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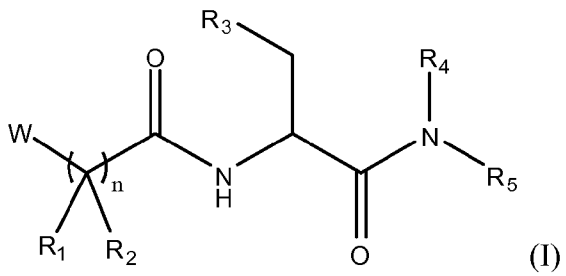
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(54) **Title**: ANTIVIRAL COMPOUNDS



(I)

(57) **Abstract**: The present invention relates to a compound of formula: (I) or a pharmaceutically acceptable salt thereof, wherein the symbols are as defined in the specification; a pharmaceutical composition comprising the same, a method for treating or preventing a viral infection such as HIV using the same.

WO 2013/006792 A1

ANTIVIRAL COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of Chinese Application No. 201110190069.1, filed July 7, 2011, and U.S. Provisional Patent Application No. 61/507,309, filed July 13, 2011, the entire contents of which are hereby incorporated by reference herein.

FIELD OF THE INVENTION

[0002] This invention relates to novel compounds as anti-viral agents, which can be useful in the treatment of viral infections such as HIV, HBV and HCV; to processes for their preparation; to pharmaceutical compositions comprising them; and to methods of using them.

BACKGROUND OF THE INVENTION

[0003] Despite the significant success of the blockading of AIDS progression in HIV-infected patients by the development of various anti-retroviral drugs targeting the envelope protein, reverse transcriptase (RT), integrase (IN) and protease (PR), there is a continuing and urgent need for novel therapy due to the emergence of acquired drug resistance and the serious side effects or intolerance of the existing drugs. Among the 20+ drugs currently on the market for treatment of HIV-1 infection, 19 of them target one of two viral enzymes, reverse transcriptase (RT) or protease (PR). Viral isolates resistant to the approved drugs eventually emerge, which reduce the choice and effectiveness of treatment options. As such, there is a major unmet need for new classes of drugs with unique mode(s) of action with activity against HIV strains resistant to currently approved therapies.

[0004] The discovery of a new class of drugs aiming at inhibition of the HIV replication cycle via new mechanism(s) offers the best hope to patients carrying resistant HIV variants, as the new drug class will not confer cross-resistance to the existing classes of drugs, and therefore will provide value to the novel combination therapies. In addition, since the current standard of care requires lifetime therapy for HIV-infected patients, novel drugs with an improved activity/toxicity/safety profile (improved therapeutic window) will provide added benefits to the AIDS patients regardless of carrying wide-type or mutant/resistant viral strains.

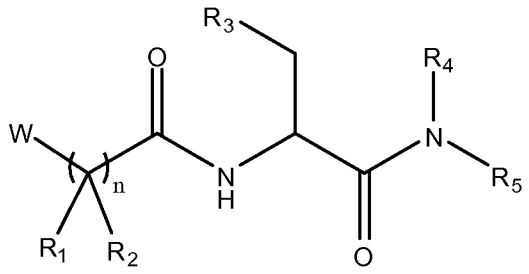
[0005] Virus assembly is a particularly attractive target for antiviral intervention because viral structures are formed by multiple, relatively weak non-covalent interactions. However, few assembly inhibitors have been identified to date in any viral systems, mainly due to insufficient information regarding particle structure and inter-subunit interactions and the lack of suitable assays.

[0006] HIV is released from the infected cells as an immature, non-infectious particle containing a spherical protein shell of approximately 5,000 Gag molecules underneath the viral membrane. Concomitant with the release, sequential proteolytic processing of Gag polyprotein by the viral protease leads to the formation of a mature infectious virus with a conical capsid containing individual structural proteins including matrix (MA), capsid (CA), nucleocapsid (NC), and the p6 protein in addition to two spacer peptides SP1 and SP2. Importantly, the last but critical proteolytic cleavage step of CA-SP1 generates a mature p24 CA protein, which is capable of forming the higher-order complexes that comprise the mature viral core. In the absence of this maturation, viral particles remain to be non-infectious.

[0007] Several antiviral drugs of novel mechanism targeting virion maturation are currently under clinic evaluation.[1-6] Inhibitors that target HIV-1 capsid have been reported to include a helical peptide inhibitor (CAI),[7-9] two small molecule inhibitors CAP-1 and CAP-2[10] and several thiaurea-based inhibitors.[11] In addition, compounds that act on capsid have been disclosed in patent applications.[12-16]

SUMMARY OF THE INVENTION

[0008] In one aspect, the present invention provides a compound of formula I,



(I)

or pharmaceutically acceptable salt thereof, wherein:

W is 5 to 7-membered monocyclic carbocycle or heterocycle;

each of R_1 and R_2 is independently H, (C_1-C_4)alkyl, (C_3-C_5)cycloalkyl, hydroxyl, fluoro, or NR_bR_c, or R_1 and R_2 together form (C_3-C_5)cycloalkyl;

R_3 is phenyl, or heteroaryl;

R_4 is H, $(C_1\text{-}C_4)$alkyl, or $(C_3\text{-}C_7)$cycloalkyl;

R_5 is $(CR_8R_9)_q$-cycloalkyl, $(CR_8R_9)_q$-aryl, or $(CR_8R_9)_q$-heterocycle;

each of R_8 and R_9 is independently H, $(C_1\text{-}C_4)$alkyl, hydroxyl, fluoro, or NR_bR_c, or R_8 and R_9 together form $(C_3\text{-}C_5)$cycloalkyl;

each of R_b and R_c is independently hydrogen or alkyl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle;

each q is independently 0, 1, 2, 3, or 4; and

n is 1 or 2.

[0009] In another aspect, the present invention provides a pharmaceutical composition comprising at least one compound as described herein and a pharmaceutically-acceptable carrier.

[0010] In yet another aspect, the present invention provides a method for treating or preventing a viral infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein.

[0011] In a further aspect, the present invention provides a method for treating or preventing HIV infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0012] The following are definitions of terms used in the present specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated.

[0013] The terms "alkyl" and "alk" refer to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms. Exemplary "alkyl" groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl,

undecyl, dodecyl, and the like. The term "(C_1-C_4)alkyl" refers to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, and isobutyl. The terms "alkyl" and "alk" may include substituted alkyl. "Substituted alkyl" refers to an alkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. In the aforementioned exemplary substitutents, groups such as alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, heterocycle and aryl can themselves be optionally substituted.

[0014] The term "alkenyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon-carbon double bond. Exemplary such groups include ethenyl or allyl. The term "C_2-C_6 alkenyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 6 carbon atoms and at least one carbon-carbon double bond, such as ethylenyl, propenyl, 2-propenyl, (*E*)-but-2-enyl, (*Z*)-but-2-enyl, 2-methy(*E*)-but-2-enyl, 2-methy(*Z*)-but-2-enyl, 2,3-dimethy-but-2-enyl, (*Z*)-pent-2-enyl, (*E*)-pent-1-enyl, (*Z*)-hex-1-enyl, (*E*)-pent-2-enyl, (*Z*)-hex-2-enyl, (*E*)-hex-2-enyl, (*Z*)-hex-1-enyl, (*E*)-hex-1-enyl, , (*Z*)-hex-3-enyl, (*E*)-hex-3-enyl, and (*E*)-hex-1,3-dienyl. The term "alkenyl" may include substituted alkenyl. "Substituted alkenyl" refers to an alkenyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or

multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted.

[0015] The term "alkynyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond. Exemplary such groups include ethynyl. The term "C_2-C_6 alkynyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 6 carbon atoms and at least one carbon-carbon triple bond, such as ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, pent-1-ynyl, pent-2-ynyl, hex-1-ynyl, hex-2-ynyl, hex-3-ynyl. The term "alkynyl" may include substituted alkynyl. "Substituted alkynyl" refers to an alkynyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each

occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted.

[0016] The term "cycloalkyl" refers to a fully saturated cyclic hydrocarbon group containing from 1 to 4 rings and 3 to 8 carbons per ring. "C_3-C_7 cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. The term "cycloalkyl" may include substituted cycloalkyl. "Substituted cycloalkyl" refers to a cycloalkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cylic substituents, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substitutents can themselves be optionally substituted.

[0017] The term "cycloalkenyl" refers to a partially unsaturated cyclic hydrocarbon group containing 1 to 4 rings and 3 to 8 carbons per ring. Exemplary such groups include cyclobutenyl, cyclopentenyl, cyclohexenyl, *etc*. The term "cycloalkenyl" may include substituted cycloalkenyl. "Substituted cycloalkenyl" refers to a cycloalkenyl group substituted with one more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo

substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cylic substituents, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

[0018] The term "aryl" refers to cyclic, aromatic hydrocarbon groups that have 1 to 5 aromatic rings, especially monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two or more aromatic rings (bicyclic, *etc.*), the aromatic rings of the aryl group may be joined at a single point (*e.g.*, biphenyl), or fused (*e.g.*, naphthyl, phenanthrenyl and the like). The term "aryl" may include substituted aryl. "Substituted aryl" refers to an aryl group substituted by one or more substituents, preferably 1 to 3 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl,

cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted. Exemplary substituents also include fused cylic groups, especially fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

[0019] The term "carbocycle" refers to a fully saturated or partially saturated cyclic hydrocarbon group containing from 1 to 4 rings and 3 to 8 carbons per ring, or cyclic, aromatic hydrocarbon groups that have 1 to 5 aromatic rings, especially monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. The term "carbocycle" encompasses cycloalkyl, cycloalkenyl, cycloalkynyl and aryl as defined hereinabove. The term "carbocycle" may include substituted carbocycle. The term "substituted carbocycle" refers to carbocycle or carbocyclic groups substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, those described above for substituted cycloalkyl, substituted cycloalkenyl, substituted cycloalkynyl and substituted aryl. Exemplary substituents also include spiro-attached or fused cyclic substituents at any available point or points of attachment, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

[0020] The terms "heterocycle" and "heterocyclic" refer to fully saturated, or partially or fully unsaturated, including aromatic (*i.e.*, "heteroaryl") cyclic groups (for example, 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 8 to 16 membered tricyclic ring systems) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3, or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. (The term "heteroarylium" refers to a heteroaryl group bearing a quaternary nitrogen atom and thus a positive charge.) The heterocyclic group may be attached to the remainder of the molecule at any heteroatom or carbon atom of the ring or ring system. Exemplary monocyclic heterocyclic groups include azetidinyl, pyrrolidinyl,

pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, hexahydrodiazepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, and the like. Exemplary bicyclic heterocyclic groups include indolyl, isoindolyl, benzothiazolyl, benzoxazolyl, benzoxadiazolyl, benzothienyl, benzo[d][1,3]dioxolyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, quinuclidinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, benzofurazanyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), triazinylazepinyl, tetrahydroquinolinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzindolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like. The terms "heterocycle" may include substituted heterocycle.

[0021] "Substituted heterocycle" and "substituted heterocyclic" (such as "substituted heteroaryl") refer to heterocycle or heterocyclic groups substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF_3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl,

heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cyclic substituents at any available point or points of attachment, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

[0022] The term "alkylamino" refers to a group having the structure -NHR', wherein R' is hydrogen, alkyl or substituted alkyl, cycloalkyl or substituted cyclolakyl, as defined herein. Examples of alkylamino groups include, but are not limited to, methylamino, ethylamino, n-propylamino, iso-propylamino, cyclopropylamino, n-butylamino, tert-butylamino, neopentylamino, n-pentylamino, hexylamino, cyclohexylamino, and the like.

[0023] The term "dialkylamino" refers to a group having the structure -NRR', wherein R and R' are each independently alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cyclolalkenyl, aryl or substituted aryl, heterocylyl or susbstituted heterocyclyl, as defined herein. R and R' may be the same or different in an dialkyamino moiety. Examples of dialkylamino groups include, but are not limited to, dimethylamino, methyl ethylamino, diethylamino, methylpropylamino, di(n-propyl)amino, di(iso-propyl)amino, di(cyclopropyl)amino, di(n-butyl)amino, di(tert-butyl)amino, di(neopentyl)amino, di(n-pentyl)amino, di(hexyl)amino, di(cyclohexyl)amino, and the like. In certain embodiments, R and R' are linked to form a cyclic structure. The resulting cyclic structure may be aromatic or non-aromatic. Examples of cyclic diaminoalkyl groups include, but are not limited to, aziridinyl, pyrrolidinyl, piperidinyl, morpholinyl, pyrrolyl, imidazolyl, 1,3,4-trianolyl, and tetrazolyl.

[0024] The terms "halogen" or "halo" refer to chlorine, bromine, fluorine or iodine.

[0025] Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

[0026] The compounds of the present invention may form salts which are also within the scope of this invention. Reference to a compound of the present invention is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of the present invention contains both a basic moiety, such as but not limited to a pyridine or imidazole, and an acidic moiety such as but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included

within the term "salt(s)" as used herein. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, *e.g.*, in isolation or purification steps which may be employed during preparation. Salts of the compounds of the present invention may be formed, for example, by reacting a compound I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0027] The compounds of the present invention which contain a basic moiety, such as but not limited to an amine or a pyridine or imidazole ring, may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, hydroxyethanesulfonates (*e.g.*, 2-hydroxyethanesulfonates), lactates, maleates, methanesulfonates, naphthalenesulfonates (*e.g.*, 2-naphthalenesulfonates), nicotinates, nitrates, oxalates, pectinates, persulfates, phenylpropionates (*e.g.*, 3-phenylpropionates), phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates, tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

[0028] The compounds of the present invention which contain an acidic moiety, such but not limited to a carboxylic acid, may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl) ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glycamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.,* methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.,* dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.,* decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.,* benzyl and phenethyl bromides), and others.

[0029] Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug" as employed herein denotes a compound that, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the present invention, or a salt and/or solvate thereof. Solvates of the compounds of the present invention include, for example, hydrates.

[0030] Compounds of the present invention, and salts or solvates thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

[0031] All stereoisomers of the present compounds (for example, those which may exist due to asymmetric carbons on various substituents), including enantiomeric forms and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers (*e.g.*, as a pure or substantially pure optical isomer having a specified activity), or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention may have the S or R configuration as defined by the International Union of Pure and Applied Chemistry (IUPAC) 1974 Recommendations. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by any suitable method, including without limitation, conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

[0032] Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 90%, for example, equal to greater than 95%, equal to or greater than 99% of the compounds ("substantially pure" compounds), which is then used or formulated as described herein. Such "substantially pure" compounds of the present invention are also contemplated herein as part of the present invention.

[0033] All configurational isomers of the compounds of the present invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds of the present invention embraces both *cis* (*Z*) and *trans* (*E*) alkene isomers, as well as *cis* and *trans* isomers of cyclic hydrocarbon or heterocyclic rings.

[0034] Throughout the specifications, groups and substituents thereof may be chosen to provide stable moieties and compounds.

[0035] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, the entire contents of which are incorporated herein by reference.

[0036] Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[0037] Isomeric mixtures containing any of a variety of isomer ratios may be utilized in accordance with the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are all contemplated by the present invention. Those of ordinary skill in the art will readily appreciate that analogous ratios are contemplated for more complex isomer mixtures.

[0038] The present invention also includes isotopically labeled compounds, which are identical to the compounds disclosed herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{11}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, or an enantiomer, diastereomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example

those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, *i.e.*, ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

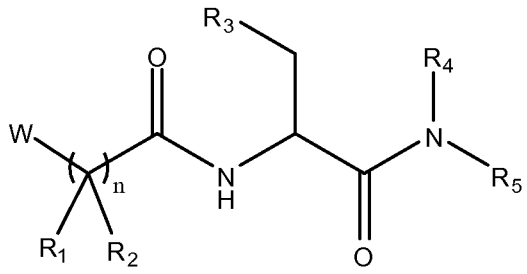
[0039] If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

[0040] It will be appreciated that the compounds, as described herein, may be substituted with any number of substituents or functional moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, and substituents contained in formulas of this invention, refer to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. Furthermore, this invention is not intended to be limited in any manner by the permissible substituents of organic compounds. Combinations of substituents and variables envisioned by this invention are preferably those that result in the formation of stable compounds useful in the treatment, for example, of infectious diseases or proliferative

disorders. The term "stable", as used herein, preferably refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

Compounds

[0041] In one aspect, the present invention provides a compound of the formula (I):



(I)

or pharmaceutically acceptable salt thereof, wherein:

W is 5 to 7-membered monocyclic carbocycle or heterocycle;

each of R_1 and R_2 is independently H, $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_5)$cycloalkyl, hydroxyl, fluoro, or NR_bR_c, or R_1 and R_2 together form $(C_3\text{-}C_5)$cycloalkyl;

R_3 is phenyl, or heteroaryl;

R_4 is H, $(C_1\text{-}C_4)$alkyl, or $(C_3\text{-}C_7)$cycloalkyl;

R_5 is $(CR_8R_9)_q$-cycloalkyl, $(CR_8R_9)_q$-aryl, or $(CR_8R_9)_q$-heterocycle;

each of R_8 and R_9 is independently H, $(C_1\text{-}C_4)$alkyl, hydroxyl, fluoro, or NR_bR_c, or R_8 and R_9 together form $(C_3\text{-}C_5)$cycloalkyl;

each of R_b and R_c is independently hydrogen or alkyl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle;

each q is independently 0, 1, 2, 3, or 4; and

n is 1 or 2.

[0042] In certain embodiments, W is 5-membered heteroaryl, 6-membered heteroaryl, or phenyl, in which said heteroaryl and phenyl are each independently substituted with $(R_6)_m$; each of R_1 and R_2 is independently H or $(C_1\text{-}C_4)$alkyl;

R_3 is phenyl, or heteroaryl;

R_4 is H, $(C_1\text{-}C_4)$alkyl, or $(C_3\text{-}C_7)$cycloalkyl;

R_5 is $(CR_8R_9)_q$-cycloalkyl, $(CR_8R_9)_q$-aryl, or $(CR_8R_9)_q$-heteroaryl;

each R_6 is independently hydrogen, halogen, cyano, nitro, CF_3, OCF_3, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, OR_a, SR_a, $S(=O)R_a$, $S(=O)_2R_a$, $S(=O)_2OR_a$, NR_bR_c, $C(=O)OR_a$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_a$, $NR_aC(=O)NR_bR_c$, $NR_bC(=O)R_a$, $(CR_8R_9)_q$-OH, $(CR_8R_9)_q$-O-$(C_1\text{-}C_4)$alkyl, $(CR_8R_9)_q$-$(C=O)$O-$(C_1\text{-}C_4)$alkyl, $(CR_8R_9)_q$-$(C=O)$O-aryl, $(CR_8R_9)_q$-$(C=O)$OH, $(CR_8R_9)_q$-NR_bR_c, $(CR_8R_9)_q$-cycloalkyl, $(CR_8R_9)_q$-phenyl, or $(CR_8R_9)_q$-heteroaryl;

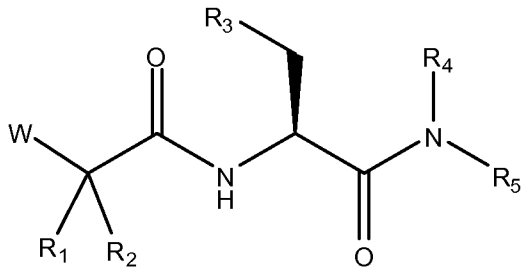
each of R_8 and R_9 is independently H or $(C_1\text{-}C_4)$alkyl;

each occurrence of R_a, R_b, and R_c is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycle, or aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle;

m and q are each independently 0, 1, 2, 3, or 4; and

n is 1 or 2.

[0043] In certain other embodiments, the compound of Formula (I) has the structure of Formula (II):

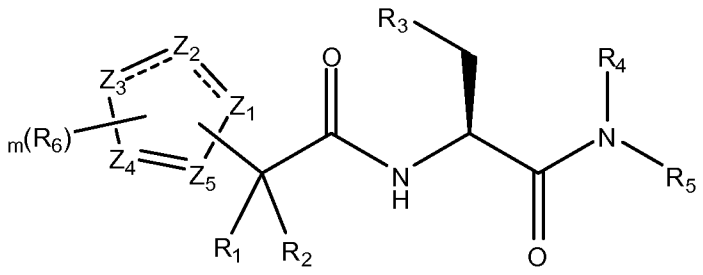


(II),

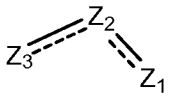
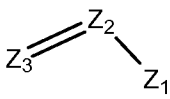
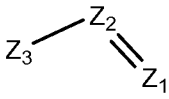
wherein W, R_1, R_2, R_3, R_4, and R_5 are as defined in claim 1 or 2.

[0044] In certain other embodiments, W is 5-membered heteroaryl, in which said heteroaryl is substituted with $(R_6)_m$. In certain other embodiments, wherein W is 6-membered heteroaryl, in which said heteroaryl is substituted with $(R_6)_m$. In yet other embodiments, W is phenyl, in which said phenyl is independently substituted with $(R_6)_m$.

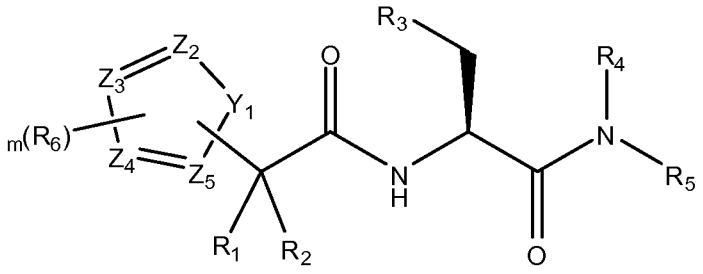
[0045] In yet other embodiments, the compound of Formula (I) has the structure of Formula (III):



(III),

wherein  denotes  or ; each of Z1, Z2, Z3, Z4 and Z_5 is independently carbon or nitrogen, provided that at least one of Z_1, Z_2, Z_3, Z_4 and Z_5 is nitrogen; and R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

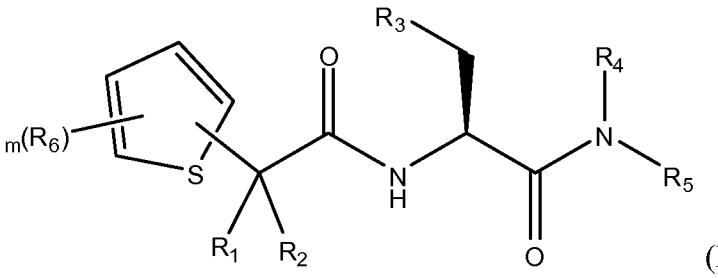
[0046] In yet other embodiments, the compound of Formula (I) has the structure of Formula (IV):



(IV),

wherein each of Z_2, Z_3, Z_4 and Z_5 is independently carbon or nitrogen; Y_1 is oxygen or sulfur; and R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

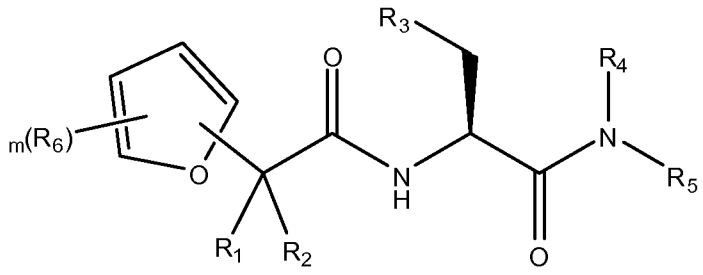
[0047] In yet other embodiments, the compound of Formula (I) has the structure of Formula (IVa):



(IVa),

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

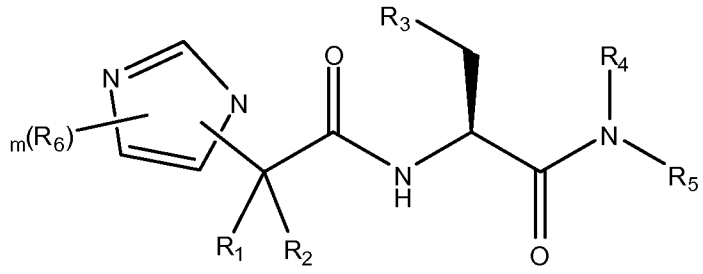
[0048] In yet other embodiments, the compound of Formula (I) has the structure of Formula (IVb):



(IVb),

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

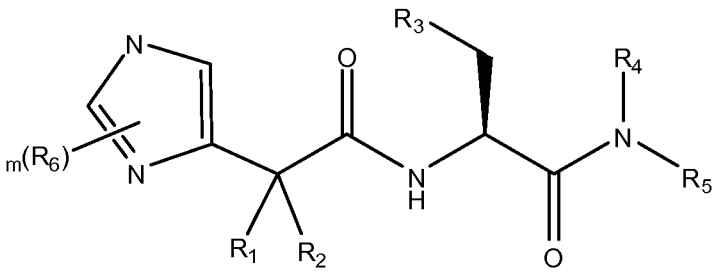
[0049] In yet other embodiments, the compound of Formula (I) has the structure of Formula (IVc):



(IVc),

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

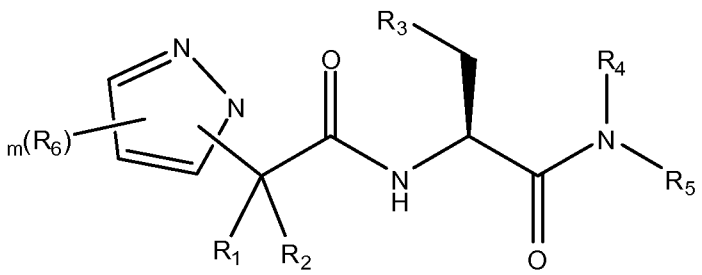
[0050] In yet other embodiments, the compound of Formula (I) has the structure of Formula (IVd):



(IVd),

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

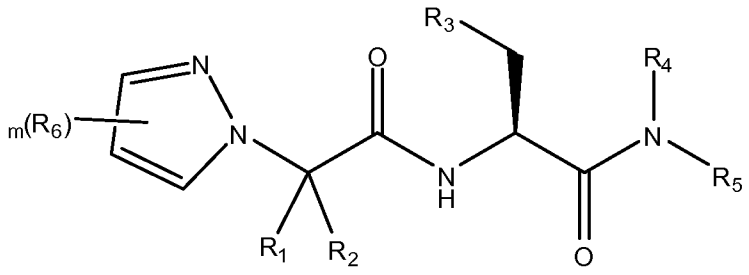
[0051] In yet other embodiments, the compound of Formula (I) has the structure of Formula (V):



(V)

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 1, 2, or 3.

