective amount can be selected with reference to any toxicity, or other undesirable side effect, that might occur during administration of one or more of the compounds described herein.

[0030] In some embodiments, the compounds of the various embodiments described herein can have an HIV-1 protease inhibition constant (K_i) of from about 1 fM to about 200 nM (e.g., about 100 fM to about 200 nM, about 100 fM to about 100 pM, about 250 fM to about 100 pM, about 500 fM to about 5 pM, about 5 pM to about 100 pM, about 50 pM to about 250 pM, about 500 pM to about 100 nM or about 300 pM to about 75 nM).

[0031] In other embodiments, the compounds of the various embodiments described herein have an antiviral activity in vitro against a wild-type laboratory strain, HIV-1_{LAI}, with half-maximal inhibitory concentration (IC_{50}) of from about 1 fM to about 200 nM (e.g., about 100 fM to about 200 nM, about 100 fM to about 100 pM, about 250 fM to about 100 pM, about 500 fM to about 5 pM, from about 10 pM to about 50 nM, about 10 pM to about 500 pM, about 100 pM to about 750 pM, about 500 pM to about 1 nM or about 500 pM to about 50 nM).

[0032] In still other embodiments, the compounds of the various embodiments described herein have a darunavir-resistant HIV-1 variant (e.g., NL4-3R, DRV_RP20, DRV_RP30, and DRV_RP51) antiviral IC_{50} of from about 200 fM to about 100 nM (e.g., from about 200 fM to about 600 fM, about 200 fM to about 50 pM, about 500 fM to about 500 pM, about 300 fM to about 1 pM). In yet other embodiments, the compounds of the various embodiments described herein have a darunavir-resistant HIV-1 variants (e.g., NL4-3R, DRV_RP20, DRV_RP30, and DRV_RP51) IC_{50} of from about 50 pM to about 50 nM (e.g., from about 100 pM to about 50 nM or about 500 pM to about 10 nM). In still other embodiments, the compounds of the various embodiments described herein have a darunavir-resistant HIV-1 protease (e.g., NL4-3R, DRV_RP20, DRV_RP30, and DRV_RP51) antiviral IC_{50} of from about 1 nM to about 100 nM (e.g., from about 10 nM to about 75 nM or about 10 nM to about 75 nM).

[0033] Values expressed in a range format should be interpreted in a flexible manner to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if

each numerical value and sub-range were explicitly recited. For example, a range of "about 0.1% to about 5%" or "about 0.1% to 5%" should be interpreted to include not just about 0.1% to about 5%, but also the individual values *(e.g.,* 1%, 2%, 3%, and 4%) and the sub-ranges *(e.g.,* 0.1% to 0.5%, 1.1% to 2.2%, 3.3% to 4.4%) within the indicated range. The statement "about X to Y" has the same meaning as "about X to about Y," unless indicated otherwise. Likewise, the statement "about X, Y, or about Z" has the same meaning as "about X, about Y, or about Z," unless indicated otherwise.

[0034] In this document, the terms "a," "an," or "the" are used to include one or more than one unless the context clearly dictates otherwise. The term "or" is used to refer to a nonexclusive "or" unless otherwise indicated. In addition, it is to be understood that the phraseology or terminology employed herein, and not otherwise defined, is for the purpose of description only and not of limitation. Any use of section headings is intended to aid reading of the document and is not to be interpreted as limiting. Further, information that is relevant to a section heading may occur within or outside of that particular section. In the event of inconsistent usages between this document and documents referred to herein, the usage in the referenced document should be considered supplementary to that of this document; for irreconcilable inconsistencies, the usage in this document controls.

[0035] In the methods described herein, the steps can be carried out in any order without departing from the principles of the invention, except when a temporal or operational sequence is explicitly recited. Furthermore, specified steps can be carried out concurrently unless explicit claim language recites that they be carried out separately. For example, a claimed step of doing X and a claimed step of doing Y can be conducted simultaneously within a single operation, and the resulting process will fall within the literal scope of the claimed process.

[0036] The term "about" as used herein can allow for a degree of variability in a value or range, for example, within 10%, within 5%, or within 1% of a stated value or of a stated limit of a range.

[0037] The term "substantially" as used herein refers to a majority of, or mostly, as in at least about 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, 99.99%, or at least about 99.999% or more.

[0038] The term "substituted" or "substituent" as used herein refers to a group that can be or is substituted onto a molecule or onto another group (e.g., on an aryl or an alkyl group). Examples of substituents include, but are not limited to, a halogen (e.g., F, Cl, Br, and I), OR, $OC(O)N(R)_2$, CN, NO, NO_2, ONO_2, azido, CF_3, OCF_3, R, O (oxo), S (thiono), C(O), S(O), methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, SO_2R, $SO_2N(R)_2$, SO_3R, $-(CH_2)_{0-2}P(O)(OR)_2$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}N(R)C(O)R$, $(CH_2)_{0-2}N(R)C(O)OR$, $(CH_2)_{0-2}N(R)N(R)_2$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$,

C(O)N(OR)R, or C(=NOR)R wherein each R can be, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl or two R groups bonded to a nitrogen atom or to adjacent nitrogen atoms can together with the nitrogen atom or atoms form a heterocyclyl, which can be mono- or independently multi-substituted.

[0039] The term "alkyl" as used herein refers to substituted or unsubstituted straight chain and branched alkyl groups and cycloalkyl groups having from 1 to 40 carbon atoms (C_1-C_{40}), 1 to about 20 carbon atoms (C_1-C_{20}), 1 to 12 carbons (C_1-C_{12}), 1 to 8 carbon atoms (C_1-C_8), or, in some embodiments, from 1 to 6 carbon atoms (C_1-C_6). Examples of straight chain alkyl groups include those with from 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. As used herein, the term "alkyl" encompasses n-alkyl, isoalkyl, and anteisoalkyl groups as well as other branched chain forms of alkyl. Representative substituted alkyl groups can be substituted one or more times with any of the groups listed herein, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups.

[0040] The term "cycloalkyl" as used herein refers to substituted or unsubstituted cyclic alkyl groups such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group can have 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 4, 5, 6, or 7. In some embodiments, cycloalkyl groups can have 3 to 6 carbon atoms (C_3-C_6). Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalinyl.

[0041] The term "cycloalkylalkyl" as used herein refers to substituted or unsubstituted alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group as defined herein is replaced with a bond to a cycloalkyl group as defined herein. Representative cycloalkylalkyl groups include, but are not limited to, cyclopentylalkyl.

[0042] The term "alkylcycloalkyl" as used herein refers to substituted or unsubstituted cycloalkyl groups as defined herein in which a hydrogen of a cycloalkyl group as defined herein is replaced with a bond to an alkyl group as defined herein. Representative alkylcycloalkyl groups include, but are not limited to, alkylcyclopropyl.

[0043] The term "acyl" as used herein refers to a group containing a carbonyl moiety wherein the group is bonded via the carbonyl carbon atom. The carbonyl carbon atom is also bonded to another carbon atom, which can be part of a substituted or unsubstituted alkyl, aryl, aralkyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl group or the like. In the special case wherein the carbonyl carbon atom is bonded to a hydrogen, the group is a "formyl" group, an acyl group as the term is defined herein. An acyl group can

include 0 to about 12-40, 6-10, 1-5 or 2-5 additional carbon atoms bonded to the carbonyl group. An acryloyl group is an example of an acyl group. An acyl group can also include heteroatoms within the meaning here. A nicotinoyl group (pyridyl-3-carbonyl) is an example of an acyl group within the meaning herein. Other examples include acetyl, benzoyl, phenylacetyl, pyridylacetyl, cinnamoyl, and acryloyl groups. When the group containing the carbon atom that is bonded to the carbonyl carbon atom contains a halogen, the group is termed a "haloacyl" group. An example is a trifluoroacetyl group.

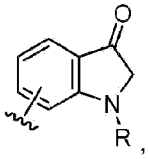
[0044] The term "heterocyclylcarbonyl" is an example of an acyl group that is bonded to a substituted or unsubstituted heterocyclyl group, as the term "heterocyclyl" is defined herein. An example of a heterocyclylcarbonyl group is a prolyl group, wherein the prolyl group can be a D- or an L-prolyl group.

