COMPOUNDS, COMPOSITIONS, AND METHODS

FIELD

[0001] The present disclosure relates generally to small molecule modulators of caspase 1 and their use as therapeutic agents.

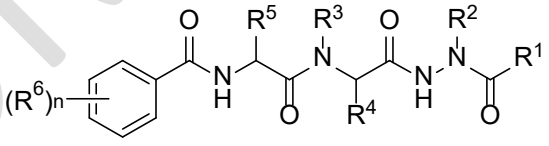
BACKGROUND

[0002] Caspases are conserved family of aspartic acid-directed cysteinyl proteases that have essential functions in apoptosis, inflammation, cell survival, proliferation and differentiation. Caspases are cysteine proteases so named due to strict specificity for cleaving peptide sequences C-terminal to aspartic acids residues. Currently, 12 caspase isozymes have been identified in humans with numerous reported activities. Caspases are often subcategorized as either pro-apoptotic or pro-inflammatory enzymes. A prominent member of the pro-inflammatory class is caspase 1 (also known as interleukin-converting enzyme or ICE) which is responsible for the proteolytic activation of interleukin (IL)-1β and IL-18. IL-1β and IL-18 are cytokines that play a major role in the immune response and within numerous autoimmune and inflammatory diseases. Caspase 1 is constitutively and inducibly expressed in immune response elements such as T cells, macrophages and neutrophils.

DESCRIPTION

[0003] Provided herein are compounds, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, that are useful in treating and/or preventing diseases mediated, at least in part, by caspase 1.

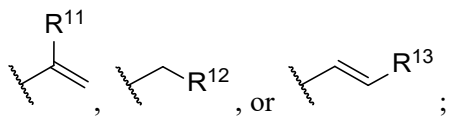
[0004] Provided herein are compounds of Formula I:



I

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

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

R^1 is  ;

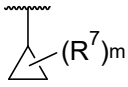
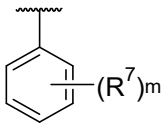
R^{11} is hydrogen, fluoro, chloro, cyano, $-CF_3$, or aryl; wherein the aryl is independently optionally substituted with one to five halo;

R^{12} is hydrogen, fluoro, chloro, cyano, $-CF_3$, aryl, or -O-aryl; wherein the aryl or -O-aryl is independently optionally substituted with one to five halo;

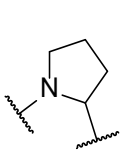
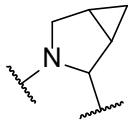
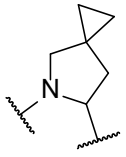
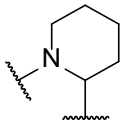
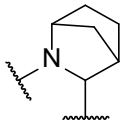
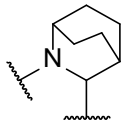
R^{13} is C_{1-6} alkyl, $-C(O)OR^8$, or $-C(O)N(R^8)_2$;

R^2 is hydrogen or C_{1-6} alkyl substituted with one to six substituents independently selected from halo, hydroxy, -C(O)OH, $-C(O)OC_{1-6}$ alkyl, and tetrazolyl, wherein each $-C(O)OC_{1-6}$ alkyl or tetrazolyl is independently optionally substituted with one to five Z^{1a};

R^3 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

R^4 is  or  , wherein m is 0, 1, 2, 3, 4, or 5;

or R^3 and R^4 together with the atoms to which they are attached form a ring selected from

 ,  ,  ,  ,  , and  ; wherein each is optionally substituted by oxo or a C_{3-6} spirocycle;

R^5 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1b};

each R^6 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-C(O)N(R^{16})_2$, $-NR^{16}C(O)R^{16}$, $-OC(O)N(R^{16})_2$, $-NR^{16}C(O)OR^{16}$, $-S(O)_{0-2}R^{16}$, $-NR^{16}S(O)_{1-2}R^{16}$, $-NR^{16}C(O)N(R^{16})_2$, or $-NR^{16}S(O)_{1-2}N(R^{16})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a}; or two R^6 together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each R^7 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-OR^{17}$, $-N(R^{17})_2$, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-OC(O)R^{17}$, $-C(O)N(R^{17})_2$, $-NR^{17}C(O)R^{17}$, $-OC(O)N(R^{17})_2$, $-NR^{17}C(O)OR^{17}$, $-S(O)_{0-2}R^{17}$, $-NR^{17}S(O)_{1-2}R^{17}$, $-NR^{17}C(O)N(R^{17})_2$, or $-NR^{17}S(O)_{1-2}N(R^{17})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a}; or two R^5 together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each R^8 is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each R^{16} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each Z^{1a} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-C(O)N(R^{10})_2$, $-NR^{10}C(O)R^{10}$, $-OC(O)N(R^{10})_2$, $-NR^{10}C(O)OR^{10}$, $-S(O)_{0-2}R^{10}$, $-NR^{10}S(O)_{1-2}R^{10}$, $-NR^{10}C(O)N(R^{10})_2$, or $-NR^{10}S(O)_{1-2}N(R^{10})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1b};

each R^{10} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1b};

each R^{17} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each Z^{1b} is independently halo, cyano, -OH, -SH, $-NH_2$, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C_{1-6} alkyl, -L-C_{2-6} alkenyl, -L-C_{2-6} alkynyl, -L-C_{1-6} haloalkyl, -L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, $-S(O)_2-$, -N(C_{1-6} alkyl)-, -N(C_{2-6} alkenyl)-, -N(C_{2-6} alkynyl)-, -N(C_{1-6} haloalkyl)-, -N(C_{3-10} cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C_{1-6} alkyl)-, -C(O)N(C_{2-6} alkenyl)-, -C(O)N(C_{2-6} alkynyl)-, -C(O)N(C_{1-6} haloalkyl)-, -C(O)N(C_{3-10} cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -OC(O)NH-, -OC(O)N(C_{1-6} alkyl)-, -OC(O)N(C_{2-6} alkenyl)-, -OC(O)N(C_{2-6} alkynyl)-, -OC(O)N(C_{1-6} haloalkyl)-, -OC(O)N(C_{3-10} cycloalkyl)-, -OC(O)N(heterocyclyl)-, -OC(O)N(aryl)-, -OC(O)N(heteroaryl)-, -NHC(O)-, -N(C_{1-6} alkyl)C(O)-, -N(C_{2-6} alkenyl)C(O)-, -N(C_{2-6} alkynyl)C(O)-, -N(C_{1-6} haloalkyl)C(O)-, -N(C_{3-10} cycloalkyl)C(O)-, -N(heterocyclyl)C(O)-, -N(aryl)C(O)-, -N(heteroaryl)C(O)-, -NHC(O)O-, -N(C_{1-6} alkyl)C(O)O-, -N(C_{2-6} alkenyl)C(O)O-, -N(C_{2-6} alkynyl)C(O)O-, -N(C_{1-6} haloalkyl)C(O)O-, -N(C_{3-10} cycloalkyl)C(O)O-, -N(heterocyclyl)C(O)O-, -N(aryl)C(O)O-, -N(heteroaryl)C(O)O-, -NHC(O)NH-, -NHS(O)-, -S(O)NH-, $-S(O)_2NH-$, -NHS(O)NH-, or $-NHS(O)_2NH-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1b} and L is further independently optionally substituted with one to six halo, cyano, hydroxy, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl.