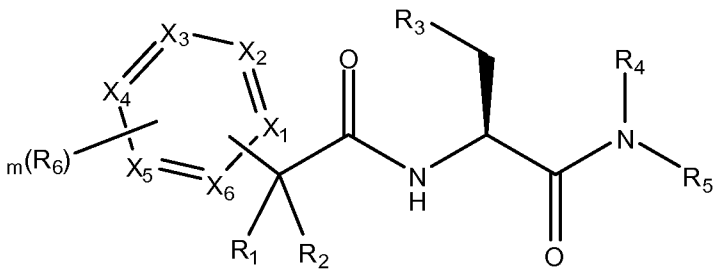
[0052] In yet other embodiments, the compound of Formula (I) has the structure of Formula (VI):



(VI),

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

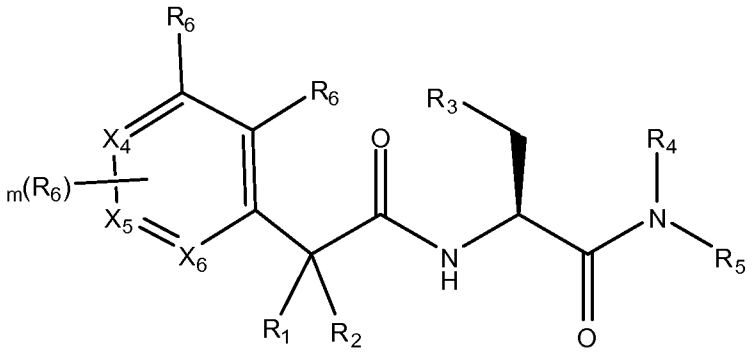
[0053] In yet other embodiments, the compound of Formula (I) has the structure of Formula (VII):



(VII),

each of X_1, X_2, X_3, X_4 , X_5 and X_6 is independently carbon or nitrogen, provided that at least one of X_1, X_2, X_3, X_4 , X_5 and X_6 is nitrogen; and R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

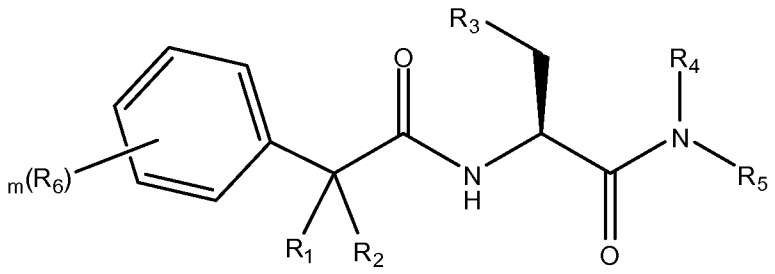
[0054] In yet other embodiments, the compound of Formula (I) has the structure of Formula (VIIa):



(VIIa),

each of X_4 , X_5 and X_6 is independently carbon or nitrogen, provided that only one of X_4 , X_5 and X_6 is nitrogen, and the remaining of X_4 , X_5 and X_6 is carbon; and R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, or 2.

[0055] In yet other embodiments, the compound of Formula (I) has the structure of Formula (VIII):



(VIII),

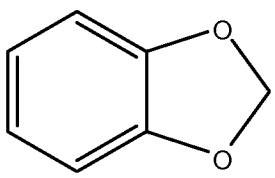
wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

[0056] In certain embodiments, each of R_1 and R_2 is independently H. In certain other embodiments, R_3 is phenyl. In yet other embodiments, R_3 is phenyl substituted with one to three substituents selected from H, $(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$alkyl, halogen, nitro, CN, CF_3, and OCF_3. In yet other embodiments, R_3 is unsubstituted phenyl. In yet other embodiments, R_3 is heteroaryl substituted with one to three substituents selected from H, $(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$alkyl, halogen, nitro, CN, CF_3, and OCF_3. In yet other embodiments, R_3 is unsubstituted heteroaryl.

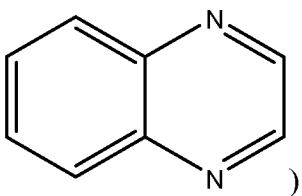
[0057] In certain embodiments, R_4 is H. In certain other embodiments, R_4 is $(C_1$-$C_4)$alkyl. In yet other embodiments, R_4 is methyl.

[0058] In certain embodiments, R_5 is $(CH_2)_q$-cycloalkyl, $(CH_2)_q$-aryl, or $(CH_2)_q$-heteroaryl, in which q is 0 or 1. In certain other embodiments, R_5 is aryl, or heteroaryl. In yet other embodiments, R_5 is phenyl. In yet other embodiments, R_5 is pyridyl.

[0059] In certain embodiments, R_5 is aryl (e.g., phenyl) or heteroaryl (e.g., pyridyl,



or



) substituted with one to four substituents selected from hydrogen, halogen, cyano, nitro, CF_3, OCF_3, $(C_1$-$C_4)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_3$-$C_7)$cycloalkenyl, 3-10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from N, O and S, phenyl, naphthyl, OR_a, SR_a, $S(=O)R_a$, $S(=O)_2R_a$, $S(=O)_2OR_a$, NR_bR_c, $C(=O)OR_a$, $C(=O)R_a$, $C(=O)NR_bR_c$,

$OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_a$, $NR_aC(=O)NR_bR_c$, $NR_bC(=O)R_a$, $(CR_8R_9)_q$-OH, $(CR_8R_9)_q$-O-$(C_1$-$C_4)$alkyl, $(CR_8R_9)_q$-NR_bR_c, $(CR_8R_9)_q$-cycloalkyl, $(CR_8R_9)_q$-phenyl, and $(CR_8R_9)_q$-heteroaryl;

each of R_8 and R_9 is independently H or $(C_1$-$C_4)$alkyl;

each occurrence of R_a, R_b, and R_c is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycle, or aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and

each q is independently 0, 1, 2, 3, or 4.

[0060] In certain embodiments, R_5 is phenyl or heteroaryl substituted with one to four substituents selected from hydrogen, halogen, cyano, nitro, CF_3, OCF_3, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl, 3-10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from N, O and S, phenyl, naphthyl, $(CH_2)_q$-OH, $(CH_2)_q$-O-$(C_1$-$C_4)$alkyl, $(CH_2)_q$-NR_bR_c, $(CH_2)_q$-$(C_3$-$C_7)$cycloalkyl, , $(CH_2)_q$-phenyl, and $(CH_2)_q$-heteroaryl;
each occurrence of R_b, and R_c is independently hydrogen, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl, 3-10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from N, O and S, or aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and

each q is independently 0, 1, 2, 3, or 4.

[0061] In certain embodiments, each R_6 is independently hydrogen, halogen, cyano, nitro, CF_3, OCF_3, $(C_1$-$C_4)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_3$-$C_7)$cycloalkenyl, 3-10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from N, O and S, phenyl, naphthyl, OR_a, SR_a, $S(=O)R_a$, $S(=O)_2R_a$, $S(=O)_2OR_a$, NR_bR_c, $C(=O)OR_a$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_a$, $NR_aC(=O)NR_bR_c$, $NR_bC(=O)R_a$, $(CR_8R_9)_q$-OH, $(C_1$-$C_4)$alkyl substituted with one or more halogen, $(CR_8R_9)_q$-O-$(C_1$-$C_4)$alkyl, $(CR_8R_9)_q$-$(C=O)O$-$(C_1$-$C_4)$alkyl, $(CR_8R_9)_q$-$(C=O)O$-aryl, $(CR_8R_9)_q$-$(C=O)OH$, $(CR_8R_9)_q$-NR_bR_c, $(CR_8R_9)_q$-cycloalkyl, $(CR_8R_9)_q$-phenyl, or $(CR_8R_9)_q$-heteroaryl;
each of R_8 and R_9 is independently H or $(C_1$-$C_4)$alkyl;

each occurrence of R_a, R_b, and R_c is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycle, or aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and

each q is independently 0, 1, 2, 3, or 4.

[0062] In certain other embodiments, each R_6 is independently hydrogen, halogen, cyano, nitro, CF_3, OCF_3, $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, 3-10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from N, O and S, phenyl, naphthyl, $(CH_2)_q$-OH, $(CH_2)_q$-O-$(C_1\text{-}C_4)$alkyl, $(CH_2)_q$-(C=O)O-$(C_1\text{-}C_4)$alkyl, $(CH_2)_q$-(C=O)O-aryl, $(CH_2)_q$-(C=O)OH, $(CH_2)_q$-NR_bR_c, $(CH_2)_q$-$(C_3\text{-}C_7)$cycloalkyl or $(CH_2)_q$-substituted $(C_3\text{-}C_7)$cycloalkyl, $(CH_2)_q$-phenyl, or $(CH_2)_q$-heteroaryl;
each occurrence of R_b, and R_c is independently hydrogen, $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, 3-10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from N, O and S, or aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and

each q is independently 0, 1, 2, 3, or 4.

[0063] In certain other embodiments, each occurrence of R_b, and R_c is independently hydrogen or $(C_1\text{-}C_4)$alkyl, or said R_b and R_c together with the N to which they are bonded optionally form a 3-8 membered heterocycle.

[0064] In one aspect, the present invention provides a compound selected from Examples 1 through 52 as described herein.

[0065] In another aspect, the present invention provides a pharmaceutical composition comprising at least one compound described herein and a pharmaceutically-acceptable carrier or diluent.

[0066] In a further aspect, the present invention provides a method for treating or preventing a viral infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound described herein. In certain embodiments, the viral infection is HIV infection. In certain other embodiments, the viral infection is HBV infection. In yet other embodiments, the viral infection is HCV infection. In yet other embodiments, the viral infection is influenza A virus infection, severe acute respiratory syndrome coronavirus infection or vaccinia virus infection.

[0067] In another aspect, the present invention provides a method for treating or preventing HIV infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound described herein.

Abbreviations

ACN	Acetonitrile
EA	Ethyl acetate
DMF	Dimethyl formamide
PE	Petroleum ether
DCM	Dichloromethane
THF	Tetrahydrofuran
HOBT	1-Hydroxybenzotriazole
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
HBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HATU	2-(7-Azabenzotriazol)-N,N,N',N'-tetramethyluronium hexafluorophosphate
PyBOP	1H-Benzotriazol-1-yloxytripyrrolidinophosphoniumhexafluorophosphate
BOPCl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BOP	Benzotriazol-1-yloxytris(diethylamino)phosphonium hexafluorophospahte
TEA	Triethylamine
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
9-BBN	9-Borabicyclo[3.3.1]nonane
TFA	Trifluoroacetic acid
TMSCl	Trimethylsilyl chloride
TLC	Thin layer chromatography
NMP	*N*-Methylpyrrolidinone
Boc	*t*-Butoxy carbonyl
DME	1,2-Dimethoxyethane
LiHMDS	Lithium hexamethyldisilazide
LDA	Lithium diisopropylamide
CAN	Cerium (IV) ammonium nitrate
n-BuLi	n-Butyl lithium

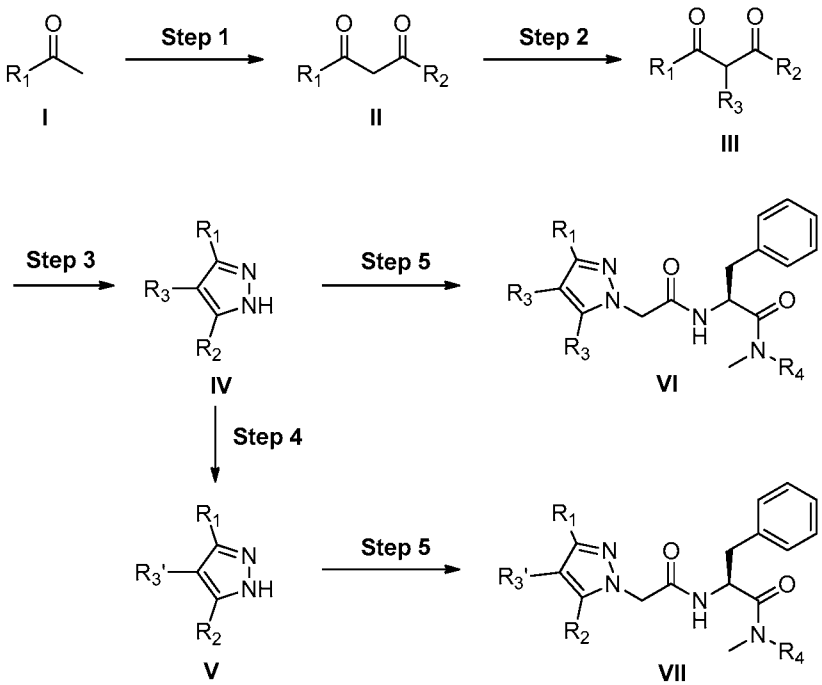
METHODS OF PREPARATION

[0068] The compounds of the present invention may be synthesized using conventional techniques known in the art. Advantageously, these compounds are conveniently synthesized from readily available starting materials. Following are general synthetic schemes for manufacturing compounds of the present invention. These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to manufacture compounds disclosed herein. Different methods will be evident to those skilled in the art. Additionally, the various steps in the synthesis may be performed in an alternate sequence or order to give the desired compound(s). All documents cited herein are incorporated herein by reference in their entirety.

[0069] Compounds of formula I may generally be prepared according to the following schemes and the knowledge of one skilled in the art. Schemes **1**–**7** describe various methods for the synthesis of intermediates that may be used to prepare compounds of formula I–VIII described in this invention. Various modifications to these methods may be envisioned by those skilled in the art to achieve similar results to that of the authors given below.

[0070] The compounds **VI** and **VII** are prepared as shown in **Scheme 1**.

Scheme 1



Step 1

[0071] Reaction of ketone **I** with a base, such as sodium hydride, potassium *tert*-butoxide or sodium *tert*-butoxide, followed by treatment with the ester R_2COOR', affords the carbonyl ketone intermediate **II**.

Step 2

[0072] Treatment of intermediate **II** with halide, such as iodomethane, bromoethane ethyl bromoacetate and so on, in the presence of a base, such as sodium hydride, potassium carbonate, in the solvent such as DME, dioxane, THF and so on, affords the intermediate **III**.

Step 3

[0073] Reaction of intermediate **III** with hydrazine or its hydrate in the solvent, such as THF, alcohol, or acetic acid, affords pyrazole **IV**.

Step 4

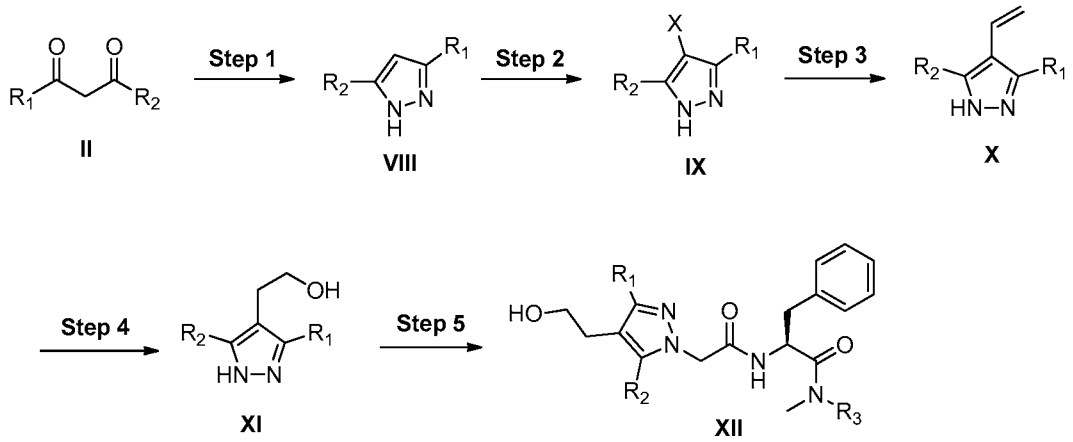
[0074] If R_3 group of **IV** was ester or acid, reaction of **IV** with reducing reagents, such as lithium aluminium hydride or borane, affords alcohol intermediate **V**.

Step 5

[0075] Reaction of the pyrazole **IV** or **V** and haloacetic amide in the presence of a base such as K_2CO_3, TEA, DIPEA or DMAP, in the solvent such as DCM, DMF, THF and so on, affords the final compounds **VI** or **VII**.

[0076] The compounds **XII** are prepared as shown in **Scheme 2**.

Scheme 2



Step 1

[0077] Reaction of intermediate **II** with hydrazine or its hydrate in the solvent, such as THF, alcohol, or acetic acid, affords pyrazole **VIII**.

Step 2

[0078] Reaction of pyrazole intermediate **VIII** with halogenation reagent, such as NBS, NCS, NIS, I_2 or Br_2, in DMF or THF, affords the halide **IX**.

Step 3

[0079] Reaction of the intermediate **IX** with the vinyl coupling reagent, such as boronic acid, organotin reagents, Grignard reagents or organozinc reagents, in the presence of a catalyst, such as palladium reagents, in the solvent such as THF, DMF or DME, affords the coupling product **X**.

Step 4

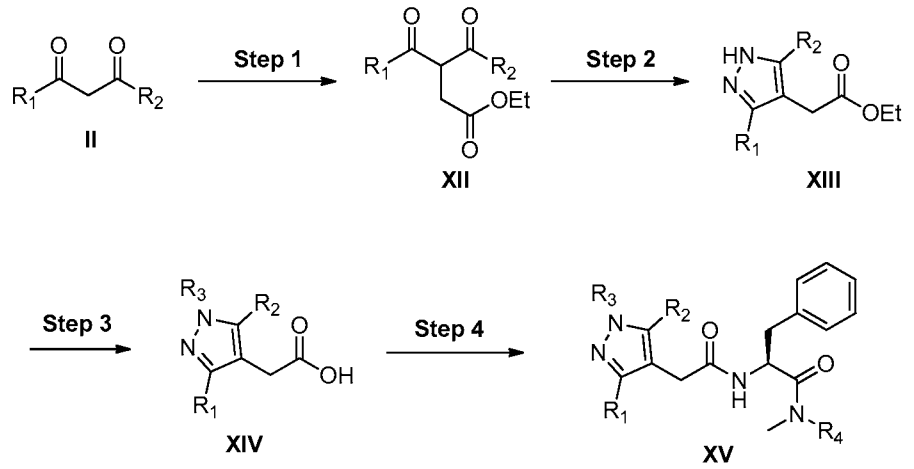
[0080] Reaction of the intermediate **X** with borane or 9-BBN, in the solvent such as THF, DME, followed by treatment with hydrogen peroxide in the presence of a base, such as sodium hydroxide, or potassium hydroxide, affords the product **XI**.

Step 5

[0081] Reaction of the amine **XI** and haloacetamide in the presence of a base such as K_2CO_3, TEA, DIPEA or DMAP, in the solvent such as DCM, DMF or THF, affords the final compounds **XII**.

[0082] The compounds **XV** are prepared as shown in **Scheme 3.**

Scheme 3



Step 1

[0083] Treatment of intermediate **II** with ethyl bromoacetate, in the presence of a base, such as sodium hydride, potassium carbonate, in the solvent such as DME, dioxane, THF and so on, affords the intermediate **XII**.

Step 2

[0084] Reaction of intermediate **XII** with hydrazine or its hydrate in the solvent, such as THF, alcohol, or acetic acid, affords pyrazole **XIII**.

Step 3

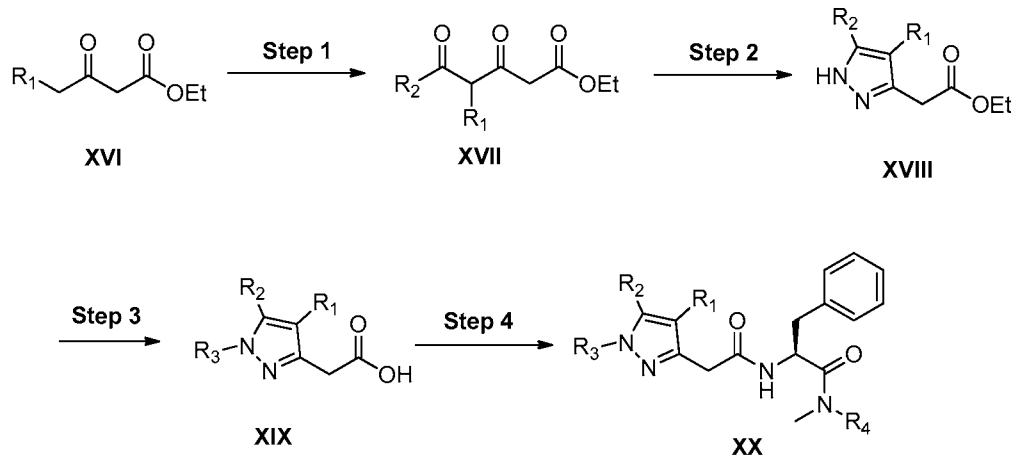
[0085] Treatment of intermediate **XIII** with halide, such as iodomethane, bromoethane and so on, in the presence of a base, such as sodium hydride, potassium carbonate, followed by saponification with another base, such as lithium hydroxide, or sodium hydroxide, or potassium hydroxide, affords indole acid **XIV**.

Step 4

[0086] Reaction of the acid **XIV** and the corresponding amines in the present of a coupling agent, such as HOBT/EDCI, HATU, HBTU, PyBOP, BOPCl, or a BOP reagent, and a base such as TEA, DIPEA or DMAP, in the solvent such as DCM, DMF, THF and so on, affords compounds **XV**.

[0087] The compounds **XX** are prepared as shown in **Scheme 4**.

Scheme 4



Step 1

[0088] Treatment of intermediate **XVI** with a base, such as NaH, and followed by addition of another base, such as n-BuLi, and subsequent reaction with Weinreb amide containing R_2 group, affords the intermediate **XVII**.

Step 2

[0089] Reaction of intermediate **XVII** with hydrazine hydrate in the solvent, such as THF, alcohol, or acetic acid, affords pyrazole **XVIII**.