[0045] The term "aryl" as used herein refers to substituted or unsubstituted cyclic aromatic hydrocarbons that do not contain heteroatoms in the ring. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain about 6 to about 14 carbons (C_6-C_{14}) or from 6 to 10 carbon atoms (C_6-C_{10}) in the ring portions of the groups. Aryl groups can be unsubstituted or substituted, as defined herein. Representative substituted aryl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or 2-8 substituted naphthyl groups, which can be substituted with carbon or non-carbon groups such as those listed herein.

[0046] The term "aralkyl" and "arylalkyl" as used herein refers to alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined herein. Representative aralkyl groups include benzyl and phenylethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl. Aralkenyl groups are alkenyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined herein.

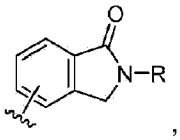
[0047] The term "heterocyclyl" or "heterocyclo" as used herein refers to substituted or unsubstituted aromatic and non-aromatic ring compounds containing 3 or more ring members, of which, one or more (e.g., 1, 2 or 3) is a heteroatom such as, but not limited to, N, O, and S. Thus, a heterocyclyl can be a cycloheteroalkyl, or a heteroaryl, or if polycyclic, any combination thereof. In some embodiments, heterocyclyl groups include 3 to about 20 ring members, whereas other such groups have 3 to about 15 ring members. In some embodiments, heterocyclyl groups include heterocyclyl groups that include 3 to 8 carbon atoms (C_3-C_8), 3 to 6 carbon atoms (C_3-C_6), 3 to 5 carbon atoms (C_3-C_5) or 6 to 8 carbon atoms (C_6-C_8). A heterocyclyl group designated as a C_2-heterocyclyl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C_4-heterocyclyl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms equals the total

number of ring atoms. A heterocyclyl ring can also include one or more double bonds. A heteroaryl ring is an embodiment of a heterocyclyl group. The phrase "heterocyclyl group" includes fused ring species including those that include fused aromatic and non-aromatic groups. Representative heterocyclyl groups include, but are not limited to pyrrolidinyl, azetidinyl, piperidynyl, piperazinyl, morpholinyl, chromanyl, indolinonyl, isoindolinonyl, furanyl, pyrrolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, triazinyl, thiophenyl, tetrahydrofuranyl, pyrrolyl, oxazolyl, oxadiazolyl, imidazolyl, triazyolyl, tetrazolyl, benzoxazolinyl, benzthiazolinyl, and benzimidazolinyl groups. Examples of indolinonyl groups include groups having the general formula:



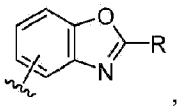
wherein R is as defined herein.

[0048] Examples of isoindolinonyl groups include groups having the general formula:



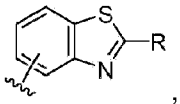
wherein R is as defined herein.

[0049] Examples of benzoxazolinyl groups include groups having the general formula:



wherein R is as defined herein.

[0050] Examples of benzthiazolinyl groups include groups having the general formula:



wherein R is as defined herein.

[0051] In some embodiments, the group R in benzoxazolinyl and benzthiazolinyl groups is an N(R)2 group. In some embodiments, each R is hydrogen or alkyl, wherein the alkyl group is substituted or unsubstituted. In some embodiments, the alkyl group is substituted with a heterocyclyl group (e.g., with a pyrrolidinyl group).

[0052] The term "heterocyclylalkyl" as used herein refers to alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group as defined herein is replaced with a bond to a heterocyclyl group as defined herein. Representative heterocyclylalkyl groups include, but are not limited to, furan-2-yl methyl, furan-3-yl methyl, pyridine-3-yl methyl, tetrahydrofuran-2-yl methyl, and indol-2-yl propyl.

[0053] The term "heterocyclylalkoxy" as used herein refers to alkyl groups as defined herein in

which a hydrogen or carbon bond of an alkyl group as defined herein is replaced with a bond to a heterocyclyl group as defined herein and the alkyl group is attached to an oxygen. Representative heterocyclylalkoxy groups include, but are not limited to, -O-$(CH_2)_q$heterocyclyl, wherein q is an integer from 1 to 5. In some embodiments, heterocyclylalkoxy groups include -O-$(CH_2)_q$morpholinyl such as -O-CH_2CH_2-morpholine.

[0054] The term "heteroarylalkyl" as used herein refers to alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heteroaryl group as defined herein.

[0055] The term "alkoxy" as used herein refers to an oxygen atom connected to an alkyl group, including a cycloalkyl group, as are defined herein. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentyloxy and hexyloxy. Examples of branched alkoxy include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy and isohexyloxy. Examples of cyclic alkoxy include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy. An alkoxy group can include one to about 12-20 or about 12-40 carbon atoms bonded to the oxygen atom, and can further include double or triple bonds, and can also include heteroatoms. For example, an allyloxy group is an alkoxy group within the meaning herein. A methoxyethoxy group is also an alkoxy group within the meaning herein, as is a methylenedioxy group in a context where two adjacent atoms of a structure are substituted therewith.

[0056] The term "amine" as used herein refers to primary, secondary, and tertiary amines having, e.g., the formula $N(group)_3$ wherein each group can independently be H or non-H, such as alkyl and aryl. Amines include but are not limited to R-NH2, for example, alkylamines, arylamines, alkylarylamines; R2NH wherein R is defined herein, such as dialkylamines, diarylamines, aralkylamines and heterocyclylamines; and R_3N wherein each R is independently selected, such as trialkylamines, dialkylarylamines, alkyldiarylamines and triarylamines. The term "amine" also includes ammonium ions as used herein.

[0057] The term "amino group" as used herein refers to a substituent of the form -NH2, -NHR, -NR2, -NR_3^+, wherein each R is defined herein, and protonated forms of each, except for -NR_3^+, which cannot be protonated. Accordingly, any compound substituted with an amino group can be viewed as an amine. An "amino group" within the meaning herein can be a primary, secondary, tertiary, or quaternary amino group. An "alkylamino" group includes a monoalkylamino, dialkylamino, and trialkylamino group.

[0058] An example of a "alkylamino" is -NH-alkyl and -$N(alkyl)_2$.

[0059] An example of a "cycloalkylamino" group is -NH-cycloalkyl and -N(cycloalkyl)2.

[0060] An example of a "cycloalkyl heterocycloamino" group is -NH-(heterocyclo cycloalkyl), wherein the heterocyclo group is attached to the nitrogen and the cycloalkyl group is attached

to the heterocyclo group.

[0061] An example of a "heterocyclo cycloamino" group is -NH-(cycloalkyl heterocycle), wherein the cycloalkyl group is attached to the nitrogen and the heterocyclo group is attached to the cycloalkyl group.

[0062] The terms "halo," "halogen," or "halide" group, as used herein, by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

[0063] The term "haloalkyl" group, as used herein, includes mono-halo alkyl groups, poly-halo alkyl groups wherein all halo atoms can be the same or different, and per-halo alkyl groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkyl include trifluoromethyl, 1,1-dichloroethyl, 1,2-dichloroethyl, 1,3-dibromo-3,3-difluoropropyl, perfluorobutyl and - $CF(CH_3)_2$.