[0005] In another embodiment, provided is a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

[0006] In another embodiment, provided is a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, and a pharmaceutically acceptable carrier.

[0007] In another embodiment, provided is a method for treating a disease or condition, at least in part, by a caspase 1 inhibitor, the method comprising administering an effective amount of the pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, and a pharmaceutically acceptable carrier, to a subject in need thereof.

[0008] In another embodiment, provided is a method for treating a disease or condition, at least in part, by inhibiting caspase 1, the method comprising administering an effective amount of the pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, and a pharmaceutically acceptable carrier, to a subject in need thereof.

[0009] The disclosure also provides compositions, including pharmaceutical compositions, kits that include the compounds, and methods of using (or administering) and making the compounds. The disclosure further provides compounds or compositions thereof for use in a method of treating a disease, disorder, or condition that is mediated, at least in part, by caspase 1. Moreover, the disclosure provides uses of the compounds or compositions thereof in the manufacture of a medicament for the treatment of a disease, disorder, or condition selected from chronic kidney disease, diabetic nephropathy, IgA nephropathy, uveitis, an excess dietary alcohol intake disease, a necrotic disease, a viral mediated disease, inflammatory peritonitis, osteoarthritis, pancreatitis (e.g., acute pancreatitis or chronic pancreatitis), asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes (e.g., juvenile diabetes, insulin-dependent diabetes mellitus (Type I)), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, atopic dermatitis, scarring, graft vs. host disease, organ transplant rejection, osteoporosis, multiple myeloma-related bone disorder, leukemias and related disorders, myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, hemorrhagic shock, sepsis, septic shock, burns, Shigellosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, Kennedy's disease, prion disease, cerebral ischemia, epilepsy, myocardial ischemia, acute or chronic heart disease, myocardial infarction, congestive heart failure, atherosclerosis, coronary artery bypass graft, spinal muscular atrophy, amyotrophic lateral sclerosis, multiple sclerosis, HIV- or AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, neurological damage due to stroke, ulcerative colitis, traumatic brain injury, spinal cord injury, various forms of liver disease, infectious hepatitis, hepatitis-B, hepatitis-C, hepatitis-G, yellow fever, dengue fever, Japanese encephalitis, lichenplanus, acute dermatomyositis, eczema, primary cirrhosis, Behcet's disease, atopic skin disease, pure red cell aplasia, aplastic anemia, nephrotic syndrome, renal disease, renal tubulointerstitial fibrosis, neointimal hyperplasia (NH) in the arteries, polyaptic kidney disease, H. pylori-associated gastric and duodenal ulcer disease, HIV infection, tuberculosis, and meningitis.

[0010] In another embodiment, provided is a method for treating a disease, disorder, or condition selected from chronic kidney disease, diabetic nephropathy, and IgA nephropathy by inhibiting caspase 1. In certain embodiments, the method comprising administering an effective amount of a compound which inhibits caspase 1, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, and a pharmaceutically acceptable carrier, to a subject in need thereof.

[0011] In certain embodiments, provided is a method for treating chronic kidney disease, diabetic nephropathy, or IgA nephropathy, comprising administering an effective amount of a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, and a pharmaceutically acceptable carrier, to a subject in need thereof.

DETAILED DESCRIPTION

[0012] The following description sets forth exemplary embodiments of the present technology. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

1. Definitions

[0013] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0014] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-C(O)NH_2$ is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line or a dashed line drawn through a line in a structure indicates a specified point of attachment of a group. Unless chemically or structurally required, no directionality or stereochemistry is indicated or implied by the order in which a chemical group is written or named.

[0015] The prefix "C_{u-v}" indicates that the following group has from u to v carbon atoms. For example, "C_{1-6} alkyl" indicates that the alkyl group has from 1 to 6 carbon atoms.

[0016] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. In certain embodiments, the term "about" includes the indicated amount ± 10%. In other embodiments, the term "about" includes the indicated amount ± 5%. In certain other embodiments, the term "about" includes the indicated amount ± 1%. Also, to the term "about X"

includes description of "X". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0017] "Alkyl" refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (i.e., C_{1-20} alkyl), 1 to 12 carbon atoms (i.e., C_{1-12} alkyl), 1 to 8 carbon atoms (i.e., C_{1-8} alkyl), 1 to 6 carbon atoms (i.e., C_{1-6} alkyl) or 1 to 4 carbon atoms (i.e., C_{1-4} alkyl). Examples of alkyl groups include, e.g., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, "butyl" includes n-butyl (i.e., $-(CH_2)_3CH_3$), sec-butyl (i.e., $-CH(CH_3)CH_2CH_3$), isobutyl (i.e., $-CH_2CH(CH_3)_2$) and tert-butyl (i.e., $-C(CH_3)_3$); and "propyl" includes n-propyl (i.e., $-(CH_2)_2CH_3$), and isopropyl (i.e., $-CH(CH_3)_2$).

[0018] Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent "alkyl" group, a divalent "aryl" group, etc., may also be referred to as an "alkylene" group or an "alkylenyl" group, an "arylene" group, or an "arylenyl" group, respectively. Also, unless indicated explicitly otherwise, where combinations of groups are referred to herein as one moiety, e.g., arylalkyl or aralkyl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule.

[0019] "Alkenyl" refers to an alkyl group containing at least one carbon-carbon double bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkenyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkenyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkenyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkenyl). Examples of alkenyl groups include, e.g., ethenyl, propenyl, and butadienyl (including 1,2-butadienyl and 1,3-butadienyl).

[0020] "Alkynyl" refers to an alkyl group containing at least one carbon-carbon triple bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkynyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkynyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkynyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkynyl). The term "alkynyl" also includes those groups having one triple bond and one double bond.

[0021] "Alkoxy" refers to the group "alkyl-O-". Examples of alkoxy groups include, e.g., methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy.

[0022] "Alkoxyalkyl" refers to the group "alkyl-O-alkyl".

[0023] "Alkylthio" refers to the group "alkyl-S-". "Alkylsulfinyl" refers to the group "alkyl-S(O)-". "Alkylsulfonyl" refers to the group "alkyl-$S(O)_2$-". "Alkylsulfonylalkyl" refers to -alkyl-$S(O)_2$-alkyl.

[0024] "Acyl" refers to a group -$C(O)R^y$, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include, e.g., formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethyl-carbonyl, and benzoyl.

[0025] "Amido" refers to both a "C-amido" group which refers to the group -$C(O)NR^yR^z$ and an "N-amido" group which refers to the group -$NR^yC(O)R^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein, or R^y and R^z are taken together to form a cycloalkyl or heterocyclyl; each of which may be optionally substituted, as defined herein.