Step 3

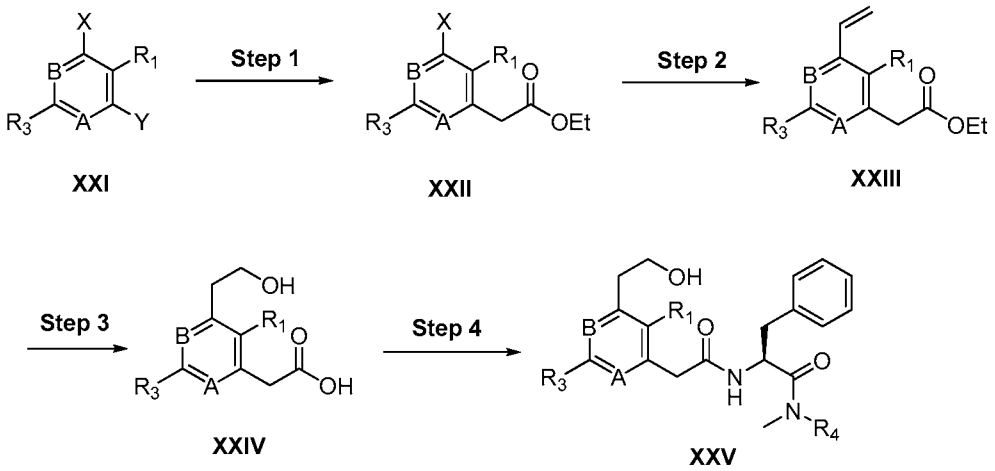
[0090] Treatment of intermediate **XVIII** with halide, such as iodomethane, bromoethane and so on, in the presence of a base, such as sodium hydride, potassium carbonate, followed by adding another base, such as lithium hydroxide, or sodium hydroxide, or potassium hydroxide, affords indole acid **XIX**.

Step 4

[0091] Reaction of the acid **XIX** and the corresponding amine in the present of a coupling agent, such as HOBT/EDCI, HATU, HBTU, PyBOP, BOPCl, or a BOP reagent, and a base such as TEA, DIPEA or DMAP, in the solvent such as DCM, DMF, THF and so on, affords compounds **XX**.

[0092] The compounds **XXV** can be prepared as shown in **Scheme 5.**

Scheme 5



(where A, B = CH or N independently or in combination, Y = Me or halogen)

Step 1

[0093] Treatment of intermediate **XII** with a base, such as *n*-BuLi, LDA, LiHMDS, in the solvent such as DME, dioxane, THF and so on, and then diethyl carbonate was added when Y is methyl, or MeCN was added when Y is halogen followed by treatment with TMSCl and ethanol, affords the intermediate **XXII**.

Step 2

[0094] Reaction of the intermediate **XXII** with the vinyl coupling reagents, such as boronic acid, organotin reagents, Grignard reagents or organozinc reagents, in the presence of

a catalyst, such as palladium reagents, in the solvent such as THF, DMF or DME, affords the coupled product **XXIII**.

Step 3

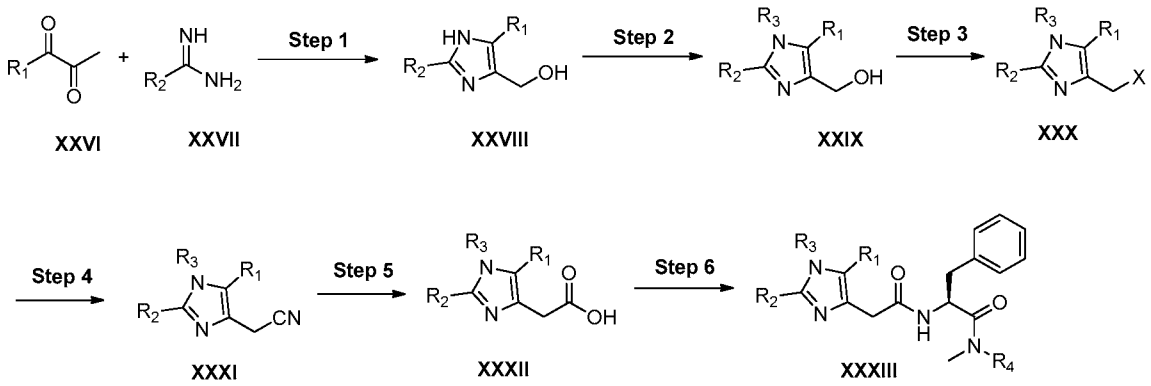
[0095] Reaction of the intermediate **XXIII** with reagent like borane or 9-BBN, in the solvent such as THF, DME, followed by treatment with hydrogen peroxide in the presence of a base, such as sodium hydroxide, or potassium hydroxide, affords the product **XXIV**.

Step 4

[0096] Reaction of the acid **XXIV** and the corresponding amine in the presence of a coupling agent, such as HOBT/EDCI, HATU, HBTU, PyBOP, BOPCl, or a BOP reagent, and a base such as TEA, DIPEA or DMAP, in the solvent such as DCM, DMF, THF and so on, affords the amide compounds **XXV**.

[0097] The compounds **XXXIII** are prepared as shown in **Scheme 6.**

Scheme 6



Step 1

[0098] Condensation of intermediate **XXVI** with amidine intermediate **XXVII** in the presence of a base, such as sodium acetate, potassium acetate, affords the intermediate **XXVIII**.

Step 2

[0099] Treatment of intermediate **XXVIII** with halide, such as iodomethane, bromoethane and so on, in the presence of a base, such as sodium hydride, potassium carbonate, followed by addition of another base, such as lithium hydroxide, or sodium hydroxide, or potassium hydroxide, affords the intermediate **XXIX**.

Step 3

[0100] Treatment of intermediate **XXIX** with a chlorination reagent, such as thionyl chloride, affords chloromethylpyrazole intermediate **XXX**.

Step 4

[0101] Treatment of intermediate **XXX** with a cyanidation reagent, such as NaCN, KCN, TMSCN, in the presence of a base, such as sodium carbonate, potassium carbonate, affords the intermediate**XXXI**.

Step 5

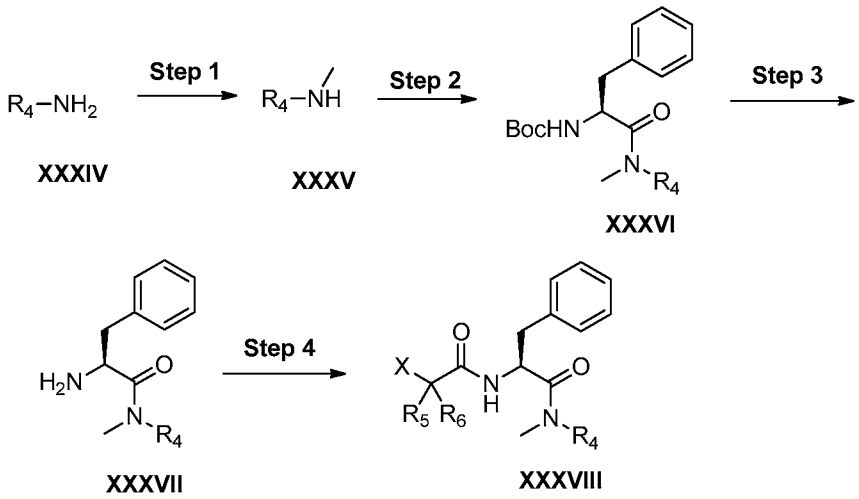
[0102] Hydrolysis of the intermediate **XXXI** with an acid, such as concentrated HCl, TMSCl, or a base, such as NaOH, KOH, and so on, affords the acid **XXXII**.

Step 6

[0103] Reaction of the acid **XXXII** and the corresponding amine in the presence of a condensating agent, such as HOBT/EDCI, HATU, HBTU, PyBOP, BOPCl, or a BOP reagent, and a base such as TEA, DIPEA or DMAP, in the solvent such as DCM, DMF, THF and so on, affords the amide compounds **XXXIII**.

[0104] The intermediates **XXXVII** and **XXXVIII** are prepared as shown in **Scheme 7.**

Scheme 7



Step 1

[0105] Reaction of primary amine **XXXIV** with aldehyde, such as paraformaldehyde, acetaldehyde and so on in the presence of a base, such as sodium methoxide, or Lewis acid, in the solvent of alcohol, followed by treatment with reductive reagents, such as $NaBH_4$, $NaBH_3CN$ or $NaBH_3OAc$, affords the secondary amine **XXXVIII**.

Step 2

[0106] Reaction of the amine **XXXV** and *N*-Boc-Phenylalanine in the presence of a condensating agent, such as HOBT/EDCI, HATU, HBTU, PyBOP, BOPCl, or a BOP reagent, and a base such as TEA, DIPEA or DMAP, in the solvent such as DCM, DMF, THF and so on, affords the amide compounds **XXXVI**.

Step 3

[0107] Treatment of the intermediates **XXXVI** with HCl solution such as HCl in MeOH, HCl in THF and so on, affords the amine intermediates **XXXVII**.

Step 4

[0108] Reaction of the amine **XXXVII** and haloacetyl halide in the presence of a base such as TEA, DIPEA or DMAP, in the solvent such as DCM, DMF, THF and so on, affords the amide compounds **XXXVIII**.

Pharmaceutical Compositions

[0109] This invention also provides a pharmaceutical composition comprising at least one of the compounds as described herein or a pharmaceutically-acceptable salt or solvate thereof, and a pharmaceutically-acceptable carrier.

[0110] The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as butylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0111] As set out above, certain embodiments of the present pharmaceutical agents may be provided in the form of pharmaceutically-acceptable salts. The term "pharmaceutically-acceptable salt", in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge *et al.*, (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19.)

[0112] The pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, *e.g.*, from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, butionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

[0113] In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge *et al.*, supra.)

[0114] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate, magnesium stearate, and polyethylene oxide-polybutylene oxide copolymer as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0115] Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any method well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated and the particular mode of administration. The amount of active ingredient, which can be combined with a carrier material to produce a single dosage form, will generally be that amount of the compound which produces a therapeutic effect. Generally, out of 100%, this amount will range from about 1% to about 99% of active ingredient, preferably from about 5% to about 70%, most preferably from about 10% to about 30%.

[0116] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0117] Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouthwashes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

[0118] In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates,

gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium carbonate, and sodium starch glycolate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and polyethylene oxide-polybutylene oxide copolymer; absorbents, such as kaolin and bentonite clay; lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0119] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxybutylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets, may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0120] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxybutylmethyl cellulose in varying butortions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions, which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form with one or more of the above-described excipients.

[0121] Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isobutyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, butylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Additionally, cyclodextrins, *e.g.*, hydroxybutyl-beta-cyclodextrin, may be used to solubilize compounds.

[0122] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0123] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0124] Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active pharmaceutical agents of the invention.

[0125] Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations.

[0126] Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier and with any preservatives or buffers which may be required.

[0127] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0128] Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary butellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and butene.

[0129] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving, or dispersing the pharmaceutical agents in the buter medium. Absorption enhancers can also be used to increase the flux of the pharmaceutical agents of the invention across the skin. The rate of such flux can be controlled, by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[0130] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[0131] Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0132] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. One strategy for depot injections includes the use of polyethylene oxide-polybutylene oxide copolymers wherein the vehicle is fluid at room temperature and solidifies at body temperature.

[0133] Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly (orthoesters) and poly (anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions, which are compatible with body tissue.

[0134] When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given *per se* or as a pharmaceutical composition containing, for example, 0.1% to 99.5% (more preferably, 0.5% to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[0135] The compounds and pharmaceutical compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutical compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, the compound of the present invention may be administered concurrently with another anti-HCV agent), or they may achieve different effects (e.g., control of any adverse effects).

[0136] The compounds of the invention may be administered intravenously, intramuscularly, intraperitoneally, subcutaneously, topically, orally, or by other acceptable means. The compounds may be used to treat arthritic conditions in mammals (i.e., humans, livestock, and domestic animals), birds, lizards, and any other organism, which can tolerate the compounds.

[0137] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

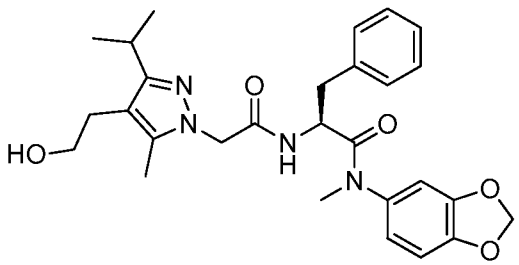
Equivalents

[0138] The representative examples which follow are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples which follow and the references to the scientific and patent literature cited herein. It should further be appreciated that the contents of those cited references are incorporated herein by reference to help illustrate the state of the art. The following examples contain important additional information, exemplification and guidance which can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

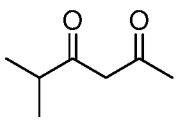
EXAMPLES

EXAMPLE 1

(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(4-(2-hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide



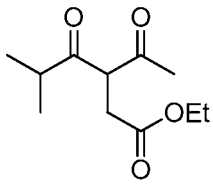
1A. Preparation of 5-methylhexane-2,4-dione



[0139] *Tert*-BuOK (20 g, 178 mmol, 1.5 eq) was added in portions to 3,3-dimethylbutan-2-one(10 g, 119 mmol, 1.0 eq) and stirred for 30min. Then ethyl acetate (35 mL, 357 mmol, 3.0 eq) was added dropwise at 55 °C. The solution was stirred at 55 °C for 12h. TLC analysis (petroleum ether/EtOAc = 1:1) showed the reaction was completed. Then the solution was poured over ice/hydrochloric acid and extracted with EtOAc (2x100 mL). The

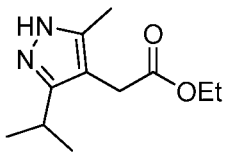
organic layer was then washed with 4M hydrochloric acid (2x30 mL) and brine (30 mL). The crude product was purified by column chromatography to give 5-methylhexane-2,4-dione (4.0 g, yield: 26%).LC/MS: m/z(M^++1) = 129.

1B. Preparation of ethyl 3-acetyl-5-methyl-4-oxohexanoate



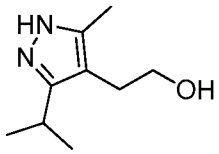
[0140] To a solution of 5-methylhexane-2,4-dione(2 g, 10.7 mmol, 1.0 eq) in dioxane (20 mL) and H_2O (10 mL) was added KOH (0.6 g, 10.7 mmol, 1.0 eq) in portions at 0 °C. The mixture was stirred at room temperature for 30 minutes. To the resulting mixture was added ethyl 2-bromoacetate (1.77 g, 10.7 mmol, 1 eq) dropwise at 0 °C, and the mixture was stirred at room temperature for 12 hours. TLC (petroleum ether/EtOAc = 1:1) showed the reaction was completed. The reaction mixture was extracted with EtOAc (2x50 mL). The combined organic extracts were washed with brine (3x20 mL), dried over Na_2SO_4 and concentrated in *vacuum* to give crude product, which was purified by column chromatography on silica gel to give compound ethyl 3-acetyl-5-methyl-4-oxohexanoate (1.5 g, yield: 75%). LC/MS: m/z (M^++1) = 215.

1C. Preparation of ethyl 2-(3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetate



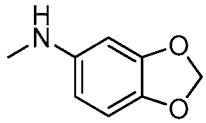
[0141] A mixture of ethyl 3-acetyl-5-methyl-4-oxohexanoate (1.5 g, 8 mmol, 1.0 eq) in hydrazine hydrate (0.43 g, 8 mmol, 1.0 eq) and acetic acid (0.5 mL) were stirred at reflux for 3 h. TLC analysis (petroleum ether/EtOAc =1:1) showed the reaction was completed. The reaction was concentrated in *vacuum* to give ethyl 2-(3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetate (1.3 g, yield: 83%).LC/MS: m/z (M^++1) = 211.

1D. Preparation of 2-(3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)ethanol



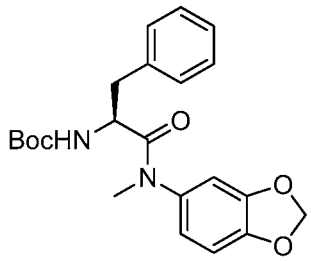
[0142] To a stirred suspension of $LiAlH_4$ (84 mg, 2 mmol, 2 eq) in dry THF (50 mL), was added dropwise a solution of ethyl 2-(3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetate (0.2g, 1mmol, 1eq) in dry THF (100 mL) at 0 °C. The resulting mixture was stirred at room temperature for 3 hours. TLC (petroleum ether/EtOAc =1:1) indicated the reaction was complete. The reaction mixture was quenched with 10% aqueous NaOH (20 mL) and diluted with EtOAc (100 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in *vacuum* to yield crude product, which was purified by column chromatography to give 2-(3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)ethanol (0.11 g, yield: 65%). LC/MS: m/z(M^++1) = 169.

1E. Preparation of *N*-methylbenzo[*d*][1,3]dioxol-5-amine



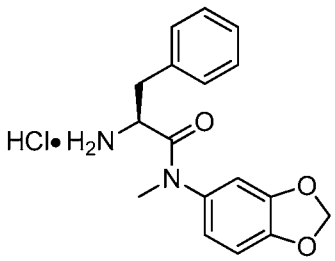
[0143] To a solution of sodium methoxide (4.13 g, 76.5 mmol, 5.0 eq) in methanol (50 mL)， paraformaldehyde (4.59 g, 153 mmol, 10.0 eq) and benzo[*d*][1,3]dioxol-5-amine (2.10 g, 15.3 mmol, 1.0 eq) were added. The mixture was stirred at R.T. for 24 h until TLC indicated the SM had disappeared. Then sodium borohydride (1.74 g, 45.9 mmol, 3.0 eq) was added portionwise slowly, and the mixture was stirred at 40°C for an additional 3h. The resulting mixture was filtrated, concentrated and dissolved in EtOAc, washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel chromatography to give the desired product *N*-methylbenzo[*d*][1,3]dioxol-5-amine(2.27 g, 15.0 mmol, yield: 98%). LC/MS: m/z (M^++1) = 152.

1F. Preparation of (*S*)-tert-butyl1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-ylcarbamate



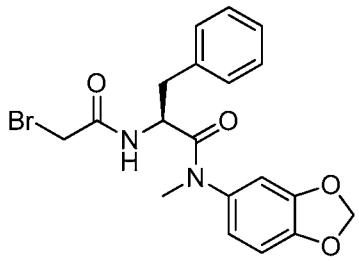
[0144] (*S*)-2-(tert-butoxycarbonyl)-3-phenylpropanoicacid (2.17 g, 8.18 mmol, 1.3 eq),*N*-methylbenzo[*d*][1,3]dioxol-5-amine (950 mg,6.29 mmol, 1.0 eq), EDCI (1.8 g, 9.43 mmol, 1.5 eq), HOBt (1.7 g, 12.6 mmol, 2.0 eq) and DIPEA (1.62 g,12.6 mmol, 2.0 eq) were dissolved in DMF (20 mL). The resulting mixture was stirred at r.t overnight. Water was added and the mixture was extracted by EA (2x25 mL), washed with aqueous LiCl solution (3x40 mL). The organic layer was dried and concentrated, and the residue was purified by silica gel chromatography column with PE and EA to give the titled product (2.2 g, yield: 88%); LC/MS: m/z (M^++1) = 399.

1G. Preparation of (*S*)-2-amino-*N*-(benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-3-phenylpropanamide hydrochloride



[0145] (*S*)-tert-butyl1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropa*N*-2-ylcarbamate (2.2 g, 5.52 mmol, 1.0 eq) was dissolved in MeOH/HCl (1 M, 6 mL). The mixture was stirred at r.t for 1h until the TLC indicated the SM had disappeared. The solvent was removed under reduced pressure to give the product (2.2 g, yield: 98%); LC/MS: m/z (M^++1) = 299.

1H. Preparation of (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-bromoacetamido)-*N*-methyl-3-phenylpropanamide



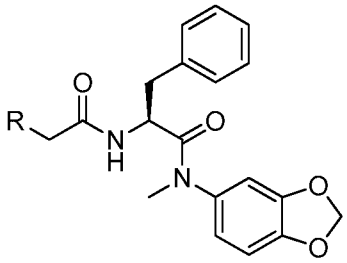
[0146] To a solution of (*S*)-2-amino-*N*-(benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-3-phenylpropamide (3.0 g, 10.0 mmol, 1.0 eq) and DIPEA (2.5 mL, 15.0 mmol, 1.5 eq) in anhydrous DCM, 2-bromoacetyl bromide (2.6 mL, 30.0 mmol, 3.0 eq) was added at 0 °C over 15 min. The mixture was stirred at R.T. for 30 min until TLC indicated the SM had disappeared. The resulting reaction mixture was quenched by water, extracted with EtOAc. The organic extract was dried over Na_2SO_4 and concentrated, the residue was recrystallized form PE and EA to give (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-bromoacetamido)-*N*-methyl-3-phenylpropanamide (1.6 g, 3.8 mmol, yield: 38.1%); LC/MS: m/z (M^++1) = 419.

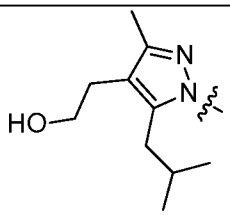
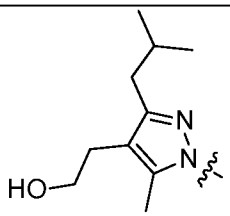
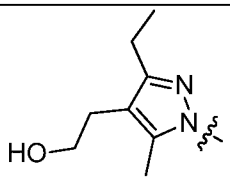
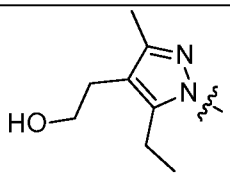
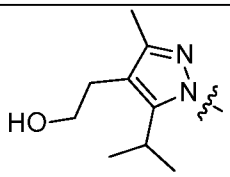
1I. Preparation of (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(4-(2-hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide

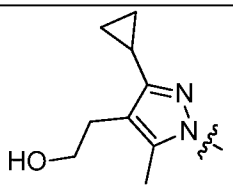
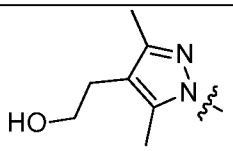
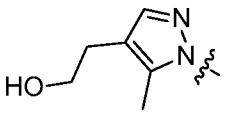
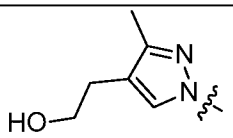
[0147] A mixture of 2-(3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)ethanol (110 mg, 0.65 mmol, 1 eq), (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-bromoacetamido)-*N*-methyl-3-phenylpropanamide (410 mg, 0.98 mmol, 1.5 eq) and K_2CO_3 (269 mg, 1.95 mmol, 3 eq) in DMF (10 mL) was stirred at 80 °C for 12h. TLC (petroleum ether: ethyl acetate = 10:1) showed the material was consumed completely. The reaction mixture was poured into ice water and extracted with EtOAc (2x30 mL). The combined organic extracts were washed with brine (3x10 mL), dried over Na_2SO_4 and concentrated in *vacuum* to give crude product, which was purified by prep-HPLC to give the final product (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(4-(2-hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide (36.7 mg, yield: 11%); LC/MS: m/z (M^++1) = 507, HPLC retention time = 2.61 min (HPLC condition: see below); ^{1}H NMR (400 MHz, MeOD) δ 7.28 – 7.21 (m, 4H), 6.94 (dd, *J* = 6.6, 2.9 Hz, 2H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.10 (d, *J* = 8.3 Hz, 1H), 6.02 (s, 2H), 4.73 (dd, *J* = 13.8, 6.8 Hz, 1H), 4.64 (t, *J* = 13.8 Hz, 2H), 3.76 (dd, *J* = 10.8, 5.9 Hz, 2H), 3.07 (d, *J* = 17.2 Hz, 3H), 3.03 (d, *J* = 6.9 Hz, 1H), 2.80 (dd, *J* = 13.3, 7.8 Hz, 1H), 2.67 (dd, *J* = 12.7, 6.7 Hz, 3H), 2.14 (s, 3H), 1.34 (dd, *J* = 13.0, 6.9 Hz, 6H).

[0148] Compounds **2-10** were prepared using a similar process as the Example **1** utilizing the corresponding pyrazoles.