[0064] As used herein, the term "salts" and "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. Pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

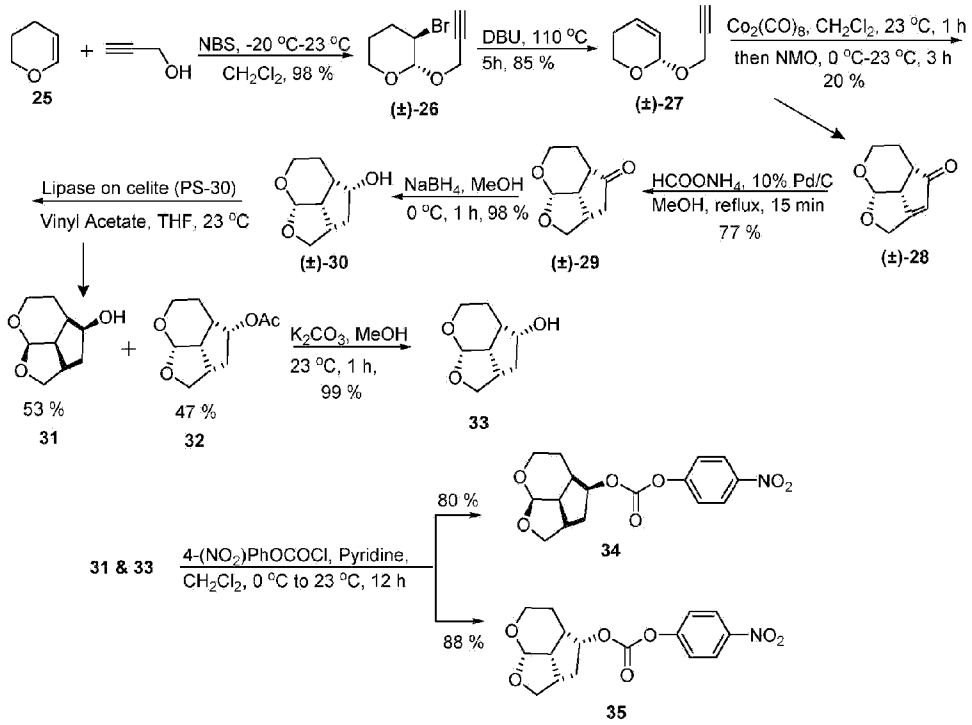
[0065] Pharmaceutically acceptable salts can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. In some instances, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985.

[0066] The term "solvate" means a compound, or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by noncovalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

Examples

[0067] The present invention can be better understood by reference to the following examples which are offered by way of illustration. The present invention is not limited to the examples given herein and the scope of protection is as defined in the appended claims.

Scheme 1: Synthesis of tricyclic Ligands:



Experimental Procedure:

trans-3-Bromo-2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (26):

[0068] To a stirred solution of olefin **25** (5.39 mL, 59.44 mmol) and propargyl alcohol (10.4 mL, 178.32 mmol) in dichloromethane (10 mL) was added NBS (11.63 g, 65.38 mmol) in small portions over 0.5 h at -20°C under argon atmosphere. The reaction mixture was stirred at -20°C for 2 h and further 15 h at 23°C. After this period, the reaction mixture was quenched by the addition of water and extracted with dichloromethane. The extracts were washed with Saturated aqueous $NaHSO_3$ solution, aqueous $K2CO_3$ solution, water, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (15 % Et_2O in hexane) to afford **26** (12.7 g, 98 %).

[0069] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.85 (d, *J* = 3.9 Hz, 1H), 4.30 (dd, *J* = 4.8, 2.4 Hz, 2H), 4.01 (dt, *J* = 5.7, 4.0 Hz, 1H), 3.89 (ddd, *J* = 11.7, 8.6, 3.5 Hz, 1H), 3.65 - 3.58 (m, 1H), 2.46 (t, *J* = 2.4 Hz, 1H), 2.44 - 2.34 (m, 1H), 1.96 (dddd, J = 18.6, 10.3, 7.6, 4.4 Hz, 2H), 1.52 (dtd, *J* =

15.1, 6.0, 3.1 Hz, 1H).

6-(Prop-2-yn-1-yloxy)-3,6-dihydro-2*H*-pyran (27):

[0070] A mixture of **26** (10 g, 45.65mmol) and DBU (34 mL, 228.25 mmol) was stirred at 110°C for 5 h under argon atmosphere. After this period, the reaction mixture was cooled, 100 mL of anhydrous ether was added and stirred for 1 h. The mixture was filtered through a plug of Celite, washed with ether and concentrated under reduced pressure by using cold bath. The crude product was purified by silica gel column chromatography (15 % Et_2O in pentane) to afford **27** (5.36 g, 85 %) as a volatile liquid.

[0071] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.09 - 6.03 (m, 1H), 5.73 (dtd, *J* = 10.1, 2.8, 1.3 Hz, 1H), 5.09 (s, 1H), 4.27 (d, *J* = 2.4 Hz, 2H), 3.88 (td, J = 11.4, 3.6 Hz, 1H), 3.72 (ddt, *J* = 11.1, 6.1, 1.1 Hz, 1H), 2.41 (t, *J* = 2.4 Hz, 1H), 2.37-2.25 (m, 1H), 1.94 - 1.85 (m, 1H).

2a^1,5,6,7a-Tetrahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-4(4*aH*)-one (28):

[0072] To a stirred solution of **27** (1.57 g, 11.4 mmol) in dichloromethane (40 mL) was added $Co_2(CO)_8$ (4.3 g, 12.5 mmol) at 23°C under argon atmosphere. The reaction mixture was stirred at 23°C for 1 h. After this period, to the above mixture was added NMO (8 g, 68.4 mmol) at 0°C and the reaction mixture was stirred for 3h at 23°C. The mixture was filtered through a plug of Celite, washed with dichloromethane and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (40 % EtOAc in Hexane) to afford **28** (380 mg, 20 %).

[0073] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.04 (s, 1H), 5.32 (d, *J* = 5.2 Hz, 1H), 4.70 (qt, *J* = 15.9, 1.7 Hz, 2H), 3.61 (ddd, *J* = 12.1, 5.3, 4.0 Hz, 1H), 3.39 (ddd, *J* = 12.0, 9.2, 2.8 Hz, 1H), 3.18 (dtt, *J* = 6.9, 4.8, 2.0 Hz, 1H), 2.92 (dt, *J* = 9.3, 6.5 Hz, 1H), 1.94-1.84 (m, 1H), 1.46 (dddd, *J* = 14.3, 9.2, 6.6, 3.9 Hz, 1H).

[0074] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.8, 180.2, 123.9, 97.7, 66.2, 61.3, 47.3, 44.1, 24.4.

Hexahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-4(4*aH*)-one (29):

[0075] To a stirred solution of **28** (165 mg, 0.99 mmol) in MeOH (5 mL) were added HCOONH4 (626 mg, 9.93 mmol) and 10 % Pd/C (25 mg) at 23°C under argon atmosphere. The reaction mixture was refluxed for 15 min. After this period, the reaction mixture was cooled to 23°C and filtered through a plug of Celite. MeOH was removed under reduced pressure. To

the crude residue was added chloroform to precipitate out of the excess HCOONH4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (45 % EtOAc in Hexane) to afford **29** (128 mg, 77 %).

[0076] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.03 (d, *J* = 4.8 Hz, 1H), 3.94 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.76 - 3.71 (m, 1H), 3.62 - 3.52 (m, 2H), 2.96 - 2.82 (m, 2H), 2.67 (dd, J = 19.0, 9.8 Hz, 1H), 2.53 - 2.45 (m, 1H), 2.18 (dd, *J* = 18.9, 3.8 Hz, 1H), 2.10 - 2.02 (m, 1H), 1.72 (ddt, *J* = 13.5, 10.7, 6.5 Hz, 1H).

[0077] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 217.1, 100.8, 73.1, 58.7, 43.6, 42.6, 41.2, 35.4, 21.1.

Octahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-4-ol (30):

[0078] To a stirred solution of **29** (88 mg, 0.52 mmol) in MeOH (5 mL) was added NaBH4 (24 mg, 0.63 mmol) at 0°C under argon atmosphere. The reaction mixture was stirred at 0°C for 1 h. After this period the reaction mixture was quenched by the addition of Saturated aqueous NH_4Cl and the layers were seperated. The aqueous layer was extrated with EtOAc, combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (50 % EtOAc in hexane) to give **30** (87 mg, 98 %).