[0026] "Amino" refers to the group -NR^yR^z wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0027] "Aminoalkyl" refers to the group "-alkyl-NR^yR^z," wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0028] "Amidino" refers to -$C(NR^y)(NR^z{}_2)$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0029] "Aryl" refers to an aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring carbon atoms (i.e., $C_{6\text{-}20}$ aryl), 6 to 12 carbon ring atoms (i.e., $C_{6\text{-}12}$ aryl), or 6 to 10 carbon ring atoms (i.e., $C_{6\text{-}10}$ aryl). Examples of aryl groups include, e.g., phenyl, naphthyl, fluorenyl and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl, the resulting ring system is heteroaryl. If one or more aryl groups are fused with a heterocyclyl, the resulting ring system is heterocyclyl.

[0030] "Arylalkyl" or "Aralkyl" refers to the group "aryl-alkyl-".

[0031] "Carbamoyl" refers to both an "O-carbamoyl" group which refers to the group -O-C(O)NR^yR^z and an "N-carbamoyl" group which refers to the group -$NR^yC(O)OR^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0032] "Carboxyl ester" or "ester" refer to both -$OC(O)R^x$ and -$C(O)OR^x$, wherein R^x is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0033] "Cyanoalkyl" refers to refers to an alkyl group as defined above, wherein one or more (e.g., one to three) hydrogen atoms are replaced by a cyano (-CN) group.

[0034] "Cycloalkyl" refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups (i.e., the cyclic group having at least one double bond) and carbocyclic fused ring systems having at least one sp^3 carbon atom (i.e., at least one non-aromatic ring). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl). Monocyclic groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic groups include, for example, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Further, the term cycloalkyl is intended to encompass any non-aromatic ring which may be fused to an aryl ring, regardless of the attachment to the remainder of the molecule. Still further, cycloalkyl also includes "spirocycloalkyl" when there are two positions for substitution on the same carbon atom, for example spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl.

[0035] "Cycloalkoxy" refers to "-O-cycloalkyl."

[0036] "Cycloalkylalkyl" refers to the group "cycloalkyl-alkyl-".

[0037] "Cycloalkylalkoxy" refers to "-O-alkyl-cycloalkyl."

[0038] "Guanidino" refers to -$NR^yC(=NR^z)(NR^yR^z)$, wherein each R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0039] "Hydrazino" refers to -$NHNH_2$.

[0040] "Imino" refers to a group -C(NR^y)R^z, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0041] "Imido" refers to a group -C(O)NR^{y}C(O)R^z, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0042] "Halogen" or "halo" refers to atoms occupying group VIIA of the periodic table, such as fluoro, chloro, bromo, or iodo.

[0043] "Haloalkyl" refers to an unbranched or branched alkyl group as defined above, wherein one or more (e.g., one to five or one to three) hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two ("di") or three ("tri") halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include, e.g., trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0044] "Haloalkoxy" refers to an alkoxy group as defined above, wherein one or more (e.g., one to five or one to three) hydrogen atoms are replaced by a halogen.

[0045] "Hydroxyalkyl" refers to an alkyl group as defined above, wherein one or more (e.g., one to five or one to three) hydrogen atoms are replaced by a hydroxy group.

[0046] "Heteroalkyl" refers to an alkyl group in which one or more (e.g., one to five or one to three) of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group, provided the point of attachment to the remainder of the molecule is through a carbon atom. The term "heteroalkyl" includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, -NR^y-, -O-, -S-, -S(O)-, -S(O)$_2$-, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkyl groups include, e.g., ethers (e.g., -CH_2OCH_3, -$CH(CH_3)OCH_3$, -$CH_2CH_2OCH_3$,
-$CH_2CH_2OCH_2CH_2OCH_3$, etc.), thioethers (e.g., -CH_2SCH_3, -$CH(CH_3)SCH_3$, -$CH_2CH_2SCH_3$, -$CH_2CH_2SCH_2CH_2SCH_3$, etc.), sulfones (e.g., -$CH_2S(O)_2CH_3$, -$CH(CH_3)S(O)_2CH_3$, -

$CH_2CH_2S(O)_2CH_3$,
$-CH_2CH_2S(O)_2CH_2CH_2OCH_3$, etc.), and amines (e.g., $-CH_2NR^yCH_3$, $-CH(CH_3)NR^yCH_3$, $-CH_2CH_2NR^yCH_3$, $-CH_2CH_2NR^yCH_2CH_2NR^yCH_3$, etc., where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein). As used herein, heteroalkyl includes 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

[0047] "Heteroalkylene" refers to a divalent alkyl group (i.e., alkylene) in which one or more (e.g., one to five or one to three) of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group. "Heteroalkylene" groups must have at least one carbon and at least one heteroatomic group within the chain. The term "heteroalkylene" includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, $-NR^y-$, -O-, -S-, -S(O)-, $-S(O)_2-$, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkylene groups include, e.g., $-CH_2OCH_2-$, $-CH(CH_3)OCH_2-$, $-CH_2CH_2OCH_2-$, $-CH_2CH_2OCH_2CH_2OCH_2-$, $-CH_2SCH_2-$, $-CH(CH_3)SCH_2-$, $-CH_2CH_2SCH_2-$, $-CH_2CH_2SCH_2CH_2SCH_2-$, $-CH_2S(O)_2CH_2-$, $-CH(CH_3)S(O)_2CH_2-$, $-CH_2CH_2S(O)_2CH_2-$, $-CH_2CH_2S(O)_2CH_2CH_2OCH_2-$, $-CH_2NR^yCH_2-$, $-CH(CH_3)NR^yCH_2-$, $-CH_2CH_2NR^yCH_2-$, $-CH_2CH_2NR^yCH_2CH_2NR^yCH_2-$, etc., where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein). As used herein, heteroalkylene includes 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom. As used herein, the term "heteroalkylene" does not include groups such as amides or other functional groups having an oxo present on one or more carbon atoms.

[0048] "Heteroaryl" refers to an aromatic group having a single ring, multiple rings or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms (i.e., C_{1-20} heteroaryl), 3 to 12 ring carbon atoms (i.e., C_{3-12} heteroaryl), or 3 to 8 carbon ring atoms (i.e., C_{3-8} heteroaryl); and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. In certain instances, heteroaryl includes 5-10 membered ring systems, 5-7 membered ring systems, or 5-6 membered ring systems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. Examples of heteroaryl groups

include, e.g., acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, phenazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, and triazinyl. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinolinyl, isoquinolinyl, benzo[b]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl, and imidazo[1,5-a]pyridinyl, where the heteroaryl can be bound via either ring of the fused system. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

[0049] "Heteroarylalkyl" refers to the group "heteroaryl-alkyl-".