EXAMPLES 2 TO 10



Ex. No.	R	Name	[M+H]	HPLC Rt (min)*
2		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(4-(2-hydroxyethyl)-5-isobutyl-3-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide	521	3.37
3		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(4-(2-hydroxyethyl)-3-isobutyl-5-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide	521	2.71
4		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(3-ethyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide	493	2.47
5		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(5-ethyl-4-(2-hydroxyethyl)-3-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide	493	2.48
6		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(4-(2-hydroxyethyl)-5-isopropyl-3-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide	507	2.62

7		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide	505	2.49
8		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(4-(2-hydroxyethyl)-3,5-dimethyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide	479	2.36
9		(S)-N-(benzo[d][1,3]dioxol-5-yl)-2-(2-(4-(2-hydroxyethyl)-5-methyl-1H-pyrazol-1-yl)acetamido)-N-methyl-3-phenylpropanamide	465	2.85
10		(S)-N-(benzo[d][1,3]dioxol-5-yl)-2-(2-(4-(2-hydroxyethyl)-3-methyl-1H-pyrazol-1-yl)acetamido)-N-methyl-3-phenylpropanamide	465	2.85

***HPLC condition:** Chromolith SpeedROD, RP-18e, 50x4.6mm; 40 °C; Solvent A: 0.05% FA in 10% MeCN/H_2O; Solvent B: 0.05% FA in 90% MeCN/H_2O; flow rate: 3 mL/min; run time: 0.8 min@10% B, 2.7 min gradient (10–95% B), then 0.8 min @95%B; wavelength: 254/220 nm.

Example 2: ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 9.8, 6.8 Hz, 4H), 6.96 (dd, *J* = 6.4, 3.0 Hz, 2H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.13 (d, *J* = 8.1 Hz, 1H), 6.02 (s, 2H), 4.82 – 4.69 (m, 1H), 4.70 – 4.56 (m, 2H), 3.73 (dq, *J* = 10.8, 4.8 Hz, 2H), 3.09 (s, 3H), 2.81 (dd, *J* = 13.2, 7.9 Hz, 1H), 2.75 – 2.68 (m, 1H), 2.63 (t, *J* = 5.8 Hz, 2H), 2.39 (ddd, *J* = 22.0, 14.8, 7.1 Hz, 2H), 2.28 (s, 3H), 1.76 (d, *J* = 6.9 Hz, 1H), 0.91 (dd, *J* = 10.6, 6.6 Hz, 6H).

Example 3: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 11.0, 8.5 Hz, 4H), 6.93 (dd, *J* = 6.5, 2.8 Hz, 2H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.02 (s, 2H), 5.99 (d, *J* = 8.6 Hz, 1H), 4.75 (dd, *J* = 14.2, 7.1 Hz, 1H), 4.65 (t, *J* = 13.4 Hz, 2H), 3.80 – 3.67 (m, 2H), 3.09 (s, 3H), 2.80 (dd, *J* = 13.2, 7.9 Hz, 1H), 2.66 (dt, *J* = 11.9, 6.2 Hz, 3H), 2.48 (dd, *J* = 14.5, 7.4 Hz, 2H), 2.15 (d, *J* = 8.7 Hz, 3H), 2.03 (d, *J* = 6.7 Hz, 1H), 0.98 (t, *J* = 10.5 Hz, 6H).

Example 4: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 11.8, 9.1 Hz, 4H), 6.93 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.11 (d, *J* = 8.4 Hz, 1H), 6.02 (s, 2H), 4.76 (dd, *J* = 14.7, 7.7 Hz, 1H), 4.72 – 4.56 (m, 2H), 3.81 – 3.66 (m, 2H), 3.10 (d, *J* = 5.5 Hz, 3H), 2.82 (dd, *J* = 13.2, 7.7 Hz, 1H), 2.73 – 2.58 (m, 5H), 2.12 (s, 3H), 1.29 (t, *J* = 7.6 Hz, 3H).

Example 5: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 10.8, 8.0 Hz, 4H), 6.94 (dd, *J* = 6.5, 3.0 Hz, 2H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.20 (d, *J* = 7.5 Hz, 1H), 6.02 (s, 2H), 4.76 (dd, *J* = 14.8, 7.9 Hz, 1H), 4.72 – 4.57 (m, 2H), 3.74 (td, *J* = 6.2, 2.1 Hz, 2H), 3.22 – 3.01 (m, 3H), 2.95 – 2.80 (m, 1H), 2.70 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.63 (t, *J* = 6.1 Hz, 2H), 2.54 (dt, *J* = 17.0, 7.5 Hz, 2H), 2.27 (s, 3H), 1.09 (t, *J* = 7.6 Hz, 3H).

Example 6: ^{1}H NMR (400 MHz, MeOD) δ 7.28 – 7.22 (m, 4H), 6.97 (d, *J* = 3.8 Hz, 2H), 6.69 (s, 1H), 6.06 (d, *J* = 8.5 Hz, 1H), 6.02 (s, 2H), 4.82 – 4.62 (m, 3H), 3.77 (t, *J* = 5.5 Hz, 2H), 3.12 (dd, *J* = 16.9, 8.7 Hz, 1H), 3.07 (s, 3H), 2.81 (dd, *J* = 13.2, 8.6 Hz, 1H), 2.71 (dd, *J* = 8.3, 5.2 Hz, 3H), 2.28 (s, 3H), 1.26 (dd, *J* = 7.2, 3.5 Hz, 6H).

Example 7: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 10.5, 7.4 Hz, 4H), 6.93 (dd, *J* = 6.0, 3.1 Hz, 2H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.14 (d, *J* = 8.4 Hz, 1H), 6.03 (s, 2H), 4.76 (dt, *J* = 14.9, 5.3 Hz, 1H), 4.67 – 4.43 (m, 2H), 3.81 (t, *J* = 6.0 Hz, 2H), 3.11 (s, 3H), 2.74 (tdd, *J* = 19.8, 13.3, 7.1 Hz, 4H), 2.11 (s, 3H), 1.87 – 1.79 (m, 1H), 0.96 – 0.87 (m, 4H).

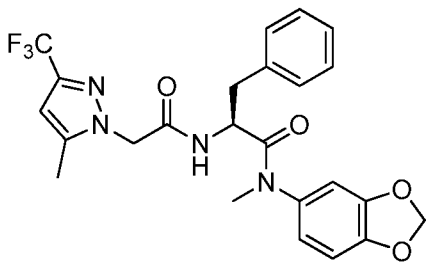
Example 8: ^{1}H NMR (400 MHz, DMSO) δ 8.41 (d, *J* = 7.8 Hz, 1H), 7.30 – 7.14 (m, 3H), 6.92 (t, *J* = 7.9 Hz, 3H), 6.69 (d, *J* = 24.1 Hz, 2H), 6.08 (s, 2H), 4.58 – 4.45 (m, 3H), 3.39 (s, 2H), 3.09 (s, 3H), 2.90 (dd, *J* = 13.4, 5.2 Hz, 1H), 2.66 (dd, *J* = 13.4, 9.0 Hz, 1H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.01 (s, 3H), 1.92 (s, 3H).

Example 9: ^{1}H NMR(400 MHz, DMSO) δ 8.47 (d, *J* = 7.7 Hz, 1H), 7.28 (s, 1H), 7.22 (q, *J* = 6.2 Hz, 3H), 6.92 (dt, *J* = 5.3, 1.8 Hz, 3H), 6.66 (s, 2H), 6.08 (d, *J* = 1.7 Hz, 2H), 4.68 – 4.51 (m, 3H), 4.50 – 4.37 (m, 1H), 3.52 – 3.40 (m, 2H), 3.08 (s, 3H), 2.90 (dd, *J* = 13.5, 5.3 Hz, 1H), 2.74 – 2.62 (m, 1H), 2.45 (t, *J* = 7.2 Hz, 2H), 1.94 (s, 3H).

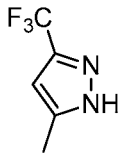
Example 10: ^{1}H NMR(400 MHz, DMSO) δ 8.47 (d, *J* = 7.7 Hz, 1H), 7.28 (s, 1H), 7.22 (q, *J* = 6.2 Hz, 3H), 6.92 (dt, *J* = 5.3, 1.8 Hz, 3H), 6.66 (s, 2H), 6.08 (d, *J* = 1.7 Hz, 2H), 4.68 – 4.51 (m, 3H), 4.50 – 4.37 (m, 1H), 3.52 – 3.40 (m, 2H), 3.08 (s, 3H), 2.90 (dd, *J* = 13.5, 5.3 Hz, 1H), 2.74 – 2.62 (m, 1H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.04 (s, 3H).

EXAMPLE 11

(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-2-(2-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetamido)-3-phenylpropanamide



11A. Preparation of 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole



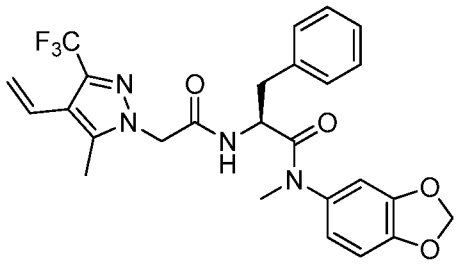
[0149] A mixture of methyl 1,1,1-trifluoropentane-2,4-dione (10 g, 65 mmol, 1 eq) in hydrazine hydrate (3.5 g, 65 mmol, 1 eq) and EtOH (30 mL) was stirred at reflux for 3 h. TLC (petroleum ether/EtOAc = 1:1) analysis showed the reaction was completed. The reaction was concentrated in *vacuum* to give 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (6.0 g, yield: 61%); LC/MS: m/z (M^++1) = 151.

11B. Preparation of (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-2-(2-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetamido)-3-phenylpropanamide

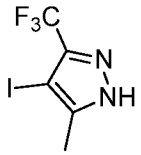
[0150] The procedure was similar to **11I** utilizing the 5-methyl-3-(trifluoromethyl)-1*H*-pyrazoleas as starting materials to give the product; LC/MS: m/z M^++1 = 489; HPLC retention time = 3.00 min; ^{1}H NMR (400 MHz, DMSO) δ 8.76 (d, *J* = 7.9 Hz, 1H), 7.27 – 7.14 (m, 3H), 6.96 – 6.86 (m, 3H), 6.70 (s, 1H), 6.64 (s, 1H), 6.45 (s, 1H), 6.07 (s, 2H), 4.81 (dd, *J* = 34.5, 16.7 Hz, 2H), 4.50 (dd, *J* = 13.5, 8.5 Hz, 1H), 3.09 (d, *J* = 5.0 Hz, 3H), 2.94 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.69 (dd, *J* = 13.5, 9.1 Hz, 1H), 2.08 (s, 3H).

EXAMPLE 12

(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-2-(2-(5-methyl-3-(trifluoromethyl)-4-vinyl-1*H*-pyrazol-1-yl)acetamido)-3-phenylpropanamide



12A. Preparation of 4-iodo-5-methyl-3-(trifluoromethyl)-1*H*-pyrazole



[0151] To a solution of 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (6.0 g, 30 mmol, 1 eq) in CH_3CN (60 mL), were added I_2 (7.6 g, 30 mmol, 1 eq) and CAN (8.22 g, 15 mmol, 0.5 eq) in one portion. Then the mixture was stirred at room temperature overnight. TLC indicated the reaction was completed. The reaction mixture was poured into ice water and extracted

with EtOAc (2x100 mL). The combined organic layers were washed with brine (3x40 mL), aq.Na_2SO_3 (2x30 mL), dried over Na_2SO_4 and concentrated in *vacuum* to give crude product, which was purified by column chromatography on silica gel to give4-iodo-5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (5.0 g, yield: 60.6%); LC/MS: m/z (M^++1) = 277.

12B. Preparation of 5-methyl-3-(trifluoromethyl)-4-vinyl-1*H*-pyrazole



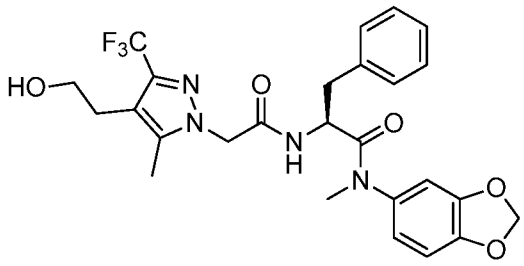
[0152] A mixture of 4-iodo-3-methyl-5-(trifluoromethyl)-4H-pyrazole (3.0 g, 10 mmol, 1 eq), tributyl(vinyl)stannane (12.68 g, 40 mmol, 4 eq) and $Pd(PPh_3)_4$ (200 mg) in DMF (30 mL) was stirred at reflux for overnight under N_2 atmosphere. TLC (Petroleum ether:EtOAc = 1:1) indicated the reaction was completed. The reaction mixture was poured into ice water and extracted with EtOAc (2x100mL). The combined organic extracts were washed with brine (3x30mL), dried over Na_2SO_4 and concentrated in *vacuum* to give crude product, which was purified by column chromatography on silica gel to give 5-methyl-3-(trifluoromethyl)-4-vinyl-1*H*-pyrazole (1.4 g, yield: 70%); LC/MS: m/z (M^++1) = 177.

12C. Preparation of (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-2-(2-(5-methyl-3-(trifluoromethyl)-4-vinyl-1*H*-pyrazol-1-yl)acetamido)-3-phenylpropanamide

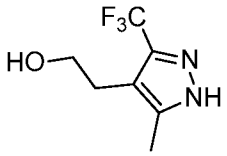
[0153] The procedure was similar to **1I** utilizing the 5-methyl-3-(trifluoromethyl)-4-vinyl-1*H*-pyrazole as starting material to give the titled product, LC/MS: m/z (M^++1) = 515; HPLC retention time = 3.20 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 3H), 6.88 (dd, *J* = 6.6, 2.9 Hz, 2H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.59 (dd, *J* = 18.0, 11.5 Hz, 1H), 6.38 (d, *J* = 7.9 Hz, 1H), 6.04 (s, 2H), 5.47 – 5.35 (m, 2H), 4.81 (d, *J* = 7.6 Hz, 1H), 4.73 (d, *J* = 7.5 Hz, 2H), 3.19 (s, 3H), 2.92 (dd, *J* = 13.4, 6.8 Hz, 1H), 2.71 (dd, *J* = 13.4, 7.5 Hz, 1H), 2.21 (s, 3H).

EXAMPLE 13

(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(4-(2-hydroxyethyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide



13A. Preparation of 2-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)ethanol



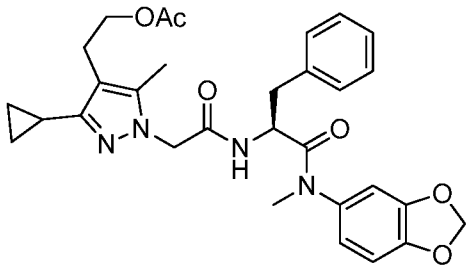
[0154] To a solution of 5-methyl-3-(trifluoromethyl)-4-vinyl-1*H*-pyrazole (0.30 g, 1.7 mmol, 1 eq) in THF (20 mL), was added 1 M BH_3/THF (5.1 mL, 5.1 mmol, 3 eq) under N_2 atmosphere. After addition, the mixture was stirred at room temperature for 5 hours. TLC (Petroleum ether:EtOAc = 1:1) indicated that the reaction was completed. The mixture was concentrated in *vacuum* to give the residue, which was dissolved in H_2O_2 (10 mL) and concentrated aqueous NaOH (2 mL, 40%) stirred at room temperature for 5 hours, TLC (Petroleum ether:EtOAc = 1:1) indicated the reaction was completed. The reaction mixture was extracted with EtOAc (3x50 mL). The combined organic extracts were washed with 6M Na_2SO_3 (2x10 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography to give 2-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)ethanol (80 mg, yield: 24%); LC/MS: m/z (M^++1) = 195.

13B. Preparation of (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(4-(2-hydroxyethyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide

[0155] The procedure was similar to **11** utilizing the 2-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)ethanol as starting materials to give the product, LC/MS: m/z (M^++1) = 533, HPLC retention time = 3.22 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 4H), 6.91 (dd, *J* = 6.3, 3.1 Hz, 2H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.03 (d, *J* = 8.6 Hz, 2H), 5.93 (d, *J* = 8.7 Hz, 1H), 4.83 (t, *J* = 11.6 Hz, 1H), 4.80 – 4.67 (m, 2H), 3.79 (s, 2H), 3.11 (d, *J* = 23.9 Hz, 3H), 2.85 (dd, *J* = 13.4, 7.2 Hz, 1H), 2.76 (dd, *J* = 11.7, 6.1 Hz, 2H), 2.71 – 2.65 (m, 1H), 2.25 – 2.15 (m, 3H).

EXAMPLE 14

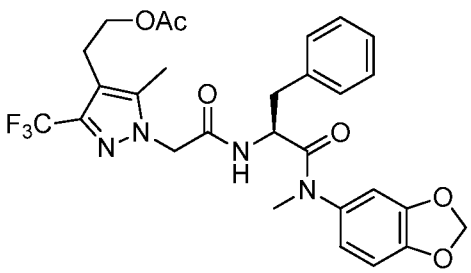
(*S*)-2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-cyclopropyl-5-methyl-1*H*-pyrazol-4-yl)ethyl acetate



[0156] A mixture of (*S*)-*N*-(benzo[d][1,3]dioxol-5-yl)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1H-pyrazol-1-yl)acetamido)-N-methyl-3-phenylpropanamide (25 mg, 0.05 mmol, 1.0 eq) and acetic anhydride (10 mg, 0.1 mmol, 2.0 eq) in pyridine (1 ml) was stirred at r.t overnight. The resulting mixture was washed with water and extracted with EA, the organic extract was evaporated to give the crude product which was purified by column chromatography on silica gel (PE:EA=3:1) to give (*S*)-2-(1-(2-((1-(benzo[d][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-cyclopropyl-5-methyl-1*H*-pyrazol-4-yl)ethyl acetate (16 mg, yield: 60%); LC/MS: m/z (M^++1) = 547; HPLC retention time = 2.91 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.18 (m, 4H), 6.91 (dd, *J* = 6.4, 2.9 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 2H), 4.75 (dd, *J* = 15.6, 6.5 Hz, 1H), 4.56 (q, *J* = 17.1 Hz, 2H), 4.15 (q, *J* = 7.6 Hz, 2H), 3.14 (s, 3H), 2.83 (dq, *J* = 30.3, 7.6 Hz, 3H), 2.69 (td, *J* = 13.2, 6.8 Hz, 1H), 2.08 (s, 3H), 1.81 (dt, *J* = 10.7, 6.9 Hz, 1H), 0.93 (dd, *J* = 8.9, 5.6 Hz, 4H).

EXAMPLE 15

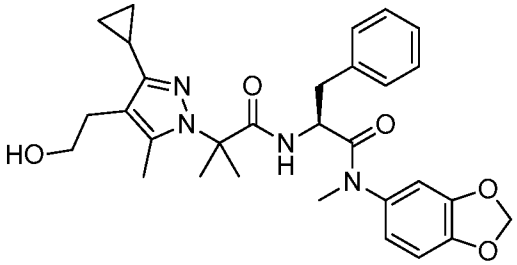
(*S*)-2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)ethyl acetate



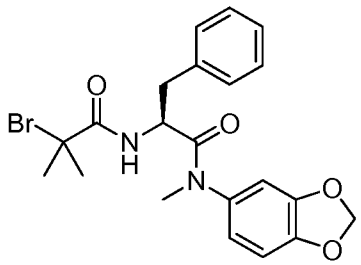
[0157] The procedure of synthesis of (S)-2-(1-(2-((1-(benzo[d][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-5-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)ethyl acetate is similar to **Example 14**; LC/MS: m/z (M^++1) = 575; HPLC retention time = 3.00 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 12.5, 10.2 Hz, 4H), 6.90 (dd, *J* = 6.3, 2.8 Hz, 2H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.52 (d, *J* = 7.9 Hz, 1H), 6.03 (s, J = 8.3 Hz, 2H), 4.89 – 4.76 (m, 1H), 4.71 (d, *J* = 16.7 Hz, 2H), 4.14 (t, *J* = 6.8 Hz, 2H), 3.18 (s, 3H), 2.92 (dd, *J* = 13.4, 7.0 Hz, 1H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.72 (dd, *J* = 13.4, 7.4 Hz, 2H), 2.17 (s, 3H), 2.06 (s, 3H).

EXAMPLE 16

(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)-2-methylpropanamido)-*N*-methyl-3-phenylpropanamide



16A. Preparation of (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-bromo-2-methylpropanamido)-*N*-methyl-3-phenylpropanamide



[0158] 2-bromo-2-methylpropanoyl bromide (1.5 g, 6.68 mmol, 2.0 eq) was added dropwise to the mixture of (*S*)-2-amino-N-(benzo[d][1,3]dioxol-5-yl)-N-methyl-3-phenylpropanamide (1.0 g, 3.34 mmol, 1.0 eq) and DIPEA (1.30 g, 10.02 mmol, 3.0 eq) in anhydrous DCM (10 mL). The mixture was stirred at RT overnight. Then water was added to quench the reaction, the mixture was extracted with DCM (2x100 mL). The combined organic extracts were washed with diluted HCl, water and brine, dried over anhydrous Na_2SO_4, purified by column chromatography to give (*S*)-N-(benzo[d][1,3]dioxol-5-yl)-2-(2-

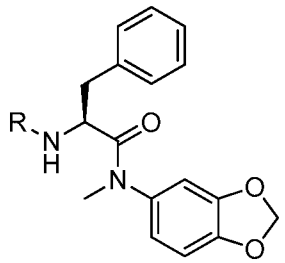
bromo-2-methylpropanamido)-N-methyl-3-phenylpropanamide (1.2 g, yield: 80.4%); LC/MS: m/z (M^++1) = 447.

16B. Preparation of (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)-2-methylpropanamido)-*N*-methyl-3-phenylpropanamide

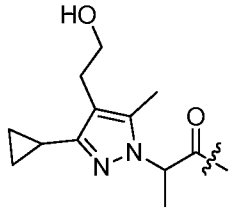
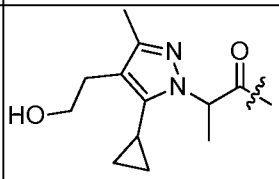
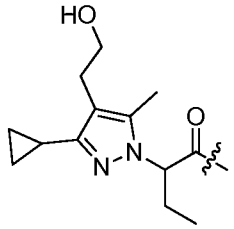
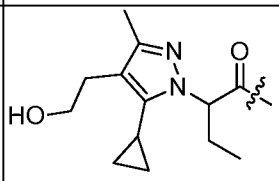
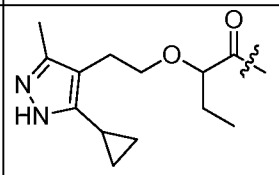
[0159] (*S*)-N-(benzo[d][1,3]dioxol-5-yl)-2-(2-bromo-2-methylpropanamido)-N-methyl-3-phenylpropanamide (100 mg, 0.22 mmol, 1.0 eq) was added dropwise to the suspension of sodium hydride (44 mg, 1.10 mmol, 5.0 eq, 60%) in anhydrous DMF (5 mL). The mixture was stirred at RT for 30 min until TLC indicated the reaction was completed. Ice water was added to quench the reaction, the mixture was extracted with EtOAc (2x10 mL) and the combined organic extracts were washed with aq. LiCl (10%) solution, water and brine, dried over anhydrous Na_2SO_4, purified by prepare TLC (PE:EA = 2:1) to give (*S*)-N-(benzo[d][1,3]dioxol-5-yl)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1H-pyrazol-1-yl)-2-methylpropanamido)-N-methyl-3-phenylpropanamide (15 mg, yield: 12.8%); LC/MS: m/z (M^++1) = 533; HPLC retention time = 2.85 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 13.5, 10.4 Hz, 4H), 6.93 – 6.85 (m, 2H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.34 (s, 1H), 6.03 (s, 2H), 5.55 (d, *J* = 8.7 Hz, 1H), 4.75 (q, *J* = 7.5 Hz, 1H), 3.82 (t, *J* = 5.8 Hz, 2H), 3.12 (s, 3H), 2.79 (dd, *J* = 13.2, 7.1 Hz, 1H), 2.75 – 2.63 (m, 2H), 2.60 (dd, *J* = 13.3, 7.4 Hz, 1H), 2.07 (d, *J* = 6.0 Hz, 3H), 1.85 – 1.75 (m, 1H), 1.70 (d, *J* = 7.1 Hz, 6H), 0.92 – 0.85 (m, 4H).

[0160] Compounds **17**–**21** were prepared using a similar process as the Example **16** utilizing the corresponding acids.