[0079] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.06 (d, *J* = 5.4 Hz, 1H), 4.14 - 4.06 (m, 1H), 4.00 (dt, *J* = 11.8, 6.8 Hz, 1H), 3.89 - 3.81 (m, 1H), 3.71 (dd, *J* = 9.3, 4.4 Hz, 1H), 3.51 (dt, *J* = 11.5, 5.6 Hz, 1H), 3.37 (d, *J* = 9.1 Hz, 1H), 2.70 (ddq, *J* = 12.6, 8.1, 4.1 Hz, 1H), 2.50 (td, *J* = 9.6, 5.4 Hz, 1H), 2.19 (dq, *J* = 11.2, 5.7 Hz, 1H), 1.93 (ddd, J = 13.6, 8.4, 5.2 Hz, 1H), 1.78 (dt, *J* = 7.8, 4.3 Hz, 2H), 1.68 (dt, *J* = 13.7, 3.4 Hz, 1H).

[0080] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 101.0, 77.4, 71.8, 59.9, 41.8, 40.8, 40.4, 38.0, 21.2.

(2a*R*,2a^{1}*R*,4*S*,4a*R*,7a*R*)-Octahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-4-ol (31) and (2a*S*,2a^{1}*S*,4*R*,4a*S*,7a*S*)-Octahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-4-yl acetate (32):

[0081] To a solution of alcohol **30** (60 mg, 0.35 mmol) in THF (5 mL) were added vinyl acetate (0.6 ml, 6.2 mmol) and Lipase PS-30 on celite (100 mg) at 23°C under argon atmosphere. The reaction mixture was stirred for 6 h (50:50 by ^{1}H-NMR). After this period, the reaction mixture was filtered through a plug of Celite and solvents were removed under reduced pressure. The crude product was purified via silica gel column chromatography (30 % to 50 % EtOAc in hexane) to yield alcohol 31 (32 mg, 53 %) and acetate **32** (35 mg, 47%).

[0082] Alcohol **31:** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.08 (d, *J* = 5.2 Hz, 1H), 4.12 (s, 1H), 4.04 (dt, *J* = 12.3, 7.0 Hz, 1H), 3.88 (t, *J* = 8.8 Hz, 1H), 3.75 (dd, *J* = 9.3, 4.1 Hz, 1H), 3.55 (dd, *J* = 11.5, 5.7 Hz, 1H), 3.31 (d, *J* = 8.5 Hz, 1H), 2.80 - 2.68 (m, 1H), 2.53 (td, *J* = 9.5, 5.5 Hz, 1H), 2.21 (dq, *J* = 10.1, 5.4 Hz, 1H), 1.96 (ddt, *J* = 13.5, 8.4, 4.8 Hz, 1H), 1.84 (t, *J* = 5.8 Hz, 2H), 1.73 (d, *J* = 13.8 Hz, 1H).

[0083] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 101.1, 77.5, 71.9, 59.9, 41.8, 41.0, 40.8, 38.2, 21.2.

[0084] Acetate **32:** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.22 (d, *J*= 5.1 Hz, 1H), 5.10 (dt, *J* = 8.7, 6.2 Hz, 1H), 4.01 - 3.89 (m, 2H), 3.70 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.41 (dt, J = 11.5, 6.5 Hz, 1H), 2.65 (qt, *J* = 7.8, 5.1 Hz, 1H), 2.54 (ddd, *J* = 14.6, 11.8, 6.8 Hz, 2H), 2.15 - 2.06 (m, 1H), 2.03 (s, 3H), 1.66 (dt, *J* = 12.8, 8.4 Hz, 1H), 1.58 - 1.51 (m, 2H).

[0085] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7, 100.6, 78.7, 72.1, 60.6, 42.2, 39.4, 35.7, 34.6, 21.9, 21.1.

(2a*S*,2a^{1}*S*,4*R*,4a*S*,7a*S*)-Octahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-4-ol (33):

[0086] To a stirred solution of acetate **32** (32 mg, 0.15 mmol) in MeOH (3 mL) was added K_2CO_3 (31 mg, 0.23 mmol) at 23°C under argon atmosphere. The reaction mixture was stirred at 23°C for 1 h. After this period the reaction mixture was quenched by the addition of Saturated aqueous NH_4Cl and the layers were seperated. The aqueous layer was extrated with EtOAc, combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (50 % EtOAc in hexane) to afford **33** (26 mg, 99 %).

[0087] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.09 (d, *J* = 5.3 Hz, 1H), 4.16 - 4.09 (m, 1H), 4.09 - 4.00 (m, 1H), 3.91 - 3.84 (m, 1H), 3.75 (dd, *J* = 9.4, 4.2 Hz, 1H), 3.56 (dt, *J* = 11.4, 5.5 Hz, 1H), 2.75 (dtt, *J* = 12.3, 8.2, 3.6 Hz, 1H), 2.53 (td, *J* = 9.6, 5.4 Hz, 1H), 2.21 (dq, *J* = 10.2, 5.5 Hz, 1H), 1.96 (ddd, *J* = 13.6, 8.4, 5.1 Hz, 1H), 1.83 (q, *J* = 8.8, 7.3 Hz, 2H), 1.73 (dt, *J* = 13.8, 2.9 Hz, 1H).

[0088] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 101.1, 77.5, 71.9, 59.9, 41.8, 41.0, 40.8, 38.2, 21.2.

4-Nitrophenyl ((2a*R*,2a^{1}*R*,4*S*,4a*R*,7a*R*)-octahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-4-yl) carbonate (34):

[0089] To a stirred solution of alcohol **31** (30 mg,0.18 mmol) in dichloromethane (4 mL) was

added pyridine (57 µL, 0.7 mmol) at at 23°C under argon atmosphere and the reaction mixture was cooled to 0°C followed by addition of 4-nitrophenyl chloroformate (53 mg, 0.26 mmol). The reaction mixture was warmed to 23°C and stirred for 12 h. Upon, completion, solvents were removed under reduced pressure and crude product was purified by silica gel column chromatography (35 % EtOAc in hexane) to give **34** (47 mg, 80 %).

[0090] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 9.2 Hz, 2H), 7.38 (d, *J* = 9.2 Hz, 2H), 5.27 (d, *J* = 5.4 Hz, 1H), 5.16 (dt, *J* = 8.8, 6.4 Hz, 1H), 4.07 - 3.97 (m, 2H), 3.77 (dd, *J* = 8.9, 6.1 Hz, 1H), 3.47 (dt, *J* = 11.4, 6.4 Hz, 1H), 2.79 - 2.66 (m, 2H), 2.59 (ddd, *J* = 10.7, 9.2, 5.5 Hz, 1H), 2.29 (ddd, *J* = 13.7, 8.0, 6.3 Hz, 1H), 1.85 (dt, *J* = 13.0, 8.3 Hz, 1H), 1.73 - 1.66 (m, 2H).

[0091] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.4, 152.1, 145.4, 125.4, 121.9, 100.6, 83.6, 72.0, 60.5, 41.9, 39.2, 35.9, 34.7, 21.8.

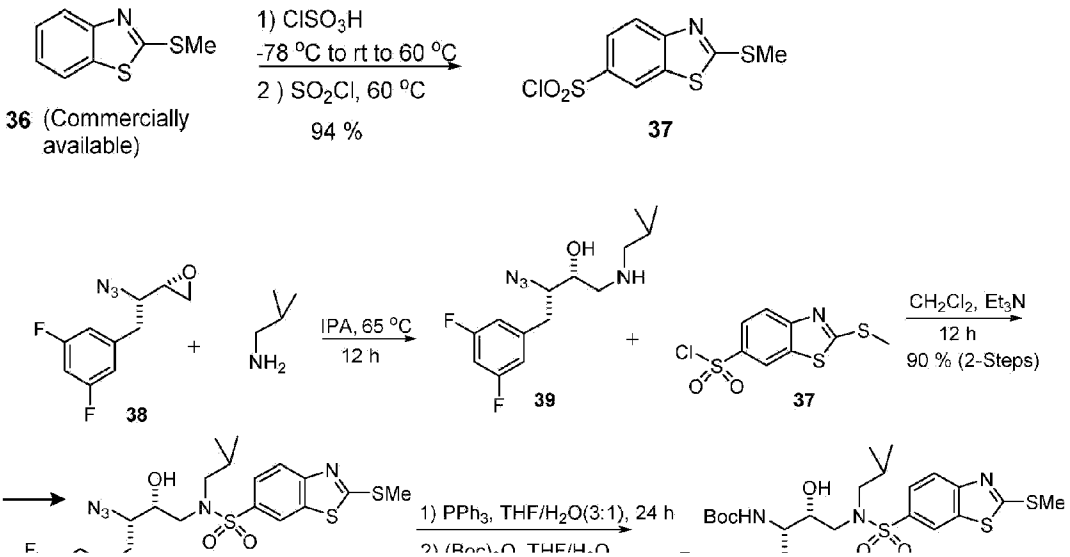
4-Nitrophenyl ((2a*S*,2a^1*S*,4*R*,4a*S*,7a*S*)-octahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-4-yl) carbonate (35):