[0050] "Heterocyclyl" refers to a saturated or partially unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. The term "heterocyclyl" includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged or spiro, and may comprise one or more (e.g., one to three or one or two) oxo (=O) or N-oxide ($-O^-$) moieties. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to an aryl or heteroaryl ring, regardless of the attachment to the remainder of the molecule. As used herein, heterocyclyl has 2 to 20 ring carbon atoms (i.e., C_{2-20} heterocyclyl), 2 to 12 ring carbon atoms (i.e., C_{2-12} heterocyclyl), 2 to 10 ring carbon atoms (i.e., C_{2-10} heterocyclyl), 2 to 8 ring carbon atoms (i.e., C_{2-8} heterocyclyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} heterocyclyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} heterocyclyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} heterocyclyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur or oxygen. Examples of heterocyclyl groups include, e.g., azetidinyl, azepinyl, benzodioxolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzopyranyl, benzodioxinyl, benzopyranonyl, benzofuranonyl, dioxolanyl, dihydropyranyl, hydropyranyl, thienyl[1,3]dithianyl,

decahydroisoquinolyl, furanonyl, imidazolinyl, imidazolidinyl, indolinyl, indolizinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, oxiranyl, oxetanyl, phenothiazinyl, phenoxazinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, tetrahydropyranyl, trithianyl, tetrahydroquinolinyl, thiophenyl (i.e., thienyl), tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl and 1,1-dioxo-thiomorpholinyl. The term "heterocyclyl" also includes "spiroheterocyclyl" when there are two positions for substitution on the same carbon atom. Examples of the spiro-heterocyclyl rings include, e.g., bicyclic and tricyclic ring systems, such as 2-oxa-7-azaspiro[3.5]nonanyl, 2-oxa-6-azaspiro[3.4]octanyl and 6-oxa-1-azaspiro[3.3]heptanyl. Examples of the fused-heterocyclyl rings include, but are not limited to, 1,2,3,4-tetrahydroisoquinolinyl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridinyl, indolinyl, and isoindolinyl, where the heterocyclyl can be bound via either ring of the fused system.

[0051] "Heterocyclylalkyl" refers to the group "heterocyclyl-alkyl-".

[0052] "Oxime" refers to the group $-CR^y(=NOH)$ wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0053] "Sulfonyl" refers to the group $-S(O)_2R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfonyl are methylsulfonyl, ethylsulfonyl, phenylsulfonyl, and toluenesulfonyl.

[0054] "Sulfinyl" refers to the group $-S(O)R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfinyl are methylsulfinyl, ethylsulfinyl, phenylsulfinyl, and toluenesulfinyl.

[0055] "Sulfonamido" refers to the groups $-SO_2NR^yR^z$ and $-NR^ySO_2R^z$, where R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0056] The terms "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term "optionally substituted" refers to any one or more (e.g., one to five or one to three) hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

[0057] In certain embodiments, R^y and R^z as used herein are optionally substituted. In certain embodiments, R^y and R^z as used herein are unsubstituted.

[0058] The term "substituted" used herein means any of the above groups (i.e., alkyl, alkenyl, alkynyl, alkylene, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, aryl, heterocyclyl, heteroaryl, and/or heteroalkyl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atom such as, but not limited to alkyl, alkenyl, alkynyl, alkoxy, alkylthio, acyl, amido, amino, amidino, aryl, aralkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, cycloalkyl, cycloalkylalkyl, guanadino, halo, haloalkyl, haloalkoxy, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydrazine, hydrazone, imino, imido, hydroxy, oxo, oxime, nitro, sulfonyl, sulfinyl, alkylsulfonyl, alkylsulfinyl, sulfinic acid, sulfonic acid, sulfonamido, thiol, thioxo, N-oxide, or $-Si(R^y)_3$ wherein each R^y is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl.

[0059] In certain embodiments, "substituted" includes any of the above alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl groups in which one or more (e.g., one to five or one to three) hydrogen atoms are independently replaced with deuterium, halo, cyano, nitro, azido, oxo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NR^gR^h$, $-NR^gC(=O)R^h$, $-NR^gC(=O)NR^gR^h$, $-NR^gC(=O)OR^h$, $-NR^gS(=O)_{1-2}R^h$, $-C(=O)R^g$, $-C(=O)OR^g$, $-OC(=O)OR^g$, $-OC(=O)R^g$, $-C(=O)NR^gR^h$, $-OC(=O)NR^gR^h$, $-OR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-OS(=O)_{1-2}R^g$, $-S(=O)_{1-2}OR^g$, $-NR^gS(=O)_{1-2}NR^gR^h$, $=NSO_2R^g$, $=NOR^g$, $-S(=O)_{1-2}NR^gR^h$, $-SF_5$, $-SCF_3$, or $-OCF_3$. In certain embodiments, "substituted" also means any of the above groups in which one or more (e.g., one to five or one to three) hydrogen atoms are replaced with $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^gR^h$, $-CH_2SO_2R^g$, or $-CH_2SO_2NR^gR^h$. In the foregoing, R^g and R^h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and/or heteroarylalkyl. In certain embodiments, "substituted" also means any of the above groups in which one or more (e.g., one to five or one to three) hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, N-heterocyclyl, heterocyclylalkyl, heteroaryl, and/or heteroarylalkyl, or two of R^g and R^h and R^i are taken together with the atoms to which they are attached form a heterocyclyl ring optionally substituted with oxo, halo or alkyl optionally substituted with oxo, halo, amino, hydroxyl, or alkoxy.

[0060] Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group,

etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substitutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to ((substituted aryl)substituted aryl)substituted aryl. Similarly, the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan. When used to modify a chemical group, the term "substituted" may describe other chemical groups defined herein.

[0061] In certain embodiments, as used herein, the phrase "one or more" refers to one to five. In certain embodiments, as used herein, the phrase "one or more" refers to one to three.

[0062] Any compound or structure given herein, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. These forms of compounds may also be referred to as "isotopically enriched analogs." Isotopically labeled compounds have structures depicted herein, except that one or more (e.g., one to five or one to three) atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

[0063] The term "isotopically enriched analogs" includes "deuterated analogs" of compounds described herein in which one or more (e.g., one to five or one to three) hydrogens is/are replaced by deuterium, such as a hydrogen on a carbon atom. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound when administered to a mammal, particularly a human. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more (e.g., one to five or one to three) hydrogens have been replaced by deuterium.

[0064] Deuterium labelled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic

advantages resulting from greater metabolic stability, for example increased *in vivo* half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F, ^{3}H, ^{11}C labeled compound may be useful for PET or SPECT or other imaging studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in a compound described herein.

[0065] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

[0066] In many cases, the compounds of this disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[0067] Provided are also or a pharmaceutically acceptable salt, isotopically enriched analog, deuterated analog, stereoisomer, mixture of stereoisomers, and prodrugs of the compounds described herein. "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0068] The term "pharmaceutically acceptable salt" of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" or "physiologically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like.