EXAMPLES 17 TO 21



Ex. No.	R	Name	[M+H]	HPLC Rt (min)

17		(2S)-N-(benzo[d][1,3]dioxol-5-yl)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1H-pyrazol-1-yl)propanamido)-N-methyl-3-phenylpropanamide	519	2.36
18		(2S)-N-(benzo[d][1,3]dioxol-5-yl)-2-(2-(5-cyclopropyl-4-(2-hydroxyethyl)-3-methyl-1H-pyrazol-1-yl)propanamido)-N-methyl-3-phenylpropanamide	519	2.36
19		N-((S)-1-(benzo[d][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-yl)-2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1H-pyrazol-1-yl)butanamide	533	3.02
20		N-((S)-1-(benzo[d][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-yl)-2-(5-cyclopropyl-4-(2-hydroxyethyl)-3-methyl-1H-pyrazol-1-yl)butanamide	533	2.92
21		N-((S)-1-(benzo[d][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-yl)-2-(2-(3-cyclopropyl-5-methyl-1H-pyrazol-4-yl)ethoxy)butanamide	533	2.82

Example 17: ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.23 (ddd, *J* = 10.7, 7.1, 2.7 Hz, 4H), 6.91 (ddd, *J* = 9.3, 7.6, 3.3 Hz, 2H), 6.72 (t, *J* = 9.6 Hz, 1H), 6.35 (d, *J* = 8.6 Hz, 1H), 6.03 (s, 2H), 4.73 – 4.62 (m, 2H), 3.92 – 3.74 (m, 2H), 3.21 – 3.05 (m, 3H), 2.85 – 2.78 (m, 1H), 2.73 (ddd, *J* = 14.6, 9.1, 3.8 Hz, 2H), 2.67 – 2.59 (m, 1H), 2.11 (d, *J* = 32.4 Hz, 3H), 1.89 – 1.79 (m, 1H), 1.67 (d, *J* = 7.2 Hz, 4H), 1.08 – 0.98 (m, 1H), 0.97 – 0.84 (m, 3H).

Example 18: ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.28 – 7.27 (m, 1H), 7.22 – 7.16 (m, 3H), 6.85 (dd, J = 7.3, 2.0 Hz, 2H), 6.72 (dd, *J* = 14.1, 8.0 Hz, 2H), 6.03 (s, 2H), 4.71 – 4.63 (m, 2H), 3.78 (tt, *J* = 10.6, 5.3 Hz, 2H), 3.15 (s, 3H), 2.81 (dd, *J* = 13.3, 7.5 Hz, 1H), 2.74 (td, *J* = 6.3, 3.3 Hz, 2H), 2.63 (dd, *J* = 13.2, 6.7 Hz, 1H), 2.07 (s, 3H), 1.84 – 1.80 (m, 1H), 1.74 (d, *J* = 7.3 Hz, 3H), 1.05 – 0.96 (m, 1H), 0.93 – 0.86 (m, 3H).

Example 19: ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 5.1, 1.8 Hz, 4H), 6.99 (dd, *J* = 7.0, 2.4 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.02 (s, 2H), 4.69 (dd, *J* = 15.8, 7.4 Hz, 1H), 4.41 (dd, *J* = 10.0, 4.9 Hz, 1H), 3.88 – 3.78 (m, 2H), 3.08 (s, 3H), 2.84 (dt,

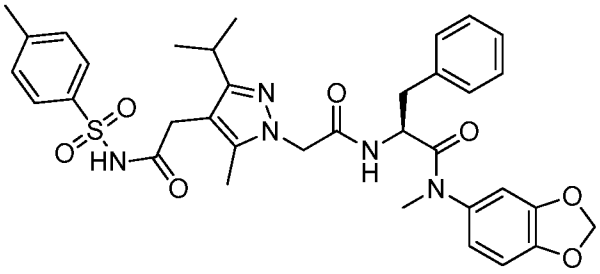
J = 13.1, 6.6 Hz, 1H), 2.74 (qd, J = 9.2, 3.0 Hz, 2H), 2.66 (dd, *J* = 12.6, 6.5 Hz, 1H), 2.19 – 2.12 (m, 4H), 2.10 – 1.95 (m, 2H), 1.85 (tt, *J* = 7.7, 5.2 Hz, 1H), 1.03 (dt, *J* = 14.2, 5.8 Hz, 1H), 0.97 – 0.87 (m, 3H), 0.83 (t, *J* = 7.3 Hz, 3H).

Example 20: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 6.5 Hz, 1H), 7.20 (t, *J* = 5.9 Hz, 4H), 6.91 – 6.82 (m, 2H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 2H), 4.65 (dd, J = 14.5, 7.5 Hz, 1H), 4.40 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.75 (dd, *J* = 13.5, 6.6 Hz, 3H), 3.16 (s, 3H), 2.83 (dd, *J* = 13.2, 7.6 Hz, 1H), 2.75 (t, *J* = 6.5 Hz, 2H), 2.63 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.27 – 2.15 (m, 2H), 2.08 (d, *J* = 5.5 Hz, 3H), 1.82 (td, *J* = 8.1, 4.2 Hz, 1H), 1.03 – 0.98 (m, 1H), 0.90 (ddd, *J* = 13.2, 8.3, 4.6 Hz, 3H), 0.83 (d, *J* = 7.3 Hz, 3H).

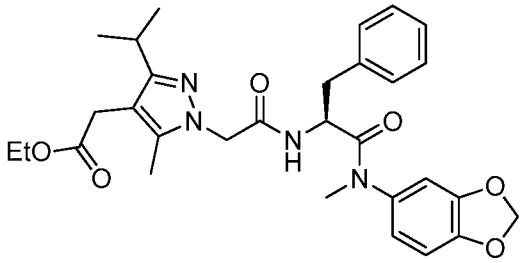
Example 21: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 5.0, 1.7 Hz, 4H), 7.00 – 6.90 (m, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.20 (d, *J* = 9.1 Hz, 1H), 6.02 (s, 2H), 4.91 (dd, *J* = 10.6, 4.7 Hz, 1H), 4.70 (dd, *J* = 15.7, 7.4 Hz, 1H), 3.81 (t, *J* = 5.1 Hz, 2H), 3.07 (s, 3H), 2.85 – 2.77 (m, 2H), 2.70 – 2.59 (m, 2H), 2.36 – 2.25 (m, 4H), 2.21 – 2.11 (m, 1H), 1.03 – 0.99 (m, 2H), 0.96 – 0.89 (m, 3H), 0.73 (d, *J* = 5.6 Hz, 1H), 0.65 (d, *J* = 5.6 Hz, 1H).

EXAMPLE 22

(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(3-isopropyl-5-methyl-4-(2-(4-methylphenylsulfonamido)-2-oxoethyl)-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide

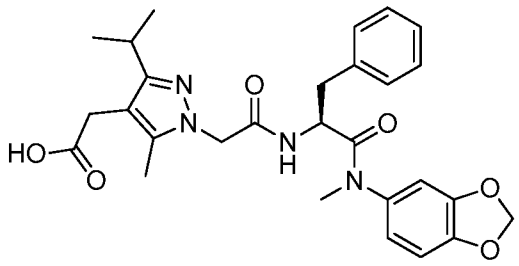


22A. Preparation of (*S*)-ethyl 2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetate



[0161] The procedure was similar to **1I** utilizing the ethyl 2-(3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetate as starting materials to give the product; LC/MS: m/z M^++1 = 549; HPLC retention time = 3.00 min.

22B. Preparation of (*S*)-2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetic acid



[0162] To a solution of (*S*)-ethyl 2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetate (200 mg, 0.36 mmol, 1.0 eq) in methanol (5 mL), was added dropwise aqueous solution of sodium hydroxide (1.0 mL, 1.0 mmol, 1M, 2.7 eq). The mixture was stirred at R.T. for 30 min until TLC (PE:EA = 1:1) indicated the SM was disappeared. Water (10 mL) was added and the mixture was extracted with EtOAc (2x5 mL). The organic extracts were evaporated to give the residue which was purified by prep-HPLC to give (*S*)-2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetic acid (150 mg,0.29 mmol, 79%); LC/MS: m/z (M^++1) = 521; HPLC retention time = 2.58 min.

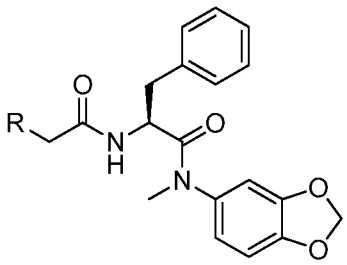
22C. Preparation of (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-2-(2-(5-methyl-3-(trifluoromethyl)-4-vinyl-1*H*-pyrazol-1-yl)acetamido)-3-phenylpropanamide

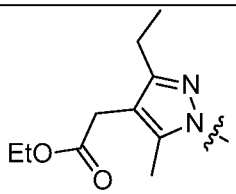
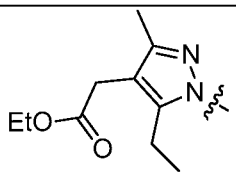
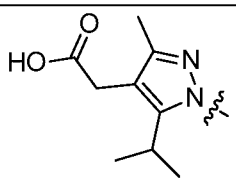
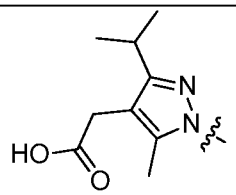
[0163] (*S*)-2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetic acid (80 mg, 0.15 mmol, 1.0 eq), EDCI (57 mg, 0.30 mmol, 2.0 eq), DMAP (8 mg) and 4-methylbenzenesulfonamide (31 mg, 0.18 mmol, 1.2 eq) were dissolved in DMF (3mL). The mixture was stirred at r.t overnight under N_2 atmosphere. The resulting solution was washed with water (2x3 mL), dried and concentrated, and the residue was purified by prep-HPLC to give (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(3-isopropyl-5-methyl-4-(2-(4-methylphenylsulfonamido)-2-oxoethyl)-1*H*-pyrazol-1-yl)acetamido)-N-methyl-3-phenylpropanamide (20 mg, yield: 23%); LC/MS: m/z (M^++1) = 674; HPLC retention time =

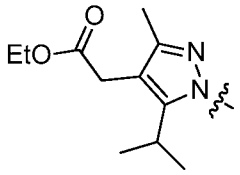
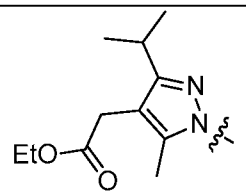
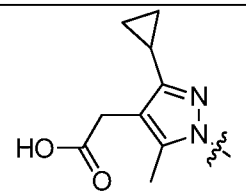
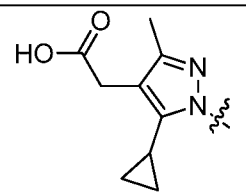
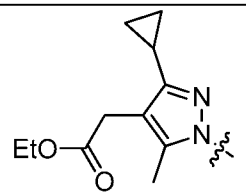
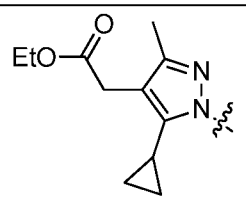
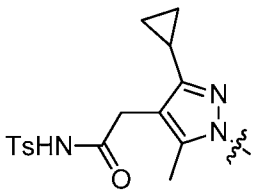
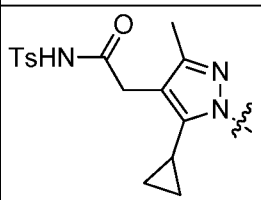
2.92 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 2H), 7.69 (s, 1H), 7.31 (d, *J* = 7.7 Hz, 2H), 7.26 (d, *J* = 22.0 Hz, 4H), 6.99 (s, 2H), 6.73 (d, *J* = 7.4 Hz, 1H), 6.41 (s, 1H), 6.01 (d, *J* = 2.0 Hz, 2H), 5.12 (s, 1H), 4.81 (d, *J* = 49.8 Hz, 2H), 3.53 (s, 2H), 3.17 (s, 3H), 2.99 (s, 1H), 2.93 – 2.67 (m, 2H), 2.43 (s, 3H), 2.09(s, 3H), 1.35 – 1.08 (m, *J* = 18.4, 10.3 Hz, 6H).

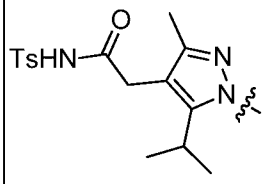
[0164] Compounds **23-35** were prepared using a similar process to Example **22** utilizing the corresponding acids and amines.

EXAMPLES 23 TO 35



Ex. No.	R	Name	[M+H]	HPLC Rt (min)
23		(*S*)-ethyl 2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropa*N*-2-yl)amino)-2-oxoethyl)-3-ethyl-5-methyl-1*H*-pyrazol-4-yl)acetate	535	2.83
24		(*S*)-ethyl 2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropa*N*-2-yl)amino)-2-oxoethyl)-5-ethyl-3-methyl-1*H*-pyrazol-4-yl)acetate	535	2.83
25		(*S*)-2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropa*N*-2-yl)amino)-2-oxoethyl)-5-isopropyl-3-methyl-1*H*-pyrazol-4-yl)acetic acid	521	2.55
26		(*S*)-2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropa*N*-2-yl)amino)-2-oxoethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetic acid	521	2.58

27		(*S*)-ethyl 2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropa*N*-2-yl)amino)-2-oxoethyl)-5-isopropyl-3-methyl-1*H*-pyrazol-4-yl)acetate	549	3.00
28		(*S*)-ethyl 2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropa*N*-2-yl)amino)-2-oxoethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetate	549	3.03
29		(*S*)-2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropa*N*-2-yl)amino)-2-oxoethyl)-3-cyclopropyl-5-methyl-1*H*-pyrazol-4-yl)acetic acid	519	2.48
30		(*S*)-2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropa*N*-2-yl)amino)-2-oxoethyl)-5-cyclopropyl-3-methyl-1*H*-pyrazol-4-yl)acetic acid	519	2.48
31		(*S*)-ethyl2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropa*N*-2-yl)amino)-2-oxoethyl)-3-cyclopropyl-5-methyl-1*H*-pyrazol-4-yl)acetate	547	2.92
32		(*S*)-ethyl 2-(1-(2-((1-(benzo[*d*][1,3]dioxol-5-yl(methyl)amino)-1-oxo-3-phenylpropa*N*-2-yl)amino)-2-oxoethyl)-5-cyclopropyl-3-methyl-1*H*-pyrazol-4-yl)acetate	547	2.92
33		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(3-cyclopropyl-5-methyl-4-(2-(4-methylphenylsulfonamido)-2-oxoethyl)-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide	672	2.91
34		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(5-cyclopropyl-3-methyl-4-(2-(4-methylphenylsulfonamido)-2-oxoethyl)-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-	672	2.91

		phenylpropanamide		
35		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(5-isopropyl-3-methyl-4-(2-(4-methylphenylsulfonamido)-2-oxoethyl)-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenylpropanamide	674	2.92

Example 23: ^{1}H NMR (400 MHz, DMSO) δ 7.27 – 7.15 (m, *J* = 4.9 Hz, 4H), 6.96 – 6.88 (m, 2H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 6.09 – 5.98 (m, 3H), 4.76 (dd, *J* = 16.4, 9.3 Hz, 1H), 4.68 – 4.54 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.38 (d, *J* = 4.4 Hz, 2H), 3.14 (d, *J* = 4.1 Hz, 3H), 2.88 (dd, *J* = 12.9, 7.6 Hz, 1H), 2.67 (ddd, *J* = 22.8, 14.2, 7.0 Hz, 3H), 2.12 (s,3H), 1.28 (dd, *J* = 7.8, 6.2 Hz, 6H).

Example 24: ^{1}H NMR (400 MHz, DMSO) δ 7.27 – 7.15 (m, *J* = 4.9 Hz, 4H), 6.96 – 6.88 (m, 2H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 6.09 – 5.98 (m, 3H), 4.76 (dd, *J* = 16.4, 9.3 Hz, 1H), 4.68 – 4.54 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.38 (d, *J* = 4.4 Hz, 2H), 3.14 (d, *J* = 4.1 Hz, 3H), 2.88 (dd, *J* = 12.9, 7.6 Hz, 1H), 2.67 (ddd, *J* = 22.8, 14.2, 7.0 Hz, 3H), 2.27(s,3H), 1.28 (dd, *J* = 7.8, 6.2 Hz, 6H).

Example 25: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 4H), 6.97 – 6.88 (m, 2H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 6.02 (s, 2H), 4.75 (d, *J* = 7.5 Hz, 1H), 4.69 (d, *J* = 1.8 Hz, 2H), 3.52 (s, 2H), 3.11 (s, 3H), 3.03 – 2.97 (m, 1H), 2.86 (dd, *J* = 13.1, 8.0 Hz, 1H), 2.70 (dd, *J* = 13.2, 6.7 Hz, 1H), 2.25 (s, 3H), 1.25 (dd, *J* = 7.1, 2.3 Hz, 6H).

Example 26: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.26 – 7.16 (m, 3H), 6.91 (dd, *J* = 6.4, 2.8 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.02 (s, 2H), 4.75 (q, *J* = 7.4 Hz, 1H), 4.60 (q, *J* = 17.0 Hz, 2H), 3.45 (s, 2H), 3.13 (s, 3H), 3.01 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.87 (dd, *J* = 13.2, 7.6 Hz, 1H), 2.67 (dd, *J* = 13.2, 7.0 Hz, 1H), 2.10 (s, 3H), 1.31 (dd, *J* = 6.9, 3.5 Hz, 6H).

Example 27: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 4H), 6.94 (dd, *J* = 6.4, 3.3 Hz, 2H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.50 (d, *J* = 7.7 Hz, 1H), 6.02 (s, 2H), 4.72 (dd, *J* = 24.7, 7.4 Hz, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.47 (s, 2H), 3.13 (d, *J* = 10.6 Hz, 3H), 3.05 – 2.99 (m, 1H), 2.88 – 2.83 (m, 1H), 2.73 – 2.66 (m, 1H), 2.25 (s, 3H), 1.28 – 1.21 (m, 9H).

Example 28: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 2H), 7.08 – 6.88 (m, 3H), 6.76 (dd, *J* = 32.4, 8.1 Hz, 2H), 6.02 (s, 3H), 4.62 (q, *J* = 17.1 Hz, 2H), 4.26 – 4.09 (m, 2H), 4.00 – 3.86 (m, 1H), 3.41 (s, 2H), 3.17 – 3.11 (m, 3H), 3.01 – 2.97 (m, 1H), 2.89 – 2.82 (m, 1H), 2.67 (dd, *J* = 13.1, 6.8 Hz, 1H), 2.13 (s, 3H), 1.34 – 1.23 (m, 9H).

Example 29: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.28 (m, 1H), 7.26 – 7.20 (m, 3H), 6.95 – 6.87 (m, 2H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.03 (s, 2H), 4.83 – 4.67

(m, 2H), 4.56 (q, *J* = 17.1 Hz, 2H), 3.54 (s, 2H), 3.14 (s, 3H), 2.86 (dd, *J* = 13.3, 7.5 Hz, 1H), 2.67 (dd, *J* = 13.3, 6.9 Hz, 1H), 2.11 (s,3H), 0.91 (dd, *J* = 14.1, 6.3 Hz, 4H).

Example 30: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.28 (m, 1H), 7.26 – 7.20 (m, 3H), 6.95 – 6.87 (m, 2H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.03 (s, 2H), 4.83 – 4.67 (m, 2H), 4.56 (q, *J* = 17.1 Hz, 2H), 3.54 (s, 2H), 3.14 (s, 3H), 2.86 (dd, *J* = 13.3, 7.5 Hz, 1H), 2.67 (dd, *J* = 13.3, 6.9 Hz, 1H), 2.24 (s,3H), 0.91 (dd, *J* = 14.1, 6.3 Hz, 4H).

Example 31: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.28 (m, 1H), 7.26 – 7.20 (m, 3H), 6.91 (dd, *J* = 6.6, 3.0 Hz, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.03 (s, 2H), 4.84 – 4.70 (m, 2H), 4.56 (q, *J* = 17.0 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.48 (s, 2H), 3.14 (s, 3H), 2.87 (dd, *J* = 13.2, 7.6 Hz, 1H), 2.69 (td, *J* = 13.1, 6.9 Hz, 1H), 2.11 (s,3H), 1.28 (td, *J* = 7.1, 1.5 Hz, 3H), 0.92 (dd, *J* = 8.8, 5.2 Hz, 4H).

Example 32: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.28 (m, 1H), 7.26 – 7.20 (m, 3H), 6.91 (dd, *J* = 6.6, 3.0 Hz, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.03 (s, 2H), 4.84 – 4.70 (m, 2H), 4.56 (q, *J* = 17.0 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.48 (s, 2H), 3.14 (s, 3H), 2.87 (dd, *J* = 13.2, 7.6 Hz, 1H), 2.69 (td, *J* = 13.1, 6.9 Hz, 1H), 2.23 (s,3H), 1.28 (td, *J* = 7.1, 1.5 Hz, 3H), 0.92 (dd, *J* = 8.8, 5.2 Hz, 4H).

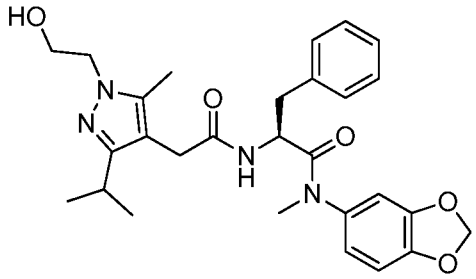
Example 33: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.25 (dd, *J* = 11.3, 8.3 Hz, 4H), 6.94 (dd, *J* = 6.3, 3.0 Hz, 2H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.02 (s, 2H), 4.79 (t, *J* = 7.7 Hz, 1H), 4.67 – 4.41 (m, 2H), 3.46 (s, 2H), 3.17 (s, 3H), 3.02 – 2.87 (m, 1H), 2.70 (dd, *J* = 13.4, 7.3 Hz, 1H), 2.44 (s, 3H), 2.01(s, 3H), 1.62 – 1.47 (m, 1H), 0.93 – 0.68 (m, 4H).

Example 34: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.25 (dd, *J* = 11.3, 8.3 Hz, 4H), 6.94 (dd, *J* = 6.3, 3.0 Hz, 2H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.02 (s, 2H), 4.79 (t, *J* = 7.7 Hz, 1H), 4.67 – 4.41 (m, 2H), 3.46 (s, 2H), 3.17 (s, 3H), 3.02 – 2.87 (m, 1H), 2.70 (dd, *J* = 13.4, 7.3 Hz, 1H), 2.44 (s, 3H), 2.03(s, 3H), 1.62 – 1.47 (m, 1H), 0.93 – 0.68 (m, 4H).

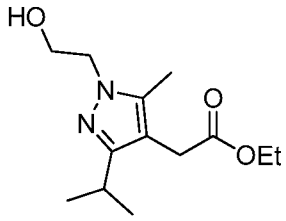
Example 35: ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 2H), 7.69 (s, 1H), 7.31 (d, *J* = 7.7 Hz, 2H), 7.26 (d, *J* = 22.0 Hz, 4H), 6.99 (s, 2H), 6.73 (d, *J* = 7.4 Hz, 1H), 6.41 (s, 1H), 6.01 (d, *J* = 2.0 Hz, 2H), 5.12 (s, 1H), 4.81 (d, *J* = 49.8 Hz, 2H), 3.53 (s, 2H), 3.17 (s, 3H), 2.99 (s, 1H), 2.93 – 2.67 (m, 2H), 2.43 (s, 3H), 2.19(s, 3H), 1.35 – 1.08 (m, *J* = 18.4, 10.3 Hz, 6H).

EXAMPLE 36

(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(1-(2-hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetamido)-*N*-methyl-3-phenylpropanamide

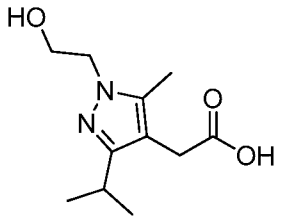


36A. Preparation of ethyl 2-(1-(2-hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetate



[0165] A mixture of ethyl 2-(3-isopropyl-5-methyl-4*H*-pyrazol-4-yl)acetate (200 mg, 0.95 mmol,1.0 eq) and K_2CO_3 (196 mg, 1.4 mmol, 1.5 eq) in 2-bromoethanol was stirred at 100 °C for 2 hours until LC-MS indicated the SM had disappeared, and the reaction mixture was evaporated to give the residue which was purified by prep-HPLC to give ethyl 2-(1-(2-hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetate (150 mg, yield: 62%); LC/MS: m/z (M^++1) = 255.