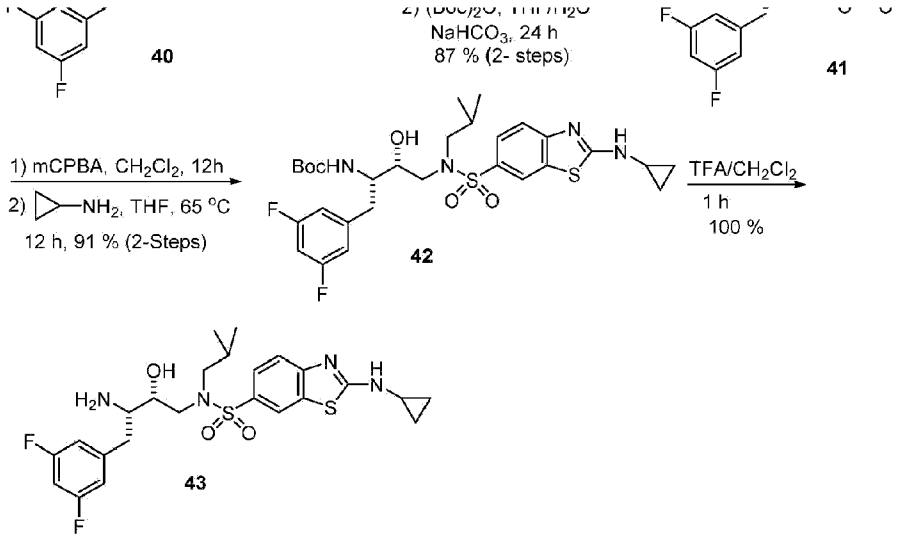
[0092] The title compound **(35)** was obtained by following the procedure outlined for compound **34** (51 mg, 88 % yield).

[0093] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (d, *J* = 9.0 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 2H), 5.26 (d, *J* = 5.4 Hz, 1H), 5.19 - 5.10 (m, 1H), 4.00 (ddd, *J* = 16.4, 11.4, 6.6 Hz, 2H), 3.75 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.46 (dt, *J* = 11.9, 6.4 Hz, 1H), 2.71 (tt, *J* = 15.2, 7.9 Hz, 2H), 2.63 - 2.55 (m, 1H), 2.28 (dt, *J* = 13.7, 7.2 Hz, 1H), 1.84 (dt, *J* = 13.0, 8.3 Hz, 1H), 1.72 - 1.65 (m, 2H).

[0094] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.5, 152.1, 145.5, 125.4, 121.9, 100.5, 83.6, 72.0, 60.4, 41.9, 39.2, 35.9, 34.6, 21.8.

Scheme 2: Synthesis of Benzothiazole Isoster 43:





Experimental Procedure:

2-(Methylthio)benzo[*d*]thiazole-6-sulfonyl chloride (37).

[0095] Chlorosulfonic acid (5.1 mL, 77.35 mmol) was added to 2-(Methylthio)benzothiazole **(36)** (2 g, 11 mmol) slowly (very exothermic) at -78°C under argon atmosphere. The reaction mixture was warmed to 23°C and stirred at 60° C for 90 min. Again, the mixture was cooled to 23°C before adding thionyl chloride (1.2 mL, 16.57 mmol). The reaction mixture was stirred at reflux for 1 h and cool to 23°C. EtOAc and water were added to the cooled mixture slowly until bubbles ceased. Two layers were separated, organic layer was concentrated, dried (Na_2SO_4) and purified by silica gel column chromatography to give **37** (2.9 g, 94 % yield).

[0096] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.46 (d, *J* = 1.5 Hz, 1H), 8.07 (dd, *J* = 9.0, 2.0 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 2.85 (s, 3H).

[0097] ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.9, 157.4, 139.5, 136.0, 125.0, 122.1, 121.1, 16.3.

***N*-((2*R*,3*S*)-3-Azido-4-(3,5-difluorophenyl)-2-hydroxybutyl)-*N*-isobutyl-2-(methylthio)benzo[*d*]thiazole-6-sulfonamide (40).**

[0098] Isobutylamine (0.27 mL, 2.66 mmol) was added to a stirred solution of **38** (200 mg, 0.89 mmol) in isopropanol at 23°C under argon atmosphere. The reaction mixture was stirred at 65 °C for 12 h. After this period, isopropanol was removed under reduced pressure, to the crude product **39** in dichloromethane were added sulfonyl chloride **37** (248 mg, 0.89 mmol)

and triethyl amine (0.37 mL, 2.66 mmol) at 23°C under argon atmosphere. The reaction mixture was stirred at 23°C for 12 h. Solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (15 % EtOAc in hexane) to give **40** (433 mg, 90 % over two steps).

[0099] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.23 - 8.21 (m, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.80 - 7.76 (m, 1H), 6.79 (d, *J* = 6.2 Hz, 2H), 6.65 (t, *J* = 8.9 Hz, 1H), 3.76 (d, *J* = 17.6 Hz, 2H), 3.56 (ddd, *J* = 9.5, 6.1, 3.7 Hz, 1H), 3.27 - 3.17 (m, 2H), 3.05 (ddd, *J* = 21.8, 13.7, 5.8 Hz, 2H), 2.89 (dd, *J* = 13.4, 6.8 Hz, 1H), 2.76 (s, 3H), 2.74 - 2.70 (m, 1H), 1.88-1.78 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H).

[0100] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.6, 164.4 (d, *J* = 12.7 Hz), 161.9 (d, *J* = 12.9 Hz), 156.1, 141.3 (t, *J* = 9.1 Hz), 136.0, 133.7, 125.1, 121.9, 121.1, 112.6, 112.3, 102.6 (t, *J* = 25.3 Hz), 71.9, 66.0, 59.1, 53.2, 36.6, 27.3, 20.2, 19.9, 16.1.

Tert-butyl((2*S*,3*R*)-1-(3,5-difluorophenyl)-3-hydroxy-4-((*N*-isobutyl-2-(methylthio)benzo[*d*]thiazole)-6-sulfonamido)butan-2-yl)carbamate (41).

[0101] Triphenylphosphine (160 mg, 0.61 mmol) was added to a stirred solution of **40** (275 mg, 0.5 mmol) in THF/H_2O (3:1 ratio, 4 mL) at 23°C. The reaction mixture was stirred at 23°C for 24 h. After this period, to the reaction mixture Boc anhydride (133 mg, 0.61 mmol) and Sodium bicarbonate (85 mg, 1 mmol) were added at 23°C. The reaction mixture was stirred at 23°C for 20 h. The mixture was concentrated under reduced pressure and diluted with EtOAc. The reaction mixture was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (30 % EtOAc in hexane) to give **41** (270 mg, 87 % over two steps) as a white solid.

[0102] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (d, *J* = 1.4 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.79 (dd, *J* = 8.6, 1.6 Hz, 1H), 6.77 (d, *J* = 6.2 Hz, 2H), 6.64 (tt, *J* = 9.2, 2.2 Hz, 1H), 4.74 (d, *J* = 8.7 Hz, 1H), 4.05 (s, 1H), 3.84 (s, 1H), 3.71 (tt, *J* = 9.4, 4.9 Hz, 1H), 3.14 (qd, *J* = 15.1, 5.9 Hz, 2H), 3.01 - 2.84 (m, 4H), 2.81 (s, 3H), 1.94-1.79 (m, 1H), 1.34 (s, 9H), 0.87 (dd, *J* = 10.4, 6.6 Hz, 6H).