Salts derived from organic acids include, e.g., acetic acid, propionic acid, gluconic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, aluminum, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines (i.e., NH_2(alkyl)), dialkyl amines (i.e., HN(alkyl)$_2$), trialkyl amines (i.e., N(alkyl)$_3$), substituted alkyl amines (i.e., NH_2(substituted alkyl)), di(substituted alkyl) amines (i.e., HN(substituted alkyl)$_2$), tri(substituted alkyl) amines (i.e., N(substituted alkyl)$_3$), alkenyl amines (i.e., NH_2(alkenyl)), dialkenyl amines (i.e., HN(alkenyl)$_2$), trialkenyl amines (i.e., N(alkenyl)$_3$), substituted alkenyl amines (i.e., NH_2(substituted alkenyl)), di(substituted alkenyl) amines (i.e., HN(substituted alkenyl)$_2$), tri(substituted alkenyl) amines (i.e., N(substituted alkenyl)$_3$, mono-, di- or tri- cycloalkyl amines (i.e., NH_2(cycloalkyl), HN(cycloalkyl)$_2$, N(cycloalkyl)$_3$), mono-, di- or tri- arylamines (i.e., NH_2(aryl), HN(aryl)$_2$, N(aryl)$_3$) or mixed amines, etc. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0069] The term “hydrate” refers to the complex formed by the combining of a compound described herein and water.

[0070] A “solvate” refers to an association or complex of one or more solvent molecules and a compound of the disclosure. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, dimethylsulfoxide, ethylacetate, acetic acid and ethanolamine.

[0071] Some of the compounds exist as tautomers. Tautomers are in equilibrium with one another. For example, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown and regardless of the nature of the equilibrium among tautomers, the compounds are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, the amide containing compounds are understood to include their imidic acid tautomers. Likewise, the imidic acid containing compounds are understood to include their amide tautomers.

[0072] The compounds of the invention, or their pharmaceutically acceptable salts include an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino

acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0073] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers," which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

[0074] "Diastereomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0075] Relative centers of the compounds as depicted herein are indicated graphically using the "thick bond" style (bold or parallel lines) and absolute stereochemistry is depicted using wedge bonds (bold or parallel lines).

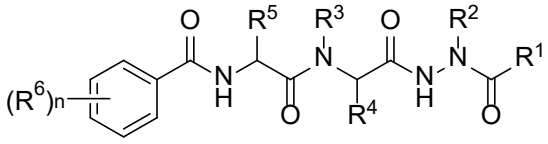
[0076] "Prodrugs" means any compound which releases an active parent drug according to a structure described herein *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound described herein are prepared by modifying functional groups present in the compound described herein in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds described herein wherein a hydroxy, amino, carboxyl, or sulfhydryl group in a compound described herein is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate and benzoate derivatives), amides, guanidines, carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds described herein and the like. Preparation, selection and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series; "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985; and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American

Pharmaceutical Association and Pergamon Press, 1987, each of which are hereby incorporated by reference in their entirety.

2. Compounds

[0077] Provided herein are compounds, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, that are modulators of caspase-1. In certain embodiments, the compounds or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof are inhibitors of caspase-1.

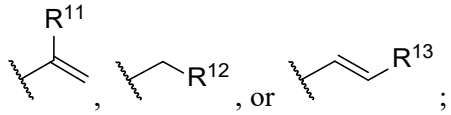
[0078] In certain embodiments, provided is a compound of Formula I:



I

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

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

R^1 is  ;

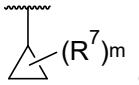
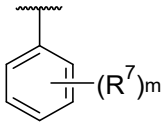
R^{11} is hydrogen, fluoro, chloro, cyano, $-CF_3$, or aryl; wherein the aryl is independently optionally substituted with one to five halo;

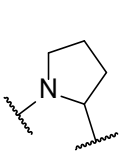
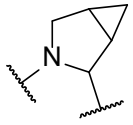
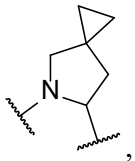
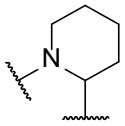
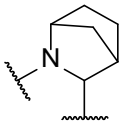
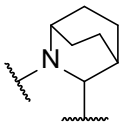
R^{12} is hydrogen, fluoro, chloro, cyano, $-CF_3$, aryl, or -O-aryl; wherein the aryl or -O-aryl is independently optionally substituted with one to five halo;

R^{13} is C_{1-6} alkyl, $-C(O)OR^8$, or $-C(O)N(R^8)_2$;

R^2 is hydrogen or C_{1-6} alkyl substituted with one to six substituents independently selected from halo, hydroxy, -C(O)OH, $-C(O)OC_{1-6}$ alkyl, and tetrazolyl, wherein each $-C(O)OC_{1-6}$ alkyl or tetrazolyl is independently optionally substituted with one to five Z^{1a};

R^3 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

R^4 is  or  , wherein m is 0, 1, 2, 3, 4, or 5;

or R^3 and R^4 together with the atoms to which they are attached form a ring selected from  ,  ,  ,  ,  , and  ; wherein each is optionally substituted by oxo or a C_{3-6} spirocycle;

R^5 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1b};

each R^6 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-C(O)N(R^{16})_2$, $-NR^{16}C(O)R^{16}$, $-OC(O)N(R^{16})_2$, $-NR^{16}C(O)OR^{16}$, $-S(O)_{0-2}R^{16}$, $-NR^{16}S(O)_{1-2}R^{16}$, $-NR^{16}C(O)N(R^{16})_2$, or $-NR^{16}S(O)_{1-2}N(R^{16})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a}; or two R^6 together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each R^7 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-OR^{17}$, $-N(R^{17})_2$, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-OC(O)R^{17}$, $-C(O)N(R^{17})_2$, $-NR^{17}C(O)R^{17}$, $-OC(O)N(R^{17})_2$, $-NR^{17}C(O)OR^{17}$, $-S(O)_{0-2}R^{17}$, $-NR^{17}S(O)_{1-2}R^{17}$, $-NR^{17}C(O)N(R^{17})_2$, or $-NR^{17}S(O)_{1-2}N(R^{17})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a}; or two R^5 together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each R^8 is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each R^{16} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each Z^{1a} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-C(O)N(R^{10})_2$, $-NR^{10}C(O)R^{10}$, $-OC(O)N(R^{10})_2$, $-NR^{10}C(O)OR^{10}$, $-S(O)_{0-2}R^{10}$, $-NR^{10}S(O)_{1-2}R^{10}$, $-NR^{10}C(O)N(R^{10})_2$, or $-NR^{10}S(O)_{1-2}N(R^{10})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1b};

each R^{10} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1b};