36B. Preparation of2-(1-(2-hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetic acid



[0166] A solution of ethyl 2-(1-(2-hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetate (150 mg, 0.6 mmol, 1.0 eq) and NaOH (48 mg, 1.2 mmol, 2.0 eq) in MeOH (5 mL) and H_2O (10 mL) was stirred at room temperature for 3 hours. TLC (petroleum ether/EtOAc = 1:1) showed the reaction was completed. The reaction mixture was concentrated to remove MeOH. The residue was acidified to pH 6–7 and extracted with EtOAc (2x20 mL) and THF (2x10 mL). The combined organic layers were washed with brine (10 mL), dried over

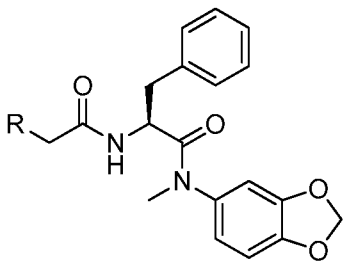
Na_2SO_4, and concentrated to give2-(1-(2-hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetic acid (100mg, yield: 75%); LC/MS: m/z (M^++1) = 227.

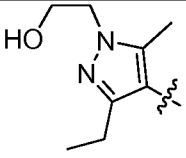
36C. Preparation of (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(1-(2-hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetamido)-*N*-methyl-3-phenylpropanamide

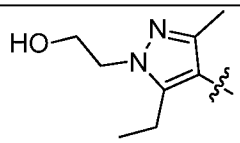
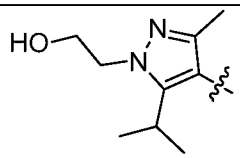
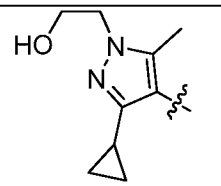
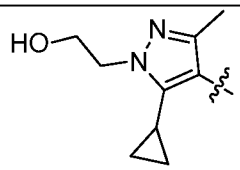
[0167] A mixture of 2-(1-(2-hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetic acid (100 mg, 0.44 mmol, 1.0 eq), (*S*)-2-amino-*N*-(benzo[*d*][1,3]dioxol-5-yl)-N-methyl-3-phenylpropanamide（157 mg, 0.53 mmol, 1.2 eq), EDCI（168 mg, 0.88 mmol, 2.0 eq), HOBt (119 mg, 0.88 mmol, 2.0 eq) and DIPEA (0.29 ml, 1.76 mmol, 4.0 eq) in DCM (3 mL), was stirred at r.t overnight under N_2 atmosphere. The resulting solution was washed with water 3 times, dried and concentrated, and the residue was purified by prep-HPLC to give the final product (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(1-(2-hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)acetamido)-*N*-methyl-3-phenylpropanamide (22 mg, yield: 11%); LC/MS: m/z (M^++1) = 507; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 4H), 6.93 (dd, *J* = 6.5, 2.8 Hz, 2H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.14 (d, *J* = 8.4 Hz, 1H), 6.03 (s, 2H), 4.81 (dd, *J* = 15.0, 7.7 Hz, 1H), 4.19 – 4.07 (m, 2H), 4.07 – 3.92 (m, 2H), 3.30 (s, 2H), 3.13 (s, 3H), 2.86 (dt, *J* = 13.6, 7.0 Hz, 2H), 2.70 (dd, *J* = 13.3, 6.7 Hz, 1H), 2.10 (d, *J* = 14.2 Hz, 3H), 1.23 (M, *J* = 6.9, 5.0 Hz, 6H).

[0168] Compounds **37-41** were prepared using a similar process to Example **36** utilizing the corresponding pyrazoles.

EXAMPLES 37 TO 41



Ex. No.	R	Name	[M+H]	HPLC Rt (min)
37		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(3-ethyl-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-4-yl)acetamido)-*N*-methyl-3-phenylpropanamide	493	2.36

38		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(5-ethyl-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yl)acetamido)-*N*-methyl-3-phenylpropanamide	493	2.36
39		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(1-(2-hydroxyethyl)-5-isopropyl-3-methyl-1*H*-pyrazol-4-yl)acetamido)-*N*-methyl-3-phenylpropanamide	507	2.50
40		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(3-cyclopropyl-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-4-yl)acetamido)-*N*-methyl-3-phenylpropanamide	505	2.37
41		(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(5-cyclopropyl-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yl)acetamido)-*N*-methyl-3-phenylpropanamide	505	2.37

Example 37: ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 4H), 6.92 (d, *J* = 3.1 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.11 (s, 1H), 6.03 (s, 2H), 4.81 (d, *J* = 7.2 Hz, 1H), 4.11 (d, *J* = 3.5 Hz, 2H), 4.01 (dd, *J* = 9.0, 4.3 Hz, 2H), 3.37 – 3.21 (m, 2H), 3.14 (d, *J* = 1.4 Hz, 3H), 2.86 (dd, *J* = 13.0, 7.7 Hz, 1H), 2.69 (dd, *J* = 13.3, 6.9 Hz, 1H), 2.52 (dt, *J* = 22.8, 7.6 Hz, 2H), 2.10(s, 3H), 1.23 – 1.09 (m, 3H).

Example 38: ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 4H), 6.92 (d, *J* = 3.1 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.11 (s, 1H), 6.03 (s, 2H), 4.81 (d, *J* = 7.2 Hz, 1H), 4.11 (d, *J* = 3.5 Hz, 2H), 4.01 (dd, *J* = 9.0, 4.3 Hz, 2H), 3.37 – 3.21 (m, 2H), 3.14 (d, *J* = 1.4 Hz, 3H), 2.86 (dd, *J* = 13.0, 7.7 Hz, 1H), 2.69 (dd, *J* = 13.3, 6.9 Hz, 1H), 2.52 (dt, *J* = 22.8, 7.6 Hz, 2H), 2.12(s, 3H), 1.23 – 1.09 (m, 3H).

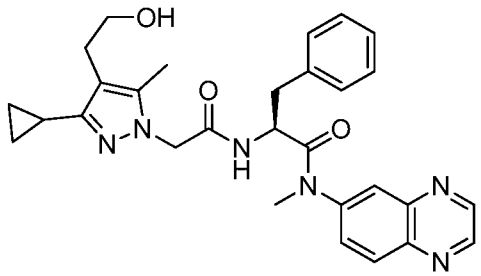
Example 39: ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 4H), 6.93 (s, 2H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.11 (d, *J* = 8.4 Hz, 1H), 6.03 (s, 2H), 4.80 (d, *J* = 7.7 Hz, 1H), 4.16 (s, 2H), 4.07 – 3.98 (m, 2H), 3.35 (q, *J* = 17.6 Hz, 2H), 3.13 (s, 3H), 3.09 (M, *J* = 7.1 Hz, 1H), 2.87 (dd, *J* = 13.0, 7.6 Hz, 1H), 2.70 (dd, *J* = 13.3, 7.0 Hz, 1H), 2.08 (s, 3H), 1.29 – 1.22 (m, 6H).

Example 40: ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 4H), 6.93 (dd, *J* = 6.1, 2.5 Hz, 2H), 6.78 – 6.71 (m, 1H), 6.15 (d, *J* = 8.7 Hz, 1H), 6.03 (s, 2H), 4.82 (dd, *J* = 15.1, 7.4 Hz, 1H), 4.34 – 4.26 (m, 1H), 4.09 – 4.06 (m, 1H), 4.03 – 3.96 (m, 2H), 3.40 – 3.31 (m, 2H), 3.14 (d, *J* = 2.3 Hz, 3H), 2.87 (dd, *J* = 13.3, 7.7 Hz, 1H), 2.76 – 2.66 (m, 1H), 2.10 (s, 3H), 0.98 – 0.79 (m, 4H), 0.60 (d, *J* = 5.4 Hz, 1H).

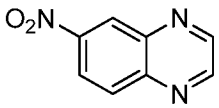
Example 41: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 4H), 6.93 (dd, *J* = 6.1, 2.5 Hz, 2H), 6.78 – 6.71 (m, 1H), 6.15 (d, *J* = 8.7 Hz, 1H), 6.03 (s, 2H), 4.82 (dd, *J* = 15.1, 7.4 Hz, 1H), 4.34 – 4.26 (m, 1H), 4.09 – 4.06 (m, 1H), 4.03 – 3.96 (m, 2H), 3.40 – 3.31 (m, 2H), 3.14 (d, *J* = 2.3 Hz, 3H), 2.87 (dd, *J* = 13.3, 7.7 Hz, 1H), 2.76 – 2.66 (m, 1H), 2.12(s, 3H), 0.98 – 0.79 (m, 4H), 0.60 (d, *J* = 5.4 Hz, 1H).

EXAMPLE 42

(*S*)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenyl-*N*-(quinoxalin-6-yl)propanamide

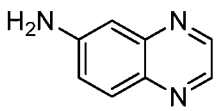


42A. Preparation of 6-nitroquinoxaline



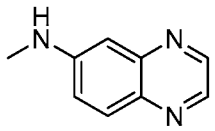
[0169] To a solution of 4-nitrobenzene-1,2-diamine (2.0 g, 13.07 mmol, 1.0 eq) in water (80 mL), was added dropwise glyoxal (4.0 mL, 31.37 mmol, 40% in H_2O, 2.4 eq). The mixture was heated to 100 °C for 2 h under N_2. After cooling, the mixture was filtrated and the solid was washed with water, dissolved in DCM, dried over Na_2SO_4 and concentrated under vacuo to give the product (2.2 g, yield: 96.17%); LC/MS: m/z (M^++1) = 176.

42B. Preparation ofQuinoxalin-6-amine



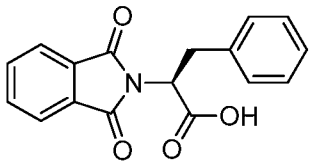
[0170] To a solution of 6-nitroquinoxaline (2.2 g, 12.57 mmol, 1.0 eq) in MeOH, was added dropwise Ranney-Ni (0.7 mL) and hydrazine hydrate (5 mL) was added at 0 °C. The mixture was stirred for 2 h at RT. The mixture was filtered and washed with MeOH. The solid was dried under vacuo to give the product (1.8 g, yield: 98.75%). LC/MS: m/z (M^++1) = 146.

42C. Preparation of *N*-methylquinoxalin-6-amine



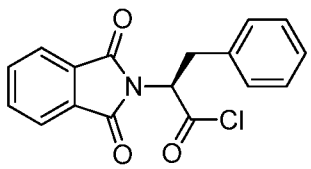
[0171] To a solution of $NaOCH_3$ (3.35 g, 62.07 mmol, 5.0 eq) in MeOH (60 mL), was added quinoxalin-6-amine (1.8 g, 12.41 mmol, 1.0 eq) and (HCHO)n (558.6 mg, 18.62 mmol, 1.5 eq). The mixture was heated to 50 °C overnight. After cooling, $NaBH_4$ (943.5 mg, 24.83 mmol, 2.0 eq) was added portwise, and the mixture was stirred at RT for 2 h. The resulting mixture was concentrated and the residue was dissolved in EtOAc, washed with water (3 times), dried over Na_2SO_4 and concentrated under vacuo. The crude product was purified by chromatograph on silica gel (PE:EA = from 5:1, to 0:1, gradient) to give the product (700 mg, yield: 35.5%); LC/MS: m/z (M^++1) = 160.

42D. Preparation of (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoic acid



[0172] A mixture of isobenzofuran-1,3-dione（9.0 g , 6.1 mmol, 1.0 eq） and (*S*)-2-amino-3-phenylpropanoic acid (10.0 g, 6.1 mmol, 1.0 eq) in pyridine (30 ml) was refluxed for 1h. The reaction mixture was added to ice-cooled HCl (150 mL H_2O and 50 mL conc. HCl). The solid precipitate that formed was collected by filtration, washed with water (3x30 mL), and dried to give (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoic acid (16.5 g, yield: 90%); LC/MS: m/z (M^++1) = 296.

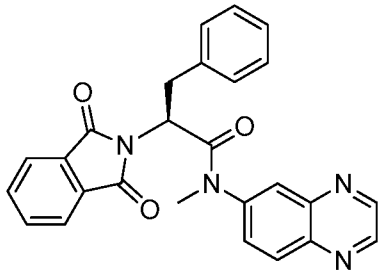
42E. Preparation of (S)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoyl chloride



[0173] A solution of (S)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoic acid (7 g, 2.4 mmol, 1.0 eq) in thionyl chloride (15 ml) was stirred at 45 °C for 2 hours, then the reaction

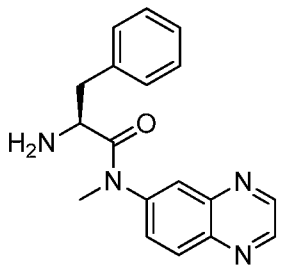
mixture was evaporated to give (S)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoyl chloride (7 g, yield: 91%).

42F. Preparation of (*S*)-2-(1,3-dioxoisoindolin-2-yl)-*N*-methyl-3-phenyl-*N*-(quinoxalin-6-yl)propanamide



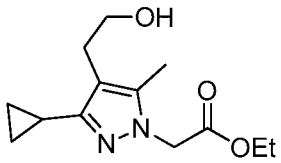
[0174] (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoyl chloride (200 mg, 0.64 mmol, 1.02 eq), N-methylquinoxalin-6-amine(100 mg,0.63 mmol,1.0 eq) and DIPEA (81 mg, 0.63 mmol, 1.0 eq) were dissolved in dioxane (5 mL). The mixture was stirred at r.t for 2 hours. The resulting solution was washed with water 3 times, dried and concentrated, and the residue was purified by column chromatography on silica gel to give (*S*)-2-(1,3-dioxoisoindolin-2-yl)-*N*-methyl-3-phenyl-*N*-(quinoxalin-6-yl)propanamide (200 mg, yield: 73%); LC/MS: m/z (M^++1) = 437.

42G. Preparation of (*S*)-2-amino-*N*-methyl-3-phenyl-*N*-(quinoxalin-6-yl)propanamide



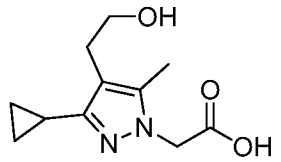
[0175] To a solution of (*S*)-2-(1,3-dioxoisoindolin-2-yl)-*N*-methyl-3-phenyl-*N*-(quinoxalin-6-yl)propanamide (130 mg, 0.46 mmol, 1.0 eq) in ethanol (5 ml), was added hydrazine hydrate (1 ml). The mixture was refluxed for 30min. After cooled to r.t, the white precipitate was filtered off, the filtrate was evaporated to give (*S*)-2-amino-*N*-methyl-3-phenyl-*N*-(quinoxalin-6-yl)propanamide (130 mg, yield: 92%); LC/MS: m/z (M^++1) = 307.

42H. Preparation of ethyl 2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)acetate



[0176] To a mixture of 2-(3-isopropyl-5-methyl-1*H*-pyrazol-4-yl)ethanol (200 mg, 1.2 mmol, 1.0 eq) and Cs_2CO_3 (782 mg, 2.4 mmol, 2.0 eq) in DMF (5 ml), was added ethyl 2-bromoacetate (400mg, 2.4mmol, 2.0eq). The mixture was stirred at 60 °C overnight. After cooled to r.t, water was addd and the mixture was extracted with EtOAc twice. The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, concentrated to give ethyl 2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)acetate (200 mg, yield: 66%); LC/MS: m/z (M^++1) = 253.

42I. Preparation of 2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)acetic acid



[0177] To a solution of ethyl 2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)acetate (200 mg, 0.79 mmol, 1.0 eq) in methanol (2 ml), was added KOH (232 mg, 4.0 mmol, 5.0 eq) in water (2 ml). The mixture was stirred at RT for 2h. Then the resulting solution was adjusted pH to 5~6, extracted with EA 3 times. The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, concentrated to give 2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)acetic acid (130 mg, yield: 72.5%); LC/MS: m/z (M^++1) = 225.

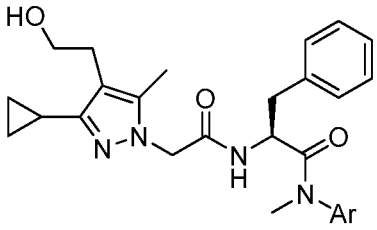
42J. Preparation of(*S*)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenyl-*N*-(quinoxalin-6-yl)propanamide

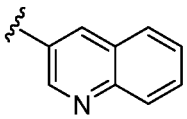
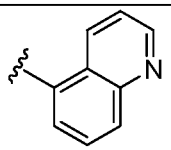
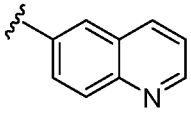
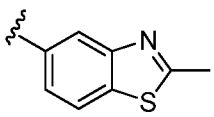
[0178] A mixture of 2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)acetic acid (36 mg, 0.16 mmol, 1.0 eq), (S)-2-(1,3-dioxoisoindolin-2-yl)-N-methyl-3-phenyl-N-(quinoxalin-6-yl)propanamide (50 mg, 0.16 mmol, 1.0 eq), EDCI（61 mg, 0.32 mmol, 2.0 eq), HOBt (43 mg, 0.32 mmol, 2.0 eq) and DIPEA (41 mg, 0.32 mmol, 2.0 eq) in DCM (2 mL) was stirred at r.t overnight under N_2 atmosphere. The resulting solution was washed with water 3 times, dried and concentrated, and the residue was purified by prep-

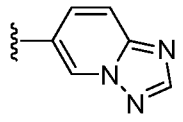
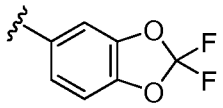
HPLC to give the final product (*S*)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-methyl-3-phenyl-*N*-(quinoxalin-6-yl)propanamide (20 mg, isolated yield: 25%); LC/MS: m/z M^++1 = 513; HPLC retention time = 2.22 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 2H), 8.06 (d, *J* = 8.9 Hz, 1H), 7.53 (s, 1H), 7.26 (s, 1H), 7.20 (t, *J* = 7.4 Hz, 3H), 6.86 (d, *J* = 7.2 Hz, 2H), 6.34 (d, *J* = 8.2 Hz, 1H), 4.79 (d, *J* = 7.3 Hz, 1H), 4.63 (s, 2H), 3.83 (s, 2H), 3.27 (s, 3H), 2.89 – 2.63 (m, 4H), 2.16 (s, 3H), 1.89 – 1.79 (m, 1H), 0.92 (t, *J* = 9.2 Hz, 4H).

[0179] Compounds **43-48** were prepared using a similar process to Example **42** utilizing the corresponding N-methyl anilines (MeNHAr).

EXAMPLES 43 TO 48



Ex. No.	Ar	Name	[M+H]	HPLC Rt (min)
43		(*S*)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1H-pyrazol-1-yl)acetamido)-N-methyl-3-phenyl-N-(quinolin-3-yl)propanamide	512	2.67
44		(*S*)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1H-pyrazol-1-yl)acetamido)-N-methyl-3-phenyl-N-(quinolin-5-yl)propanamide	512	2.00
45		(*S*)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1H-pyrazol-1-yl)acetamido)-N-methyl-3-phenyl-N-(quinolin-6-yl)propanamide	512	2.12
46		(*S*)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1H-pyrazol-1-yl)acetamido)-N-methyl-N-(2-methylbenzo[d]thiazol-5-yl)-3-phenylpropanamide	532	2.41

47		(*S*)-N-([1,2,4]triazolo[1,5-a]pyridin-6-yl)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1H-pyrazol-1-yl)acetamido)-N-methyl-3-phenylpropanamide	502	1.95
48		(*S*)-2-(2-(3-cyclopropyl-4-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-1-yl)acetamido)-*N*-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-3-phenylpropanamide	541	3.00

Example 43: ^{1}H NMR(400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.5 Hz, 1H), 7.80 – 7.68 (m, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.26 (dd, *J* = 13.3, 5.7 Hz, 3H), 6.92 (d, *J* = 7.4 Hz, 2H), 6.44 (d, *J* = 7.9 Hz, 1H), 4.70 – 4.57 (m, 3H), 3.83 (t, *J* = 6.1 Hz, 2H), 3.22 (s, 3H), 2.85 – 2.70 (m, 4H), 2.16 (s, 3H), 1.83 (td, *J* = 7.8, 4.0 Hz, 1H), 0.92 (t, *J* = 6.8 Hz, 4H).

Example 44: ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.98 (ddd, *J* = 14.4, 4.2, 1.6 Hz, 1H), 8.19 (dd, *J* = 20.8, 8.6 Hz, 0.5H), 8.02 (d, *J* = 8.6 Hz, 0.5H), 7.64 – 7.48 (m, 2H), 7.33 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.17 – 7.04 (m, 1H), 6.85 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.56 (dd, *J* = 19.4, 6.8 Hz, 1H), 6.17 (dd, *J* = 51.5, 8.3 Hz, 1H), 4.69 – 4.61 (m, 0.5H), 4.60 – 4.41 (m, 2H), 4.22 – 4.15 (m, 0.5H), 3.83 (dd, *J* = 13.6, 6.7 Hz, 2H), 3.29 (d, *J* = 5.7 Hz, 3H), 2.91– 2.85 (m, 0.5H), 2.79 – 2.64 (m, 2H), 2.50 (d, *J* = 7.6 Hz, 0.5H), 2.10 (s, 3H), 1.90– 1.78 (m, 1H), 0.98 – 0.84 (m, 4H).

Example 45: ^{1}H NMR(400 MHz, $CDCl_3$) δ8.98 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 2H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.23 (dd, *J* = 18.9, 11.3 Hz, 3H), 7.09 (s, 1H), 6.87 (d, *J* = 7.2 Hz, 2H), 6.26 (d, *J* = 8.2 Hz, 1H), 4.75 (dd, *J* = 14.4, 8.3 Hz, 1H), 4.62 (d, *J* = 1.0 Hz, 2H), 3.83 (t, *J* = 6.1 Hz, 2H), 3.24 (s, 3H), 2.88 – 2.60 (m, 4H), 2.15 (s, 3H), 1.92 – 1.79 (m, 1H), 0.93 (t, J = 6.0 Hz, 4H).

Example 46: ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 1H), 7.40 (s, 1H), 7.18 – 7.30 (m, 3H), 6.85 (d, *J* = 6.4, 2.8 Hz, 2H), 6.24 (d, *J* = 8.4 Hz, 1H), 4.75 (dd, *J* = 8.0, 15.2 Hz, 2H), 4.59 (d, J = 1.6 Hz), 3.80 (t, *J* = 6.0 Hz, 1H), 3.22 (s, 3H), 2.87 (s, 3H), 2.6-2.85 (m, 4H), 2.12 (s, 3H), 1.78–1.85 (m, 1H), 0.80–0.85 (m, 4H).

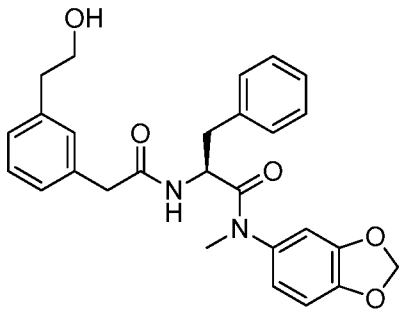
Example 47: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.33 – 7.29 (m, 2H), 7.27 (s, 1H), 6.97 (d, *J* = 7.4 Hz, 2H), 6.58 (d, *J* = 7.9 Hz, 1H), 4.64 (d, *J* = 3.1 Hz, 2H), 4.61 – 4.54 (m, 1H), 3.83 (t, *J* = 6.2 Hz, 2H), 3.16 (s, 3H), 2.89 – 2.82 (m, 1H), 2.77 (dd, *J* = 7.7, 4.0 Hz, 2H), 2.75 – 2.69 (m, 1H), 2.18 (s, 3H), 1.84 (ddd, *J* = 13.3, 8.3, 5.3 Hz, 1H), 0.96 – 0.89 (m, 4H).

Example 48: ^{1}H NMR (400 MHz, $CDCl_3$) δ7.33 – 7.28 (m, 3H), 7.27 – 7.24 (m, 1H), 7.00 – 6.92 (m, 3H), 6.26 (d, *J* = 8.2 Hz, 1H), 4.68 – 4.56 (m, 3H), 3.82 (t, *J* = 6.0 Hz, 2H), 3.10 (s,

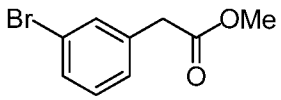
3H), 2.79 (dd, *J* = 10.6, 6.2 Hz, 1H), 2.77 – 2.72 (m, 2H), 2.72 – 2.67 (m, 1H), 2.15 (s, 3H), 1.83 (ddd, J = 13.4, 6.4, 4.0 Hz, 1H), 0.96 – 0.89 (m, 4H).