[0103] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.5, 164.3 (d, *J* = 12.7 Hz), 161.8 (d, *J* = 13.2 Hz), 156.0 (d, *J* = 7.8 Hz), 142.3 (t, *J* = 8.9 Hz), 135.9, 133.9, 125.1, 121.8, 121.1, 112.6, 112.3, 108.8, 102.0 (t, *J* = 25.4 Hz), 80.2, 73.0, 58.9, 54.7, 53.8, 35.2, 28.3, 27.3, 20.2, 20.0, 16.1.

Tert-butyl((2*S*,3*R*)-4-((2-(cyclopropylamino)-*N*-isobutylbenzo[*d*]thiazole)-6-sulfonamido)-1-(3,5-difluorophenyl)-3-hydroxybutan-2-yl)carbamate (42).

[0104] To a stirred solution of **41** (960 mg, 1.56 mmol) in dichloromethane (10 mL) was added mCPBA (807 mg, 4.68 mmol) at 0°C under argon atmosphere and the mixture was stirred at 23°C for 12 h. After this period, the reaction mixture was quenched by the addition of Saturated aqueous $Na_2S_2O_3$ (2 ml) and extracted with dichloromethane. The extracts were washed with Saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure. To the crude product in dry THF (10 mL) at 23°C under argon atmosphere was added cyclopropylamine (0.35 mL, 4.68 mmol) and the mixture was stirred at 65°C for 12 h. Solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (50 % EtOAc in hexane) to give **42** (880 mg, 91 % over two steps) as a white solid.

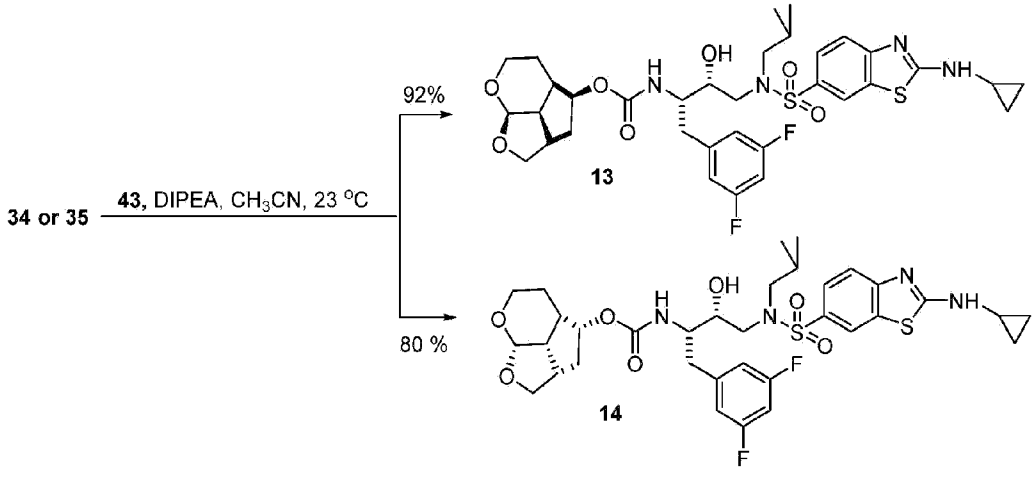
[0105] ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ: 7.93 (s, 1H), 7.57 - 7.52 (m, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 6.63 (d, *J* = 6.6 Hz, 2H), 6.49 (t, *J* = 9.0 Hz, 1H), 5.47 (d, *J* = 9.4 Hz, 1H), 3.68 - 3.60 (m, 1H), 3.58 - 3.47 (m, 1H), 3.21 - 3.10 (m, 1H), 2.83 (dtd, *J* = 39.5, 15.1, 13.3, 5.5 Hz, 4H), 2.61 - 2.50 (m, 2H), 1.84-1.71 (m, 1H), 1.18 (s, 9H), 0.75 (dd, *J* = 9.7, 5.8 Hz, 8H), 0.62 - 0.57 (m, 2H).

[0106] ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ: 173.3, 164.1 (d, *J*= 13.3 Hz), 161.7 (d, *J* = 12.5 Hz), 156.7, 155.5, 131.0, 130.4, 125.4, 120.9, 118.3, 112.4 (d, *J* = 24.1 Hz), 101.9 (d, *J* = 26.8 Hz), 79.9, 72.8, 60.6, 58.6, 54.5, 53.5, 35.4, 28.2, 27.1, 26.6, 20.0, 14.1, 7.7.

***N*-((2*R*,3*S*)-3-Amino-4-(3,5-difluorophenyl)-2-hydroxybutyl)-2-(cyclopropylamino)-*N*-isobutylbenzo[*d*]thiazole-6-sulfonamide (43).**

[0107] To a stirred solution of **42** (870 mg, 1.39 mmol) in dichloromethane (15 mL) was added TFA (5mL) at 0°C under argon atmosphere and the mixture was stirred at 23°C for 1 h. Solvent was removed under reduced pressure to give **43** (730 mg, 100 % yield).

Scheme 3: Synthesis of Inhibitors 13 and 14



Experimental Procedure:

(2a*R*,2a^1*R*,4*S*,4a*R*,7a*R*)-Octahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-4-yl ((2*S*,3*R*)-4-((2-(cyclopropylamino)-*N*-isobutylbenzo[*d*]thiazole)-6-sulfonamido)-1-(3,5-difluorophenyl)-3-hydroxybutan-2-yl)carbamate (13):

[0108] To a stirred solution of activated alcohol **34** (6 mg,0.018 mmol) and isoster **43** (11.3 mg, 0.021 mmol) in acetonitrile (2 mL) was added DIPEA (16 µL, 0.09 mmol) at 23°C under argon atmosphere. The reaction mixture was stirred at 23°C until completion. Upon completion, solvents were removed under reduced pressure and crude product was purified by silica gel column chromatography (65 % EtOAc in hexane) to give **13** (12 mg, 92 %).

[0109] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 1.6 Hz, 1H), 7.70 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 6.92 (s, 1H), 6.78 (dd, *J* = 16.1, 7.2 Hz, 2H), 6.68 - 6.61 (m, 1H), 5.21 (d, *J* = 5.1 Hz, 1H), 5.13 (d, *J* = 9.7 Hz, 1H), 4.99 (q, *J* = 6.3 Hz, 1H), 3.94 (t, *J* = 8.5 Hz, 2H), 3.89 - 3.79 (m, 3H), 3.64 (dt, *J* = 9.0, 4.4 Hz, 1H), 3.34 (q, *J* = 6.6, 6.2 Hz, 1H), 3.06 (dtd, *J* = 33.4, 14.4, 13.4, 8.1 Hz, 4H), 2.89 - 2.82 (m, 1H), 2.77 (ddq, *J* = 10.2, 6.8, 3.9 Hz, 2H), 2.68 - 2.60 (m, 1H), 2.52 - 2.39 (m, 2H), 2.07 - 1.97 (m, 1H), 1.85 (dt, *J* = 13.7, 6.6 Hz, 1H), 1.62 (dt, *J* = 13.1, 7.3 Hz, 1H), 1.38 (q, *J* = 5.8 Hz, 2H), 0.93 (d, *J* = 6.5 Hz, 4H), 0.89 (d, *J* = 6.6 Hz, 4H), 0.80 - 0.77 (m, 2H).

[0110] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 164.3 (d, *J* = 12.9 Hz), 161.8 (d, *J* = 12.9 Hz), 156.1, 156.0, 142.3 (t, *J* = 8.9 Hz), 131.6, 130.4, 125.5, 121.1, 118.9, 112.4 (d, *J* = 18.7 Hz), 102.1, 100.7, 79.4, 73.1, 72.0, 60.1, 59.1, 54.9, 53.8, 41.9, 39.6, 36.0, 35.5, 29.9, 27.5, 26.9, 21.7, 20.3, 20.1, 8.2.