each R^{17} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

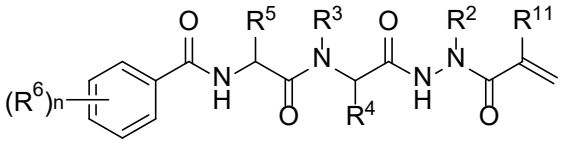
each Z^{1b} is independently halo, cyano, -OH, -SH, $-NH_2$, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C_{1-6} alkyl, -L-C_{2-6} alkenyl, -L-C_{2-6} alkynyl, -L-C_{1-6} haloalkyl, -L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, $-S(O)_2$-, -N(C_{1-6} alkyl)-, -N(C_{2-6} alkenyl)-, -N(C_{2-6} alkynyl)-, -N(C_{1-6} haloalkyl)-, -N(C_{3-10} cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C_{1-6} alkyl)-, -C(O)N(C_{2-6} alkenyl)-, -C(O)N(C_{2-6} alkynyl)-, -C(O)N(C_{1-6} haloalkyl)-, -C(O)N(C_{3-10} cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -OC(O)NH-, -OC(O)N(C_{1-6} alkyl)-, -OC(O)N(C_{2-6} alkenyl)-, -OC(O)N(C_{2-6} alkynyl)-, -OC(O)N(C_{1-6} haloalkyl)-, -OC(O)N(C_{3-10} cycloalkyl)-, -OC(O)N(heterocyclyl)-, -OC(O)N(aryl)-, -OC(O)N(heteroaryl)-, -NHC(O)-, -N(C_{1-6} alkyl)C(O)-, -N(C_{2-6} alkenyl)C(O)-, -N(C_{2-6} alkynyl)C(O)-, -N(C_{1-6} haloalkyl)C(O)-, -N(C_{3-10} cycloalkyl)C(O)-, -N(heterocyclyl)C(O)-, -N(aryl)C(O)-, -N(heteroaryl)C(O)-, -NHC(O)O-, -N(C_{1-6} alkyl)C(O)O-, -N(C_{2-6} alkenyl)C(O)O-, -N(C_{2-6} alkynyl)C(O)O-, -N(C_{1-6} haloalkyl)C(O)O-, -N(C_{3-10} cycloalkyl)C(O)O-, -

N(heterocyclyl)C(O)O-, -N(aryl)C(O)O-, -N(heteroaryl)C(O)O-, -NHC(O)NH-, -NHS(O)-, -S(O)NH-, $-S(O)_2NH-$, -NHS(O)NH-, or $-NHS(O)_2NH-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1b} and L is further independently optionally substituted with one to six halo, cyano, hydroxy, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl.

[0079] In certain embodiments, provided is a compound represented by Formula II:

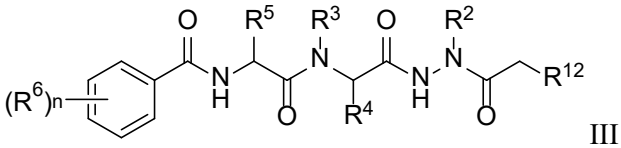


II

wherein n, R^2, R^3, R^4, R^5, R^6, and R^{11}, are each independently as defined herein.

[0080] In certain embodiments, R^{11} is hydrogen or fluoro.

[0081] In certain embodiments, provided is a compound represented by Formula III:



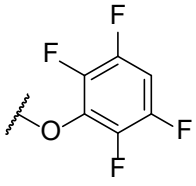
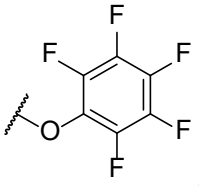
III

wherein n, R^2, R^3, R^4, R^5, R^6, and R^{12}, are each independently as defined herein.

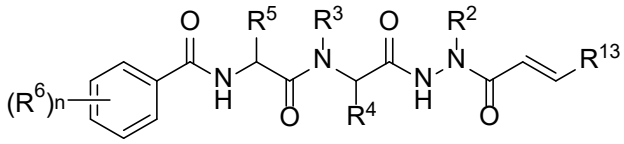
[0082] In certain embodiments, R^{12} is fluoro, chloro, cyano, or -O-aryl optionally substituted with one to five halo.

[0083] In certain embodiments, R^{12} is fluoro, chloro, or cyano.

[0084] In certain embodiments, R^{12} is -O-aryl optionally substituted with one to five halo.

[0085] In certain embodiments, R^{12} is  or  .

[0086] In certain embodiments, provided is a compound represented by Formula IV:

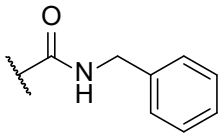


IV

wherein n, R^2, R^3, R^4, R^5, R^6, and R^{13}, are each independently as defined herein.

[0087] In certain embodiments, R^{13} is $-C(O)OR^8$ or $-C(O)N(R^8)_2$.

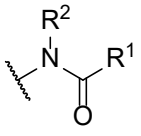
[0088] In certain embodiments, R^{13} is $-C(O)OR^8$ or $-C(O)NHR^8$.

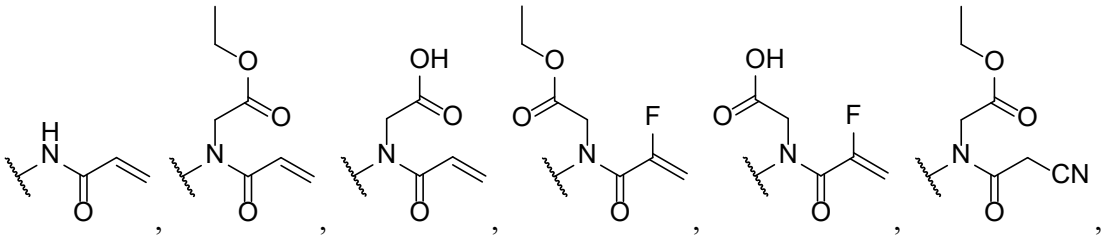
[0089] In certain embodiments, R^{13} is $-C(O)OCH_3$ or  .

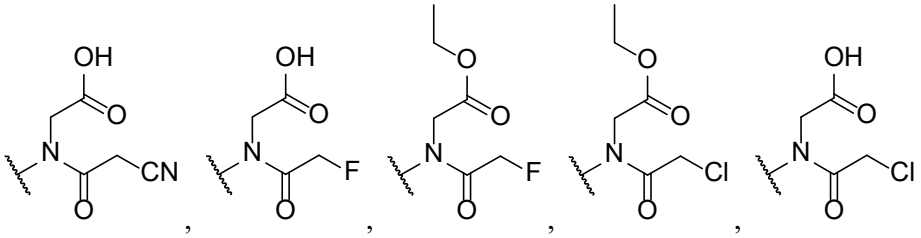
[0090] In certain embodiments, R^2 is hydrogen or C_{1-6} alkyl substituted with one to six substituents independently selected from halo, hydroxy, -C(O)OH, and $-C(O)OC_{1-6}$ alkyl.

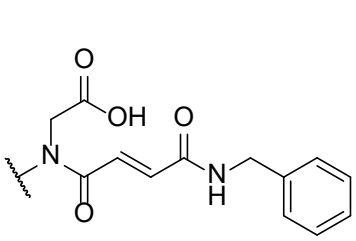
[0091] In certain embodiments, R^2 is hydrogen or C_{1-6} alkyl substituted with $-CH(OH)(CF_3)$, -C(O)OH, or $-C(O)OC_2$ alkyl.