EXAMPLE 49

(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(3-(2-hydroxyethyl)phenyl)acetamido)-*N*-methyl-3-phenylpropanamide

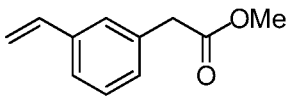


49A. Preparation of methyl 2-(3-bromophenyl)acetate



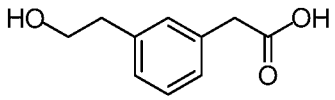
[0180] To a solution of 2-(3-bromophenyl)acetic acid (5.0 g, 23.3 mmol) in CH_3OH (30 mL), was added $SOCl_2$ (3.2 g, 27.0 mmol) at 0 °C. Then the mixture was stirred at 80 °C for 3 hours. The solvent was removed under reduced pressure to give methyl 2-(3-bromophenyl)acetate (5.0 g, yield: 94%); LC/MS: m/z (M^++1) = 231.

49B. Preparation of methyl 2-(3-vinylphenyl)acetate



[0181] A mixture of methyl 2-(3-bromophenyl)acetate (1.0 g, 4.4 mmol), tributyl(vinyl)stannane (5.6 g, 17.5 mmol) and tetrakis(triphenylphosphine)palladium(250 mg, 0.2 mmol) in *N,N*-dimethylformamide (15 mL) was stirred at 80 °C overnight. The mixture was poured into water, extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and then concentrated under vacuo. The residue was purification by column chromatography to afford methyl 2-(3-vinylphenyl)acetate (600 mg, yield: 79%); LC/MS: m/z (M^++1) = 177.

49C. Preparation of 2-(3-(2-hydroxyethyl)phenyl)acetic acid



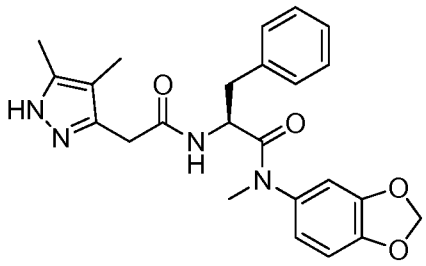
[0182] Methyl 2-(3-vinylphenyl)acetate (300 mg, 1.7 mmol) was dissolved in THF solution of 9-BBN, then the resulting mixture was stirred at room temperature overnight. The mixture was quenched with MeOH and the solvent was removed under reduced pressure. The residue was dissolved in H_2O_2 and two drops of saturated NaOH solution were added, and the resulting mixture was stirred at room temperature for 2 hours. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, concentrated in *vacuo* and the crude product was purified by column chromatography to give 2-(3-(2-hydroxyethyl)phenyl)acetic acid (100 mg, yield: 33%); LC/MS: m/z (M^++1) = 181.

49D. Preparation of (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(3-(2-hydroxyethyl)phenyl)acetamido)-*N*-methyl-3-phenylpropanamide

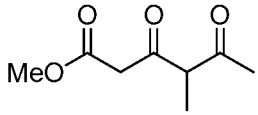
[0183] A mixture of 2-(3-(2-hydroxyethyl)phenyl)acetic acid (70 mg, 0.39 mmol), (*S*)-2-amino-*N*-(benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-3-phenylpropanamide (116 mg, 0.39 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (190 mg, 1.0 mmol), hydroxybenzotriazole (105 mg, 0.78 mmol) and *N, N*-diisopropylethylamine (200 mg, 1.6 mmol) in *N,N*-dimethylformamide was stirred at room temperature overnight. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, concentrated in *vacuo* and the crude product was purification by *prep*-HPLC to give (*S*)-*N*-(benzo[d][1,3]dioxol-5-yl)-2-(2-(3-(2-hydroxyethyl)phenyl)acetamido)-*N*-methyl-3-phenylpropanamide (12 mg, yield: 7%); LC/MS: m/z (M^++1) = 461; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.6 Hz, 1H), 7.29 (s, 2H), 7.26 – 7.20 (m, 3H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.13 (s, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.91 (dd, *J* = 7.1, 2.2 Hz, 2H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.11 (d, *J* = 8.4 Hz, 1H), 6.02 (s, 2H), 4.82 (dd, *J* = 14.8, 7.7 Hz, 1H), 3.94 – 3.81 (m, 2H), 3.52 (s, 2H), 3.14 (s, 3H), 2.86 (dd, *J* = 13.8, 7.5 Hz, 3H), 2.70 (dd, *J* = 13.2, 6.5 Hz, 1H).

EXAMPLE 50

(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(4,5-dimethyl-1*H*-pyrazol-3-yl)acetamido)-*N*-methyl-3-phenylpropanamide

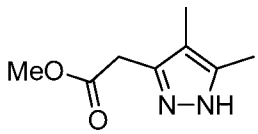


50A. Preparation of methyl 4-methyl-3,5-dioxohexanoate



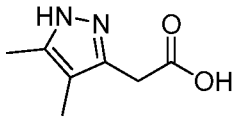
[0184] To an ice-cooled suspension of NaH (2.8 g, 70 mmol, 60% suspension in mineral oil) in anhydrous THF, was added methyl 3-oxopentanoate (3.0 g, 23 mmol) dropwise and the mixture was stirred for an additional 10 min. The solution was cooled to -10 °C and *n*-BuLi (10.2 mL, 25 mmol, 2.1 M in hexane) was added dropwise. After stirring for an additional 10 min, *N*-methoxy-*N*-methylacetamide (2.4 g, 23 mmol) was added at -10 °C. The solution was stirred at this temperature for 15 mins, warmed to room temperature, and stirred for another 30 min. Hydrolysis was carried out by pouring the solution into a ice-cooled solution of NH_4Cl, the aqueous phase was separated and extracted twice with ethyl acetate. The combined organic extracts were washed with brine and water. After drying, the solvent was removed and the residue was purified to give methyl 4-methyl-3,5-dioxohexanoate (1.3 g, yield 33%); LC/MS: m/z (M^++1) = 173.

50B. Preparation of methyl 2-(4,5-dimethyl-1H-pyrazol-3-yl)acetate



[0185] To a mixture of methyl 4-methyl-3,5-dioxohexanoate (800 mg, 4.7 mmol) in MeOH was added hydrazine hydrate (310 mg, 4.7 mmol) and AcOH (280 mg, 4.7 mmol). The solution was refluxed for 20 min. The solvent was removed and the residue was dissolved in water, basified to pH 9, extracted with ethyl acetate and concentrated to give methyl 2-(4,5-dimethyl-1H-pyrazol-3-yl)acetate (700 mg, 95%), which was used to next step without further purification; LC/MS: m/z (M^++1) = 169.

50C. Preparation of 2-(4,5-dimethyl-1*H*-pyrazol-3-yl)acetic acid



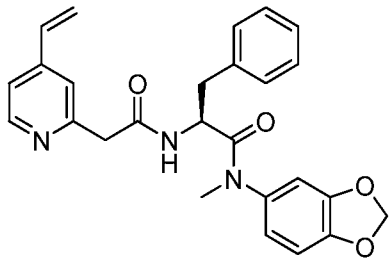
[0186] A mixture of methyl 2-(4,5-dimethyl-1H-pyrazol-3-yl)acetate (700 mg, 4.1 mmol) in MeOH and sat NaOH solution was stirred at room temperature for 1 hour. MeOH was removed and the aqueous residue was acidified to pH 3, extracted with ethyl acetate and concentrated to give 2-(4,5-dimethyl-1H-pyrazol-3-yl)acetic acid (500 mg, yield: 78%); LC/MS: m/z M^++1 = 155.

50D. Preparation of (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(4,5-dimethyl-1*H*-pyrazol-3-yl)acetamido)-*N*-methyl-3-phenylpropanamide

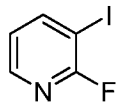
[0187] A mixture of 2-(4,5-dimethyl-1H-pyrazol-3-yl)acetic acid (100 mg, 0.65 mmol), (*S*)-2-amino-*N*-(benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-3-phenylpropanamide (195 mg, 0.65 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (310 mg, 1.6 mmol), hydroxybenzotriazole (175 mg, 1.3 mmol) and *N, N* -diisopropylethylamine (340 mg, 2.6 mmol) in *N,N*-dimethylformamide was stirred at room temperature overnight. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, concentrated in *vacuo* and the crude product was purification by *prep*-HPLC to give (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(4,5-dimethyl-1H-pyrazol-3-yl)acetamido)-*N*-methyl-3-phenylpropanamide (50 mg, 28%); LC/MS: m/z (M^++1) = 435; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.3 Hz, 1H), 7.28 (s, 1H), 7.26 – 7.17 (m, 3H), 6.95 (dd, *J* = 6.3, 2.8 Hz, 2H), 6.70 (d, *J* = 7.5 Hz, 1H), 6.01 (d, *J* = 3.9 Hz, 2H), 4.80 (dd, *J* = 14.8, 7.9 Hz, 1H), 3.52 (dd, *J* = 35.4, 16.3 Hz, 2H), 3.14 (s, 3H), 2.98 – 2.88 (m, 1H), 2.75 (dd, *J* = 13.0, 6.4 Hz, 1H), 2.23 (s, 3H), 1.90 (s, 3H).

EXAMPLE 51

(*S*)-*N*-(benzo[d][1,3]dioxol-5-yl)-*N*-methyl-3-phenyl-2-(2-(4-vinylpyridin-2-yl)acetamido)propanamide

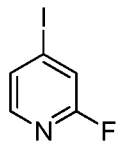


51A. Preparation of 2-fluoro-3-iodopyridine



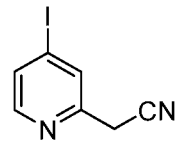
[0188] To a solution of 2-fluoropyridine (5.0 g, 51.5 mmol) in dry THF (50 mL) was added LDA (25.8 mL of a 2M solution in THF, 51.5 mmol) dropwise at -78 °C. The mixture was then stirred at -78 °C for 1 hour. A solution of I_2 (13.07 g, 51.5 mmol) in THF (30 mL) was added dropwise at -78 °C to the mixture. After stirring for 3 hours at -78°C, the reaction was quenched by addition of H_2O (10 mL) and slowly warmed to room temperature. A solution of Na_2SO_3 (50 mL, 2M in H_2O) was added. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and then concentrated to give crude product, which was purified via column chromatography to give 2-fluoro-3-iodopyridine (9.6 g, yield 83.6%) as a white solid. LC/MS: m/z (M^++H) = 224.

51B. Preparation of 2-fluoro-4-iodopyridine



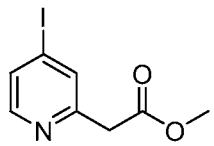
[0189] To a solution of 2-fluoro-3-iodopyridine (4.0 g, 17.9 mmol) in dry THF (50 mL), was added LDA (8.96 mL of a 2M solution in THF, 17.9 mmol) dropwise at -78 °C. After stirring for 4 hours at -78 °C, H_2O (0.5 mL) in THF (1 mL) was added. The mixture was slowly warmed to room temperature, followed by addition of brine (30 mL). The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and then concentrated to give crude product, which was purified by column chromatography to give 2-fluoro-4-iodopyridine (3.5 g, yield : 87.5%) as a white solid. LC/MS: m/z (M^++H) = 224.

51C. Preparation of 2-(4-iodopyridin-2-yl)acetonitrile



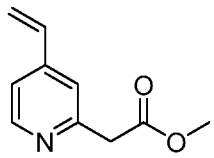
[0190] To a solution of 2-fluoro-4-iodopyridine (1.3 g, 5.83 mmol) and CH_3CN (0.57 g, 11.6 mmol) in THF (20 mL), was added LiHMDS (11.6 mL of a 1M solution in THF, 11.6 mmol) dropwise at -78°C. After stirring for 2 hours at -78 °C, the mixture was slowly warmed to room temperature for 2 hours. Saturated aq. NH_4Cl (10 mL) and EtOAc (20 mL) were then added. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and then concentrated to give crude product, which was purified by column chromatography to give 2-(4-iodopyridin-2-yl)acetonitrile (0.61 g, yield : 42.9%). LC/MS: m/z (M^++H) = 245.

51D. Preparation of methyl methyl 2-(4-iodopyridin-2-yl)acetate



[0191] To a mixture of TMSCl (0.73 g, 6.72 mmol) in MeOH (10 mL) was added, 2-(4-iodopyridin-2-yl)acetonitrile (0.41 g, 1.68 mmol). The mixture was then stirred at 50 °C overnight. The resulting mixture was concentrated to dryness and the residue was dissolved in saturated $NaHCO_3$ (10 mL) and extracted with EtOAC (20 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and then concentrated to give methyl 2-(4-iodopyridin-2-yl)acetate (0.39 g, yield : 83.8%). LC/MS: m/z (M^++H) = 278.

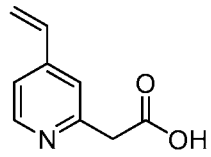
51E. Preparation of methyl 2-(4-vinylpyridin-2-yl)acetate



[0192] A mixture of methyl 2-(4-iodopyridin-2-yl)-acetate (0.36 g, 1.3 mmol), tributyl(vinyl)stannane (1.23 g, 3.9 mmol) and tetrakis(triphenylphosphine)palladium (20 mg) in toluene (8 mL) was degassed under N_2 for three times and stirred at 110 °C under N_2 atmosphere overnight. The resulting mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4

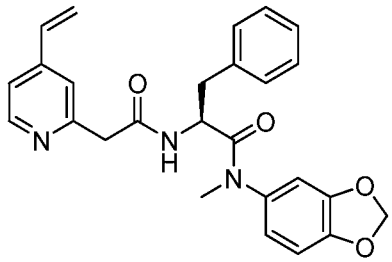
and then concentrated in *vacuum*, the residue was purified by column chromatography to afford methyl 2-(4-vinylpyridin-2-yl)acetate (110 mg, yield: 47.7%). LC/MS: m/z (M^++H) = 178.

51F. Preparation of 2-(4-vinylpyridin-2-yl)acetic acid



[0193] To a solution of methyl 2-(4-vinylpyridin-2-yl)-acetate (110 mg, 0.62 mmol) in THF (4 mL), was added KOH solution (69 mg in 1 mL H_2O). The mixture was then stirred at 50 °C for 3h. The mixture was acidified with 1 N HCl and concentrated to dryness to give crude 2-(4-vinylpyridin-2-yl)-acetic acid (120 mg), which was directly used to the next reaction. LC/MS: m/z (M^++H) = 164.

51G. Preparation of (*S*)-*N*-(benzo[d][1,3]dioxol-5-yl)-*N*-methyl-3-phenyl-2-(2-(4-vinylpyridin-2-yl)acetamido)propanamide

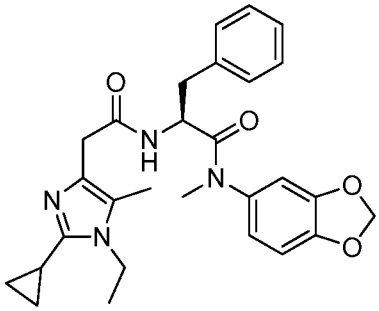


[0194] A mixture of 2-(4-vinylpyridin-2-yl)acetic acid (60 mg, 0.37 mmol), (*S*)-2-amino-*N*-(benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-3-phenylpropanamide (116 mg, 0.39 mmol), EDCI (190 mg, 1.0 mmol), HOBt (105 mg, 0.78 mmol) and DIPEA (200 mg, 1.6 mmol) in DMF (4 mL) was stirred at room temperature overnight. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, then concentrated in *vacuum*. The residue was purification by column chromatography to afford (*S*)-*N*-(benzo[d][1,3]dioxol-5-yl)-*N*-methyl-3-phenyl-2-(2-(4-vinylpyridin-2-yl)acetamido)propanamide (9 mg, yield: 5.5%). LC/MS: m/z (M^++H) = 444; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.6 Hz, 1H), 7.29 (s, 2H), 7.26 – 7.20 (m, 3H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.13 (s, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.91 (dd, *J* = 7.1, 2.2 Hz, 2H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.11 (d, *J* = 8.4 Hz, 1H), 6.02 (s, 2H), 4.82 (dd, *J* = 14.8, 7.7 Hz, 1H), 3.94 – 3.81

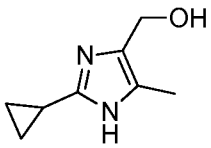
(m, 2H), 3.52 (s, 2H), 3.14 (s, 3H), 2.86 (dd, *J* = 13.8, 7.5 Hz, 3H), 2.70 (dd, *J* = 13.2, 6.5 Hz, 1H).

EXAMPLE 52

(*S*)-*N*-(benzo[d][1,3]dioxol-5-yl)-2-(2-(2-cyclopropyl-1-ethyl-5-methyl-1H-imidazol-4-yl)acetamido)-*N*-methyl-3-phenylpropanamide

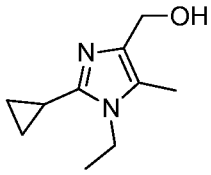


52A. Preparation of (2-cyclopropyl-5-methyl-1H-imidazol-4-yl)methanol



[0195] To a solution of cyclopropanecarboximidamide hydrochloride (6.0g, 50.3 mmol) in water at 0 °C was added 1-hydroxybutane-2,3-dione (3.6 g, 1.0 eq) and a solution of CH_3COOK (1.5 eq) in water (20 mL). The mixture was stirred at r.t for 2h, followed by addition of a.q NaOH to pH ~8. The mixture was then extracted with DCM:^{i}PrOH (V:V = 3:1). The organic layers were combined, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give compound as a white solid (3.0 g, yield: 47.0%). LC/MS: m/z (M^++H) =153.

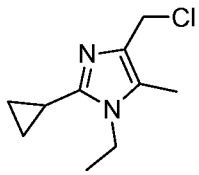
52B. Preparation of (2-cyclopropyl-1-ethyl-5-methyl-1H-imidazol-4-yl)methanol



[0196] K_2CO_3 (3.0eq) was added to a solution of (2-cyclopropyl-5-methyl-1H–imidazol -4-yl)methanol (3g, 19.7mmol, 1.0 eq) and EtI (1.2eq) in DMF. The mixture was stirred at 80

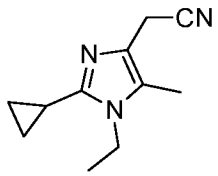
°C overnight. The mixture was then quenched with water and extracted with EA. The organic layers were combined, dried over anhydrous $NaSO_4$ and purified by column chromatography on silica gel to give a yellow oil (1.2 g, yield: 30.7%). LC/MS: m/z (M^++H) = 181.

52C. Preparation of 4-(chloromethyl)-2-cyclopropyl-1-ethyl-5-methyl-1H-imidazole



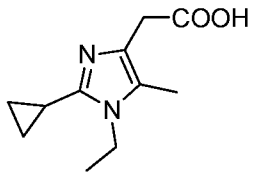
[0197] (2-cyclopropyl-1-ethyl-5-methyl-1H-imidazol-4-yl)methanol (1.0 g, 5.56 mmol, 1.0 eq) was added to $SOCl_2$ (10 mL) at 0 °C. The reaction mixture was stirred at r.t for 50 min. Excess $SOCl_2$ was removed to afford a crude product as a yellow solid. (1.0 g, yield: 90.8%). LC/MS: m/z (M^++H) =199..

52D. Preparation of 2-(2-cyclopropyl-1-ethyl-5-methyl-1H-imidazol-4-yl)acetonitrile



[0198] To a solution of 4-(chloromethyl)-2-cyclopropyl-1-ethyl-5-methyl-1H-imidazole (200 mg, 1.0, 1.0 eq) in MeCN, was added to a solution of TMSCN (1.5 eq) and $CsCO_3$ (2.0 eq) in MeCN. The mixture was stirred at 65 °C under nitrogen atmosphere for 2h. The reaction was quenched with water and extracted with ethyl acetate. The organic layers were combined, dried and concentrated. The residue was purified by column chromatography on silica gel to give a yellow oil (90 mg, yield: 53%). LC/MS: m/z (M^++H) =190.

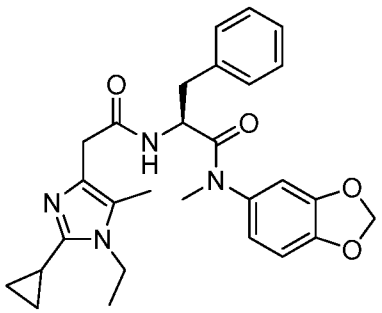
52E. Preparation of 2-(2-cyclopropyl-1-ethyl-5-methyl-1H-imidazol-4-yl)acetic acid



[0199] NaOH (5 eq) was added to a solution of 2-(2-cyclopropyl-1-ethyl-5-methyl-1H -imidazol-4-yl)acetonitrile(90 mg, 1.0 eq) in EtOH. The mixture was stirred at 90 °C and

refluxed for 4h. Excess EtOH was removed. The residue was titrated with acetone, and filtered. The filtrate was concentrated to afford the crude product as a yellow solid. (100 mg, yield: 96.0%). LC/MS: m/z (M^++H) =209.

52F. Preparation of (*S*)-*N*-(benzo[d][1,3]dioxol-5-yl)-2-(2-(2-cyclopropyl-1-ethyl-5-methyl-1H-imidazol-4-yl)acetamido)-*N*-methyl-3-phenylpropanamide



[0200] To a solution of EDCI (1.5eq), HOBt (2.0 eq), DIPEA (4.0 eq) and DMAP (0.1 eq) in DMF, was added to a solution of 2-(2-cyclopropyl-1-ethyl-5-methyl -1H-imidazol -4 -yl)-acetic acid (50 mg, 0.24 mmol, 1.0 eq) in DMF. After stirring at r.t about 1h, (*S*)-2-amino-*N*-(benzo[d][1,3]dioxol-5-yl)-*N*-methyl-3-phenylpropanamide(10 7 mg, 1.5 eq) was added to the mixture. The resulting mixture was stirred at r.t overnight. The reaction was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with aq. LiCl (10%), dried and concentrated. The residue was purified by column chromatography on silica gel to give a yellow solid (75mg, yield: 64%). LC/MS: m/z (M^++H) = 489; ^{1}H NMR (400 MHz, DMSO-d6): δ 7.27 – 7.19 (m, 3H), 6.85 (dd, *J* = 5.9, 3.5 Hz, 2H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.04 (s, 2H), 6.01 (d, *J* = 8.1 Hz, 1H), 4.77 (dd, *J* = 14.8, 7.5 Hz, 1H), 3.80 (q, *J* = 7.2 Hz, 2H), 3.48 – 3.30 (m, 2H), 3.18 (s, 3H), 2.89 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.64 (dd, *J* = 13.4, 8.0 Hz, 1H), 2.09 (s, 3H), 1.74 (d, *J* = 3.2 Hz, 1H), 1.22 (t, *J* = 7.3 Hz, 3H), 1.07 (d, *J* = 5.3 Hz, 2H), 0.97 (dd, *J* = 8.0, 3.9 Hz, 2H).

Biological Assays

[0201] MT2rep assay: MT2 cells are pelleted by centrifugation and re-suspended with appropriate volume of RPMI 1640 (10% FBS) to give a cell density about 1.34×10^5/ml. Appropriate volume HIV-1(NL4-3) stock is added to the above MT2 cells to give a MOI about 0.01 TCID50 per cell. 90μL of MT2 cells/HIV-1 mixture is added to 384-well antiviral assay plates containing compounds and 45μL of MT2 cells (1.34×10^5/ml, without virus addition) is added to 384-well cytotoxicity assay plates containing compounds. The assay

plates are incubated in a 5% CO_2 incubator at 37°C for 3 days. Three days post MT2 infection, 10µl per well of supernatant from 384-well antiviral assay plates is transferred to a new 384-well plate and 40 µL of JC53BL cells ($0.4x10^6$ cells/ml) is added to this plate. 24 hours later ß-Gal activity is measured as following. Add 30µL of the FluorAce solution to each well of the assay plate. Incubate the plates in 5% (v/v) CO_2 incubator at 37°C for 2 hours. Add 10ul stop solution to each well and read plates with PE Victor 3 under the umbelliferone channel. The compound cytotoxicity is measured three days post MT2 seeding by Celltiter Glo kit with conditions recommended by Promega except that 10 µL per well of reagent is added. IC50 and CC50 is calculated with GraphPadPrism5.00 (four-parameter logistic equation).