(2a*S*,2a^1*S*,4*R*,4a*S*,7a*S*)-Octahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-4-yl ((2*S*,3*R*)-4-((2-(cyclopropylamino)-*N*-isobutylbenzo[*d*]thiazole)-6-sulfonamido)-1-(3,5-difluorophenyl)-3-hydroxybutan-2-yl)carbamate (14):

[0111] The title inhibitor **(14)** was obtained by following the procedure outlined for inhibitor **13** (17 mg, 80 % yield).

[0112] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 7.69 (dd, *J*= 8.5, 1.8 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.11 (s, 1H), 6.79 (d, *J* = 6.2 Hz, 2H), 6.68 - 6.61 (m, 1H), 5.22 (t, *J* = 7.4 Hz, 2H), 4.99 (q, *J* = 6.0 Hz, 1H), 4.08 (s, 1H), 3.96 - 3.78 (m, 5H), 3.60 (dd, *J* = 8.7, 5.6 Hz, 1H), 3.42 - 3.33 (m, 1H), 3.10 (dd, *J* = 11.0, 4.9 Hz, 2H), 3.05 (d, *J* = 3.8 Hz, 1H), 2.98 (dd, *J* = 13.3, 8.3 Hz, 1H), 2.88 (t, *J* = 6.6 Hz, 1H), 2.75 (dq, *J* = 6.7, 3.4 Hz, 1H), 2.69 - 2.61 (m, 1H), 2.51 - 2.42

(m, 2H), 1.98 (dt, J = 13.5, 6.8 Hz, 1H), 1.84 (dd, *J* = 14.0, 6.9 Hz, 2H), 1.54 (dd, *J* = 13.2, 6.6 Hz, 2H), 0.92 (d, *J* = 6.5 Hz, 4H), 0.88 (d, *J* = 6.6 Hz, 4H), 0.80 - 0.78 (m, 2H).

[0113] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 164.3 (d, *J* = 13.0 Hz), 161.8 (d, *J* = 13.0 Hz), 156.1 (d, *J* = 31.9 Hz), 142.4 (t, *J* = 8.7 Hz), 131.5, 130.5, 125.5, 121.1, 118.8, 112.5 (d, *J* = 24.5 Hz), 102.3, 100.8, 79.6, 72.9, 71.9, 59.9, 59.1, 55.0, 53.8, 41.6, 39.8, 36.0 (d, *J* = 7.5 Hz), 35.2, 29.8, 27.5, 26.8, 21.9, 20.3, 20.1, 8.1.

REFERENCES CITED IN THE DESCRIPTION

Cited references

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Patent documents cited in the description

- WO2012031237A1 [0003]
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- **ZHANG et al.**Novel P2 tris-tetrahydrofuran group in antiviral compound 1(GRL-0519) fills the S2 binding pocket of selected mutants of HIV-1 proteaseJ Med Chem., 2013, vol. 56, 31074-1083 [0003]
- **AMANO et al.**GRL-0519, a Novel Oxatricyclic Ligand-Containing Nonpeptidic HIV-1 Protease Inhibitor (PI), Potently Suppresses Replication of a Wie Spectrum of Multi-PI-Resistant HIV-1 Variants In VitroAntimicrobial Agents and Chemotherapy, vol. 57, 52036-2046 [0003]

- **AGNISWAMY et al.**Extreme multidrug resistant HIV-1 protease with 20 mutations is resistant to novel protease inhibitors with P1'-pyrrolidinone or P2-tris-tetrahydrofuranJ Med Chem., vol. 56, 104017-42027 [0003]
- Remington, The Science And Practice of PharmacyPhiladelphia College of Pharmacy and Science20000000 [0016]
- Remington's Pharmaceutical SciencesMack Publishing Company19850000 [0065]

PATENTKRAV

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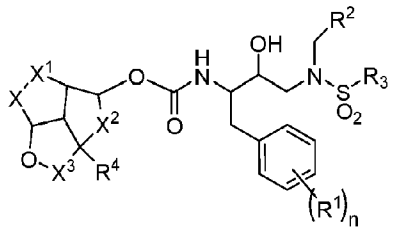


(I)

eller et/en farmaceutisk acceptabelt/acceptabel salt, polymorf, solvat eller clathrat deraf, hvor:

n er et heltal fra 0 til 3; X er $(-CHR^5-)_m$ eller -O-, hvor m er 1 eller 2, og hver R^5 uafhængigt er H, alkyl eller alkoxy;

X^1, X^2, og X^3 hver uafhængigt er $(-CHR^5-)_m$,;

R^1 er alkyl, alkoxy, aryl, heterocyclyl, halo, hydroxy eller amino;

R^2 er alkyl;

R^3 er aryl, benzthiazol, benzoxazol, benzofuranyl eller indolyl; og

R^4 er H, alkyl eller alkoxy;

hvor alkoxy henviser til et oxygenatom forbundet med en alkylgruppe indbefattende en cycloalkylgruppe; og

alkyl henviser til substituerede og usubstituerede ligekædede og forgrenede alkylgrupper og cycloalkylgrupper med fra 1 til 40 carbonatomer.

2. Forbindelse ifølge krav 1, hvor:

X^1 er $(-CHR^5-)_m$, hvor m er 2;

X^2 er $(-CHR^5-)_m$, hvor m er 1;

X^3 er $(-CHR^5-)_m$, hvor m er 1;

hvor hver R^5 er uafhængigt H, alkyl eller alkoxy; eller

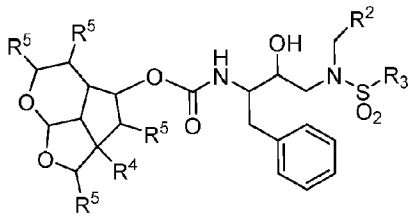
X^1 er $(-CHR^5-)_m$, hvor m er 1;

X^2 er $(-CHR^5-)_m$, hvor m er 1;

X^3 er $(-CHR^5-)_m$, hvor m er 2;

hvor hver R^5 uafhængigt er H, alkyl eller alkoxy.

3. Forbindelse ifølge krav 1, hvor forbindelsen med formlen (I) er en forbindelse med formlen:



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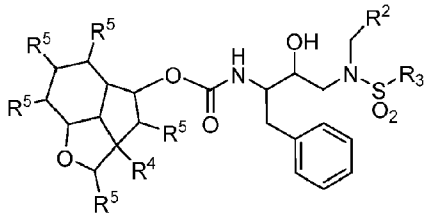
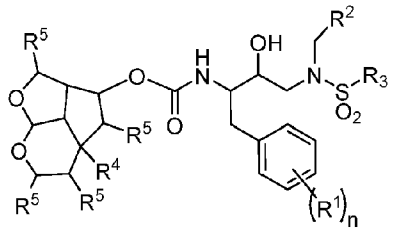


(Ib)

eller



(Ic)

eller et/en farmaceutisk acceptabelt/acceptabel salt, polymorf, solvat eller clathrat deraf, hvor n, R^1, R^2, R^3, R^4 og R^5 er som defineret i krav 1.

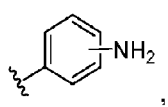
4. Forbindelse ifølge krav 1, hvor n er 0.