[0092] In certain embodiments, R^2 is hydrogen, $-CH_2CH(OH)(CF_3)$, $-CH_2C(O)OH$, or $-CH_2C(O)OC_2$ alkyl.

[0093] In certain embodiments, the moiety  is:



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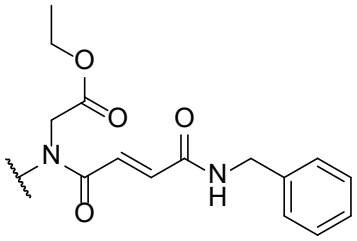
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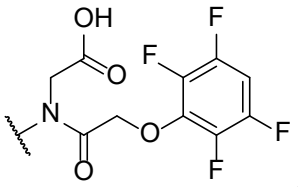
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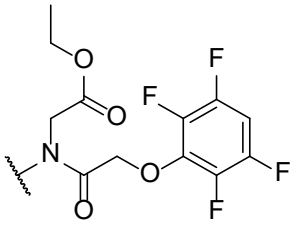
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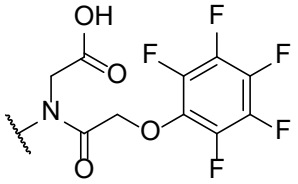
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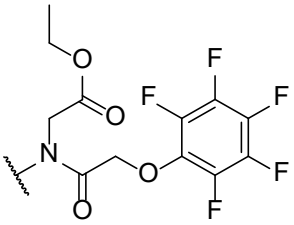
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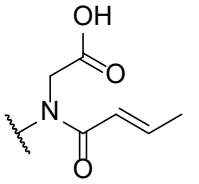
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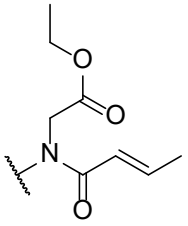
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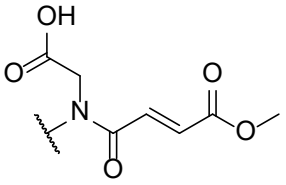
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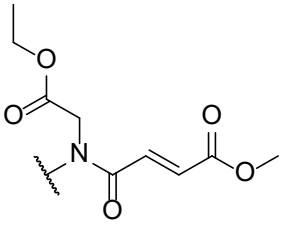
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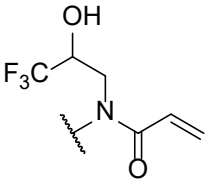
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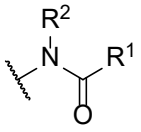
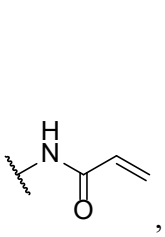
[0094] In certain embodiments, the moiety  is: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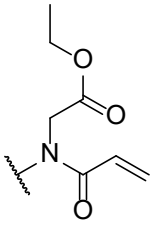
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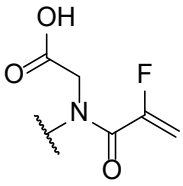
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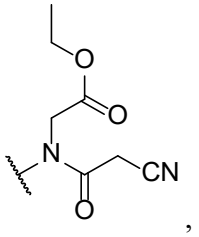
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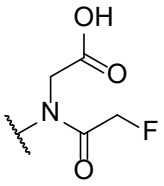
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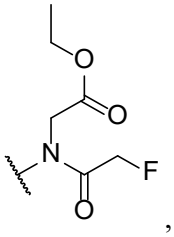
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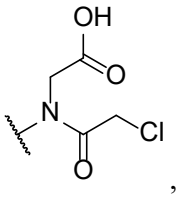
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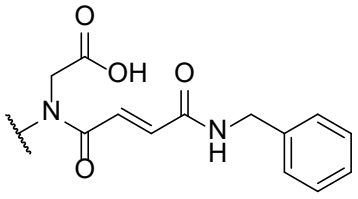
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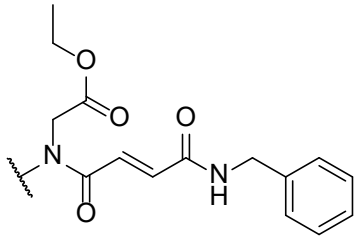
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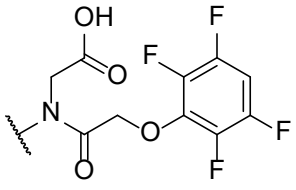
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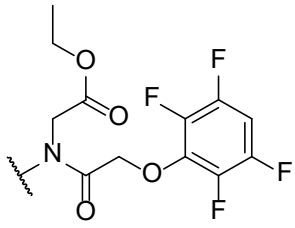
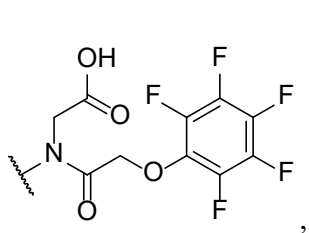
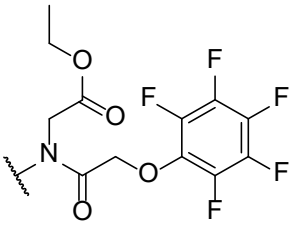
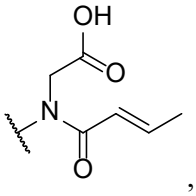
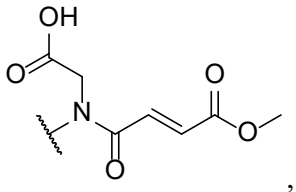
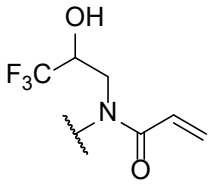
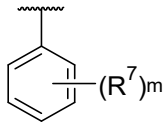
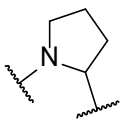
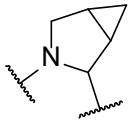
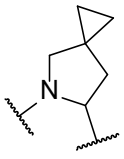
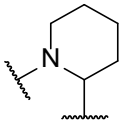
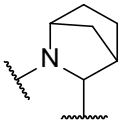
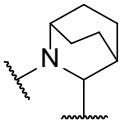
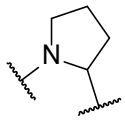
 ,  ,  ,  ,  , or  .

[0095] In certain embodiments, R^3 is hydrogen.

[0096] In certain embodiments, R^3 is hydrogen and R^4 is  or  , wherein m is 0 or 1.

[0097] In certain embodiments, m is 0 or 1, and R^7 is C_{1-6} haloalkyl.

[0098] In certain embodiments, R^3 and R^4 together with the atoms to which they are attached form a ring selected from  ,  ,  ,  ,  , and  ; wherein each is optionally substituted by oxo or a C_{3-6} spirocycle.

[0099] In certain embodiments, R^3 and R^4 together with the atoms to which they are attached form a  .

[0100] In certain embodiments, n is 2.

[0101] In certain embodiments, each R^6 is independently halo or $-N(R^{16})_2$.