[0202] The following are biological data obtained for compounds of Examples 1-52 using the biological assays described hereinabove.

Example No.	EC50 (nM)	CC50 (nM)
1	83	>20,000
2	430	>20,000
3	389	>20,000
4	48	>20,000
5	320	>20,000
6	710	>20,000
7	16	>20,000
8	33	>20,000
9	525[a, 1]	>20,000
10	525 [a, 1]	>20,000
11	182	>20,000
12	102	>20,000
13	18	>20,000
14	95	>20,000

15	78	>20,000
16	647	>20,000
17	2,630	>20,000
18	40	>20,000
19	22	>20,000
20	1,385	>20,000
21	860	>20,000
22	7,413 [a, 6]	>20,000
23	1,824 [a, 2]	>20,000
24	1,824 [a, 2]	>20,000
25	7,422	>20,000
26	6,863	>20,000
27	2,958	>20,000
28	5,947	>20,000
29	7,288 [a, 3]	>20,000
30	7,288 [a, 3]	>20,000
31	2,185 [a, 4]	>20,000
32	2,185 [a, 4]	>20,000
33	>10,000 [a, 5]	>20,000
34	>10,000 [a, 5]	>20,000
35	7,413 [a, 6]	>20,000
36	829	>20,000
37	381 [a, 7]	>20,000
38	381 [a, 7]	>20,000
39	435	>20,000

40	596 [a, 8]	>20,000
41	596 [a, 8]	>20,000
42	82	>20,000
43	161	>20,000
44	30	>20,000
45	31	>20,000
46	14	>20,000
47	1,820	>20,000
48	168	>20,000
49	1,020	>20,000
50	468	>20,000
51	2,866	>20,000
52	1,920	>20,000

Note: [a]Compounds were tested as a mixture of two regio-isomers in a ratio below: [1]Ex. 9:10 = 1:3; [2]Ex.23:24 = 2:1; [3]Ex.29:30 = 3:1; [4]Ex.30:31 = 2.6:1; [5]Ex.33:34 = 4:1; [6]Ex.22:35 = 5:1; [7]Ex.37:38 = 1:2; [8]Ex.40:41 = 1.5:1.

References:

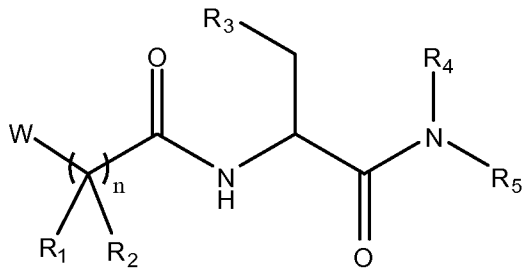
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We claim:

1. A compound of formula I:



(I)

or pharmaceutically acceptable salt thereof, wherein:

W is 5 to 7-membered monocyclic carbocycle or heterocycle;

each of R_1 and R_2 is independently H, $(C_1$-$C_4)$alkyl, $(C_3$-$C_5)$cycloalkyl, hydroxyl, fluoro, or NR_bR_c, or R_1 and R_2 together form $(C_3$-$C_5)$cycloalkyl;

R_3 is phenyl, or heteroaryl;

R_4 is H, $(C_1$-$C_4)$alkyl, or $(C_3$-$C_7)$cycloalkyl;

R_5 is $(CR_8R_9)_q$-cycloalkyl, $(CR_8R_9)_q$-aryl, or $(CR_8R_9)_q$-heterocycle;

each of R_8 and R_9 is independently H, $(C_1$-$C_4)$alkyl, hydroxyl, fluoro, or NR_bR_c, or R_8 and R_9 together form $(C_3$-$C_5)$cycloalkyl;

each of R_b and R_c is independently hydrogen or alkyl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle;

each q is independently 0, 1, 2, 3, or 4; and

n is 1 or 2.

2. The compound of claim 1, wherein W is 5-membered heteroaryl, 6-membered heteroaryl, or phenyl, in which said heteroaryl and phenyl are each independently substituted with $(R_6)_m$;

each of R_1 and R_2 is independently H or $(C_1$-$C_4)$alkyl;

R_3 is phenyl, or heteroaryl;

R_4 is H, $(C_1$-$C_4)$alkyl, or $(C_3$-$C_7)$cycloalkyl;

R_5 is $(CR_8R_9)_q$-cycloalkyl, $(CR_8R_9)_q$-aryl, or $(CR_8R_9)_q$-heteroaryl;

each R_6 is independently hydrogen, halogen, cyano, nitro, CF_3, OCF_3, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, OR_a, SR_a, $S(=O)R_a$, $S(=O)_2R_a$, $S(=O)_2OR_a$, NR_bR_c, $C(=O)OR_a$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_a$, $NR_aC(=O)NR_bR_c$, $NR_bC(=O)R_a$, $(CR_8R_9)_q$-OH, $(CR_8R_9)_q$-O-$(C_1$-$C_4)$alkyl, $(CR_8R_9)_q$-(C=O)O-$(C_1$-$C_4)$alkyl, $(CR_8R_9)_q$-(C=O)O-aryl, $(CR_8R_9)_q$-(C=O)OH, $(CR_8R_9)_q$-NR_bR_c, $(CR_8R_9)_q$-cycloalkyl, $(CR_8R_9)_q$-phenyl, or $(CR_8R_9)_q$-heteroaryl;

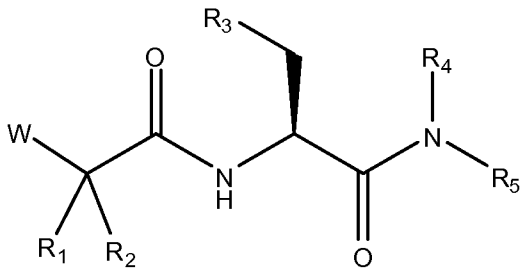
each of R_8 and R_9 is independently H or $(C_1$-$C_4)$alkyl;

each occurrence of R_a, R_b, and R_c is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycle, or aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle;

m and q are each independently 0, 1, 2, 3, or 4; and

n is 1 or 2.

3. The compound of claim 1 or 2, having the structure of Formula (II):



(II),

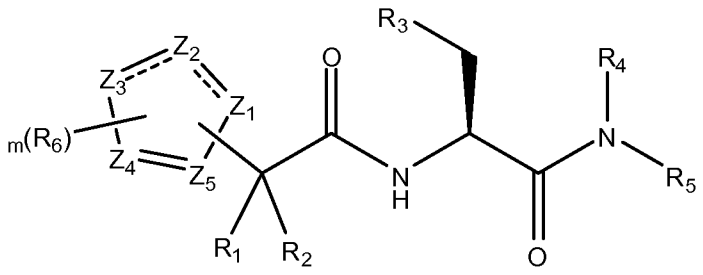
wherein W, R_1, R_2, R_3, R_4, and R_5 are as defined in claim 1 or 2.

4. The compound of claim 3, wherein W is 5-membered heteroaryl, in which said heteroaryl is substituted with $(R_6)_m$.

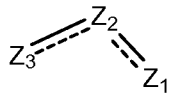
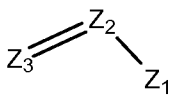
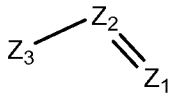
5. The compound of claim 3, wherein W is 6-membered heteroaryl, in which said heteroaryl is substituted with $(R_6)_m$.

6. The compound of claim 3, wherein W is phenyl, in which said phenyl is independently substituted with $(R_6)_m$.

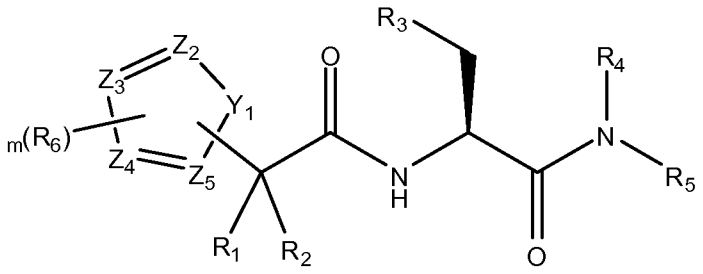
7. The compound of claim 3, having the structure of Formula (III):



(III),

wherein  denotes  or ; each of Z_1, Z_2, Z_3, Z_4 and Z_5 is independently carbon or nitrogen, provided that at least one of Z_1, Z_2, Z_3, Z_4 and Z_5 is nitrogen; and R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

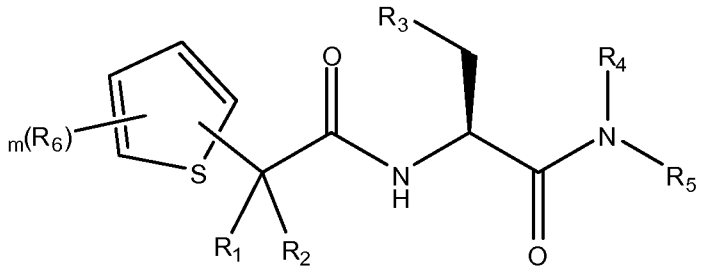
8. The compound of claim 3, having the structure of Formula (IV):



(IV),

wherein each of Z_2, Z_3, Z_4 and Z_5 is independently carbon or nitrogen; Y_1 is oxygen or sulfur; and R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

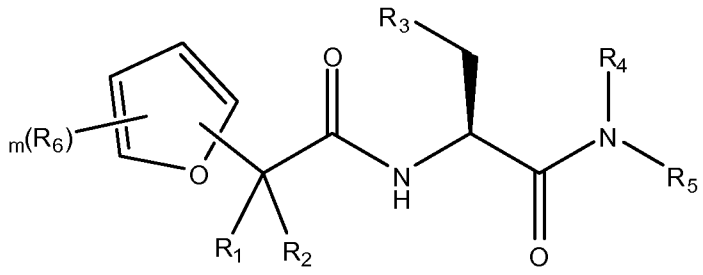
9. The compound of claim 3, having the structure of Formula (IVa):



(IVa),

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

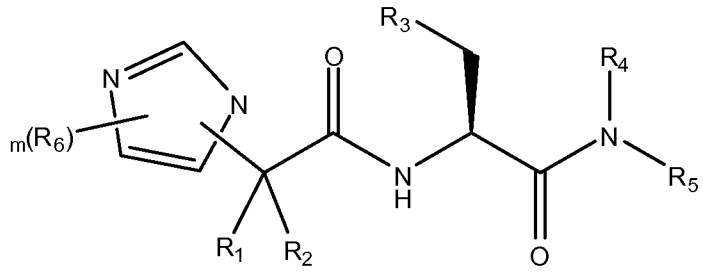
10. The compound of claim 3, having the structure of Formula (IVb):



(IVb),

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

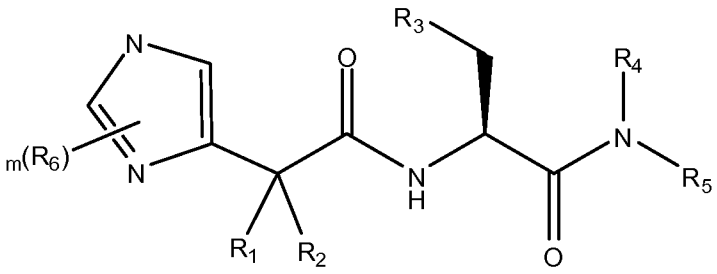
11. The compound of claim 3, having the structure of Formula (IVc):



(IVc),

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

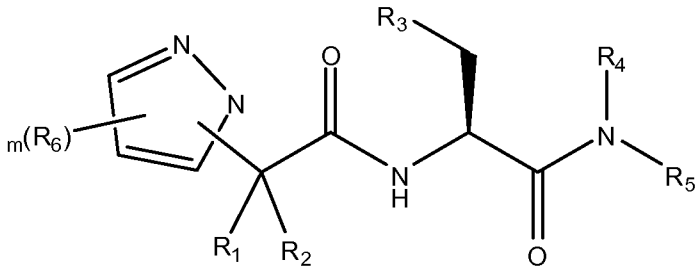
12. The compound of claim 3, having the structure of Formula (IVd):



(IVd),

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

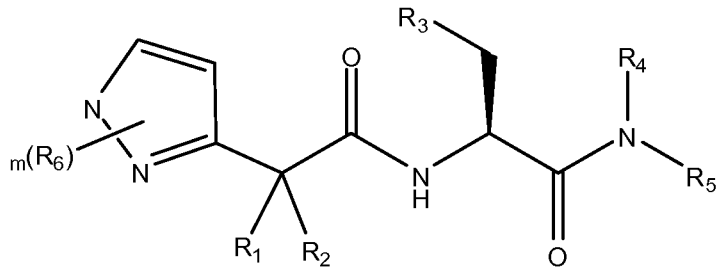
13. The compound of claim 7, having the structure of Formula (V)



(V)

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 1, 2, or 3.

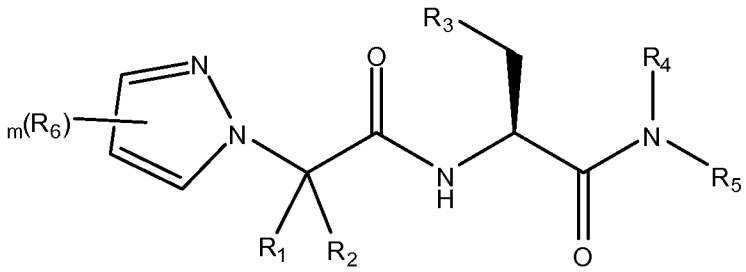
14. The compound of claim 7, having the structure of Formula (Va)



(Va)

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 1, 2, or 3.

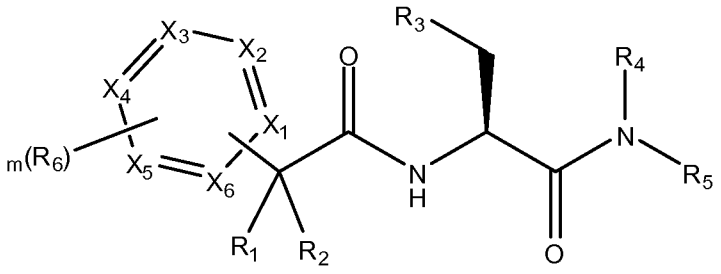
15. The compound of claim 7, having the structure of Formula (VI):



(VI),

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

16. The compound of claim 3, having the structure of Formula (VII):

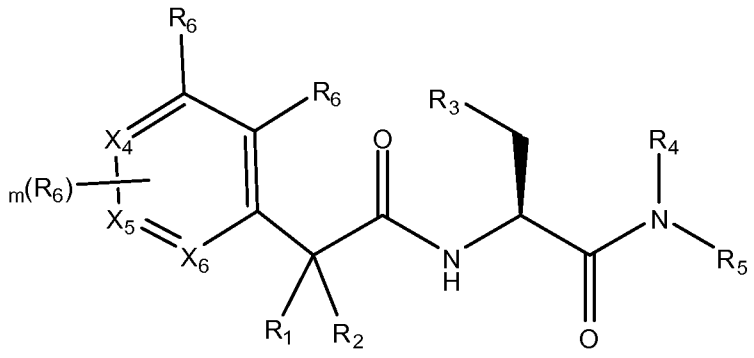


(VII),

each of X_1, X_2, X_3, X_4 , X_5 and X_6 is independently carbon or nitrogen, provided that at least one of X_1, X_2, X_3, X_4 , X_5 and X_6 is nitrogen; and R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

17. The compound of claim 16, wherein one of X_1, X_2, X_3, X_4 , X_5 and X_6 is nitrogen and the remaining of X_1, X_2, X_3, X_4 , X_5 and X_6 is carbon.

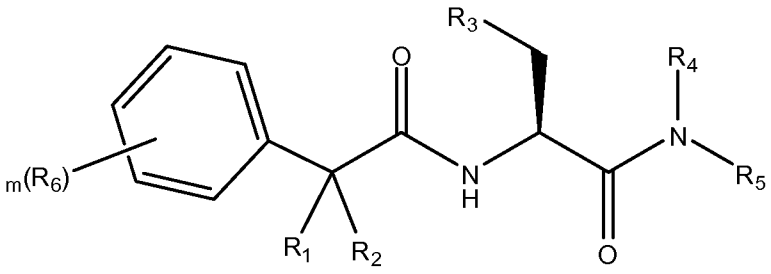
18. The compound of claim 3, having the structure of Formula (VIIa):



(VIIa),

each of X_4 , X_5 and X_6 is independently carbon or nitrogen, provided that only one of X_4 , X_5 and X_6 is nitrogen, and the remaining of X_4 , X_5 and X_6 is carbon; and R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, or 2.

19. The compound of claim 3, having the structure of Formula (VIII):



(VIII),

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are as defined in claim 2, and m is 0, 1, 2, or 3.

20. The compound of any one of claims 1-19, wherein each of R_1 and R_2 is independently H.

21. The compound of any one of claims 1-20, wherein R_3 is phenyl.

22. The compound of any one of claims 1-20, wherein R_3 is phenyl substituted with one to three substituents selected from H, $(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$alkyl, halogen, nitro, CN, CF_3, and OCF_3.

23. The compound of any one of claims 1-20, wherein R_3 is unsubstituted phenyl.

24. The compound of any one of claims 1-23, wherein R_3 is heteroaryl substituted with one to three substituents selected from H, $(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$alkyl, halogen, nitro, CN, CF_3, and OCF_3.

25. The compound of any one of claims 1-24, wherein R_3 is unsubstituted heteroaryl.

26. The compound of any one of claims 1-25, wherein R_4 is H.

27. The compound of any one of claims 1-25, wherein R_4 is $(C_1\text{-}C_4)$alkyl.

28. The compound of any one of claims 1-25, wherein R_4 is methyl.

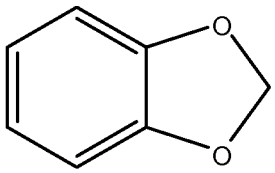
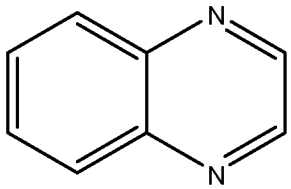
29. The compound of any one of claims 1-28, wherein R_5 is $(CH_2)_q$-cycloalkyl, $(CH_2)_q$-aryl, or $(CH_2)_q$-heteroaryl, in which q is 0 or 1.

30. The compound of any one of claims 1-29, wherein R_5 is aryl, or heteroaryl.

31. The compound of any one of claims 1-29, wherein R_5 is phenyl.

32. The compound of any one of claims 1-29, wherein R_5 is pyridyl.

33. The compound of any one of claims 1-29, wherein:

R_5 is aryl (e.g., phenyl) or heteroaryl (e.g., pyridyl,  or ) substituted with one to four substituents selected from hydrogen, halogen, cyano, nitro, CF_3, OCF_3, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, 3-10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from N, O and S, phenyl, naphthyl, OR_a, SR_a, $S(=O)R_a$, $S(=O)_2R_a$, $S(=O)_2OR_a$, NR_bR_c, $C(=O)OR_a$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_a$, $NR_aC(=O)NR_bR_c$, $NR_bC(=O)R_a$, $(CR_8R_9)_q$-OH, $(CR_8R_9)_q$-O-$(C_1\text{-}C_4)$alkyl, $(CR_8R_9)_q$-NR_bR_c, $(CR_8R_9)_q$-cycloalkyl, $(CR_8R_9)_q$-phenyl, and $(CR_8R_9)_q$-heteroaryl;

each of R_8 and R_9 is independently H or $(C_1\text{-}C_4)$alkyl;

each occurrence of R_a, R_b, and R_c is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycle, or aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and

each q is independently 0, 1, 2, 3, or 4.

34. The compound of any one of claims 1-33, wherein:

R_5 is phenyl or heteroaryl substituted with one to four substituents selected from hydrogen, halogen, cyano, nitro, CF_3, OCF_3, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl, 3-10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from N, O and S, phenyl, naphthyl, $(CH_2)_q$-OH, $(CH_2)_q$-O-$(C_1$-$C_4)$alkyl, $(CH_2)_q$-NR_bR_c, $(CH_2)_q$-$(C_3$-$C_7)$cycloalkyl, , $(CH_2)_q$-phenyl, and $(CH_2)_q$-heteroaryl;

each occurrence of R_b, and R_c is independently hydrogen, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl, 3-10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from N, O and S, or aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and

each q is independently 0, 1, 2, 3, or 4.

35. The compound of any one of claims 2-34, wherein:

each R_6 is independently hydrogen, halogen, cyano, nitro, CF_3, OCF_3, $(C_1$-$C_4)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_3$-$C_7)$cycloalkenyl, 3-10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from N, O and S, phenyl, naphthyl, OR_a, SR_a, $S(=O)R_a$, $S(=O)_2R_a$, $S(=O)_2OR_a$, NR_bR_c, $C(=O)OR_a$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_a$, $NR_aC(=O)NR_bR_c$, $NR_bC(=O)R_a$, $(CR_8R_9)_q$-OH, $(C_1$-$C_4)$alkyl substituted with one or more halogen, $(CR_8R_9)_q$-O-$(C_1$-$C_4)$alkyl, $(CR_8R_9)_q$-$(C=O)$O-$(C_1$-$C_4)$alkyl, $(CR_8R_9)_q$-$(C=O)$O-aryl, $(CR_8R_9)_q$-$(C=O)$OH, $(CR_8R_9)_q$-NR_bR_c, $(CR_8R_9)_q$-cycloalkyl, $(CR_8R_9)_q$-phenyl, or $(CR_8R_9)_q$-heteroaryl;

each of R_8 and R_9 is independently H or $(C_1$-$C_4)$alkyl;

each occurrence of R_a, R_b, and R_c is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycle, or aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and

each q is independently 0, 1, 2, 3, or 4.

36. The compound of any one of claims 2-35, wherein:

each R_6 is independently hydrogen, halogen, cyano, nitro, CF_3, OCF_3, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl, 3-10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from N, O and S, phenyl, naphthyl, $(CH_2)_q$-OH, $(CH_2)_q$-O-$(C_1$-$C_4)$alkyl, $(CH_2)_q$-$(C=O)$O-$(C_1$-$C_4)$alkyl, $(CH_2)_q$-$(C=O)$O-aryl, $(CH_2)_q$-$(C=O)$OH, $(CH_2)_q$-NR_bR_c,

$(CH_2)_q$-$(C_3$-$C_7)$cycloalkyl or $(CH_2)_q$-substituted $(C_3$-$C_7)$cycloalkyl, $(CH_2)_q$-phenyl, or $(CH_2)_q$-heteroaryl;

each occurrence of R_b, and R_c is independently hydrogen, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl, 3-10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from N, O and S, or aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and

each q is independently 0, 1, 2, 3, or 4.

37. The compound of any one of claims 2-36, wherein:

each occurrence of R_b, and R_c is independently hydrogen or $(C_1$-$C_4)$alkyl, or said R_b and R_c together with the N to which they are bonded optionally form a 3-8 membered heterocycle.

38. The compound of claim 1 selected from Examples 1 through 52.

39. A pharmaceutical composition comprising at least one compound according to any one of claims 1-38 and a pharmaceutically-acceptable carrier or diluent.

40. A method for treating or preventing a viral infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of claims 1-38.

41. A method for treating or preventing HIV infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of claims 1-38.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/45761

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 37/18 (2012.01)
USPC - 514/616; 546/169
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/616; 546/169
IPC: A01N 37/18 (2012.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC:546/169 (See search words below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST: PGPB, USPT, USOC, EPAB, JPAB
Google: Scholar/Patents: HIV-1 capsid inhibitors crystal structure pyrazole phenyl propanamide amide peptidic imidazole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SHI etal. Small-Molecule Inhibition of Human Immunodeficiency Virus Type 1 Infection by Virus Capsid Destabilization, Journal of Virology, January 2011, Vol 85, pp 542-549. pg 543, Figure 1A; pg 548, Col 2, para 2	1-41
Y	PORNILLOS etal. X-ray Structures of the Hexameric Building Block of the HIV Capsid, Cell, 2009, Vol 137, pp 1282-1292. pg 1, abstract; pg 3, para 3 to pg 4, para 1; pg 14, Figure 2; pg16, Figure 3; pg 18, Figure 4; pg 19, Figure 5	1-41

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 September 2012 (03.09.2012)	24 SEP 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)