5. Forbindelse ifølge krav 1, hvor R^2 er usubstitueret alkyl.

6. Forbindelse ifølge krav 1, hvor R^3 er aryl, benzthiazol eller benzoxazol.

7. Forbindelse ifølge krav 6, hvor R^3 er phenyl.

8. Forbindelse ifølge krav 6, hvor R^3 er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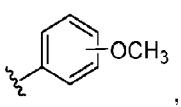
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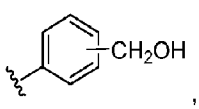
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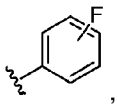
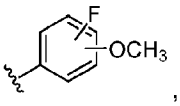
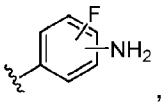
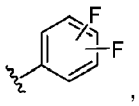
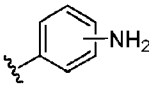
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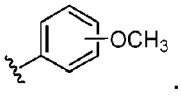
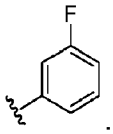
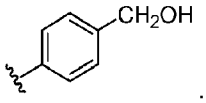
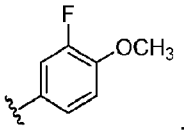
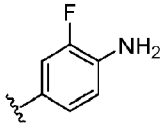


9. Forbindelse ifølge krav 8, hvor R^3 er: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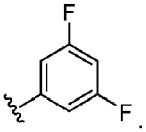
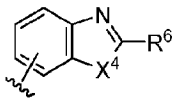


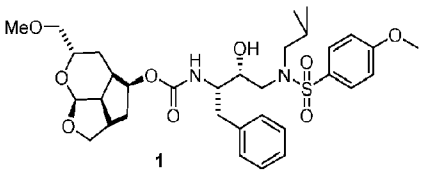
10. Forbindelse ifølge krav 6, hvor R^3 er:



hvor R^6 er alkyl, alkylamino, cycloalkylamino, cycloalkylheterocycloamino, heterocyclocycloalkylamino eller heterocycloamino; og

X^4 er S, O eller NR^7, hvor R^7 er H, alkyl, cycloalkyl eller alkylaryl.

11. Forbindelse ifølge krav 1, hvor forbindelsen er: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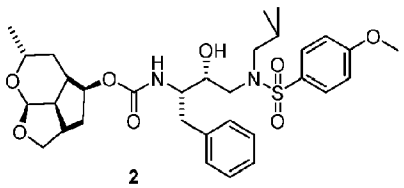
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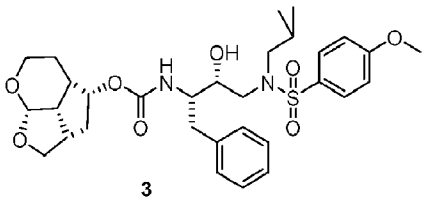
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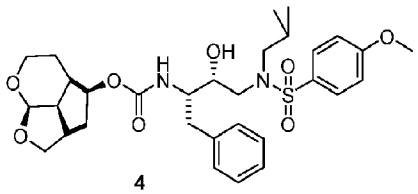
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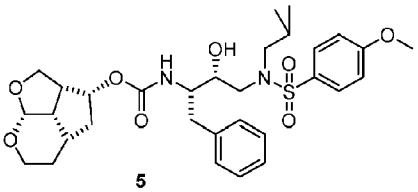

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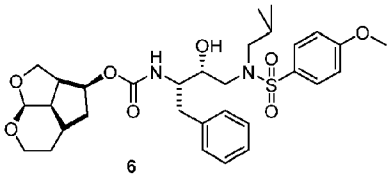

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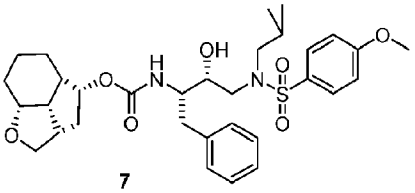

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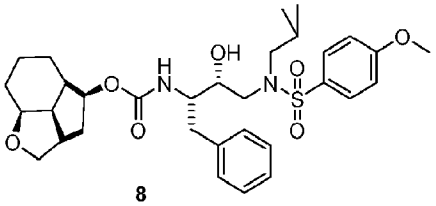

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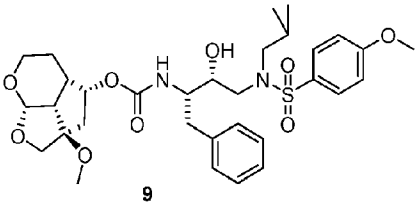

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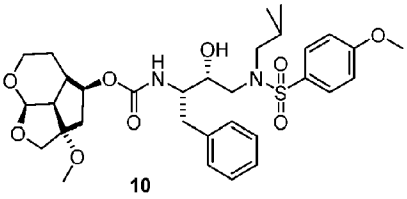

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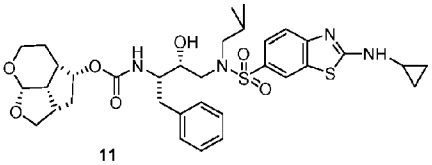

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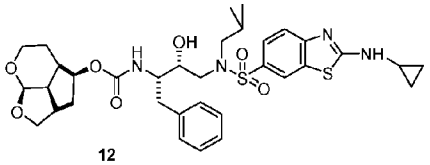

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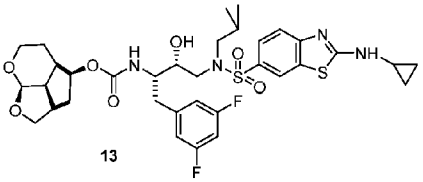

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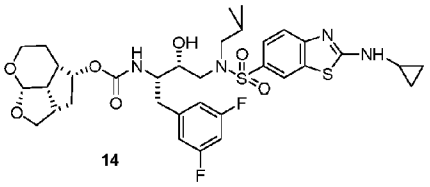

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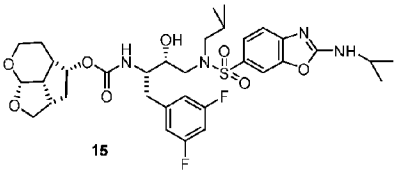

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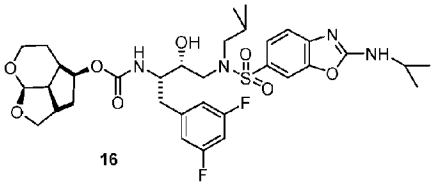

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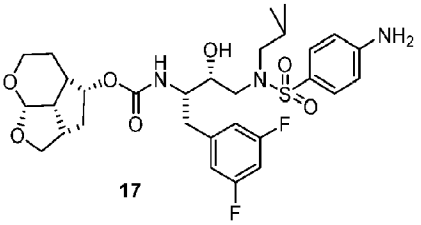

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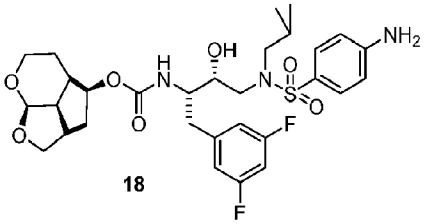

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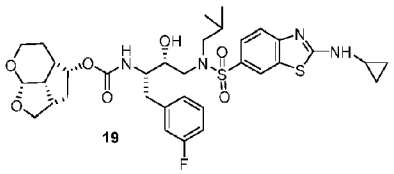

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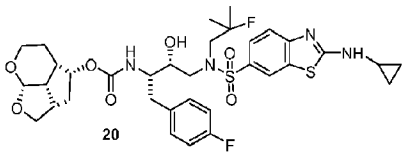

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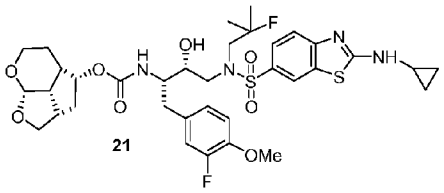

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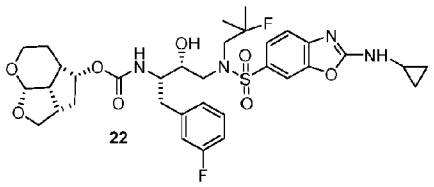

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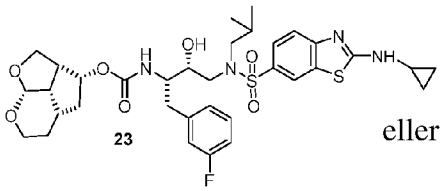

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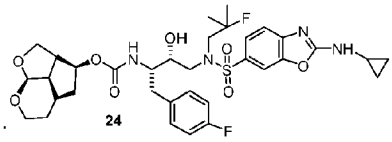
eller



24

eller et/en farmaceutisk acceptabelt/acceptabel salt, polymorf, solvat eller clathrat deraf.

12. Farmaceutisk sammensætning omfattende en forbindelse ifølge krav 1 og én eller flere farmaceutisk acceptable excipienser.

13. Forbindelse ifølge krav 1 til anvendelse i behandling af en HIV-infektion.