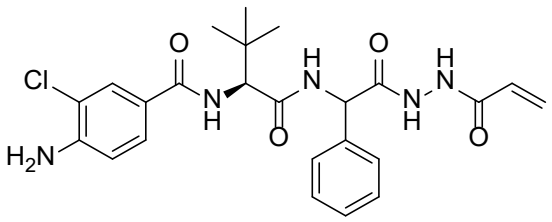
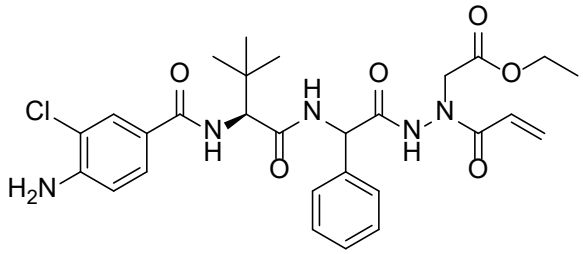
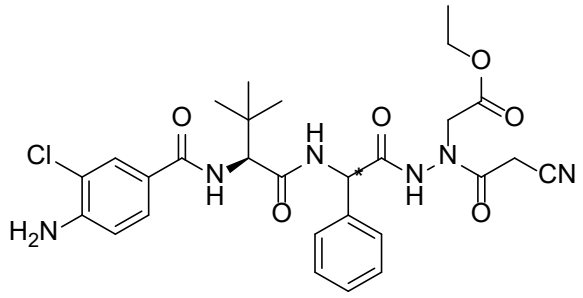
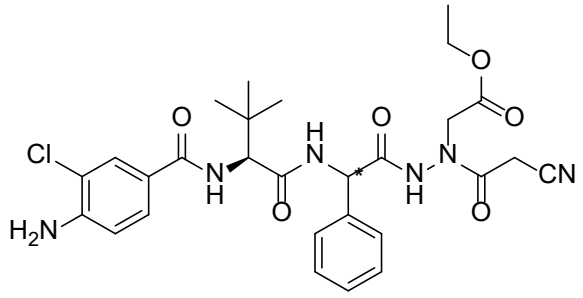
[0102] In certain embodiments, each R^6 is independently chloro or $-NH_2$.

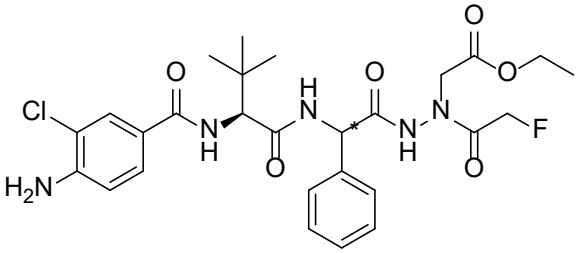
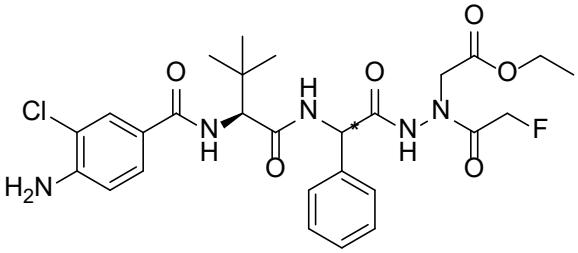
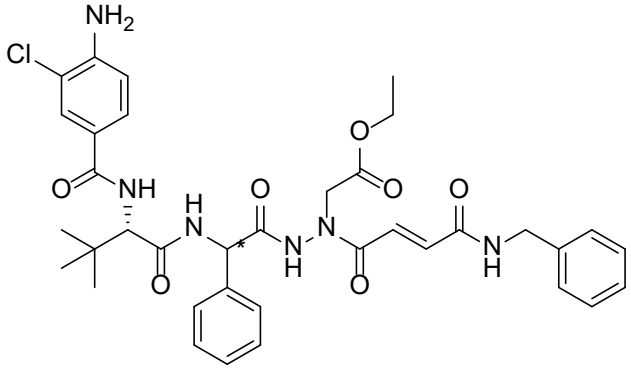
[0103] In certain embodiments, R^5 is C_{1-6} alkyl.

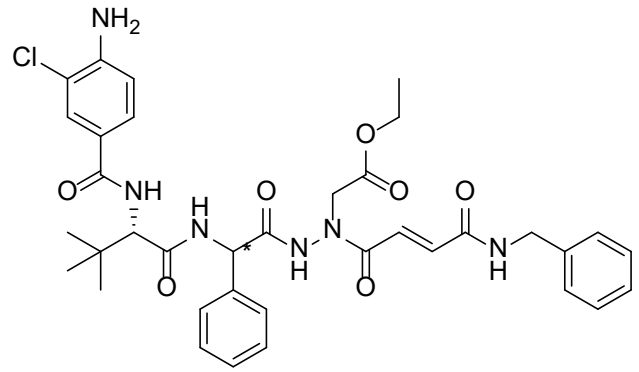
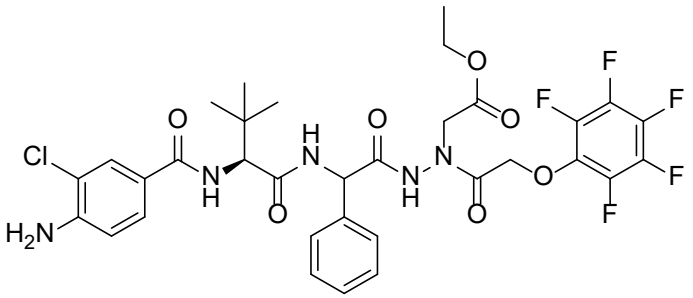
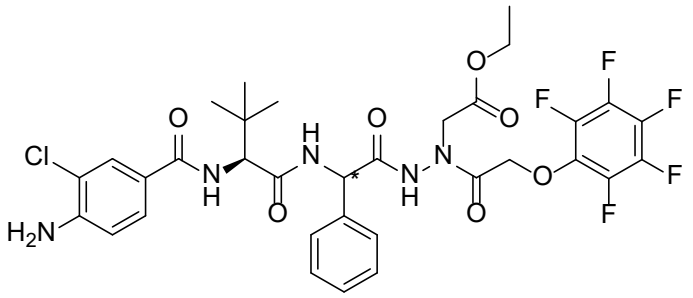
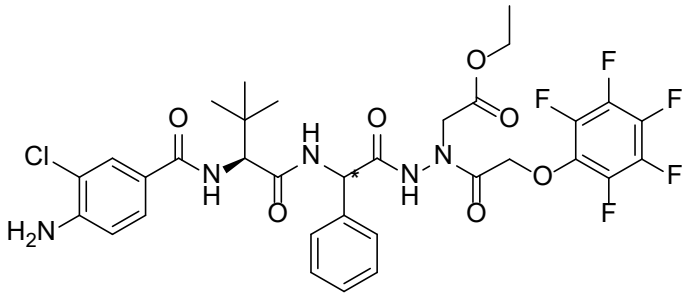
[0104] In certain embodiments, R^5 is *tert*-butyl.

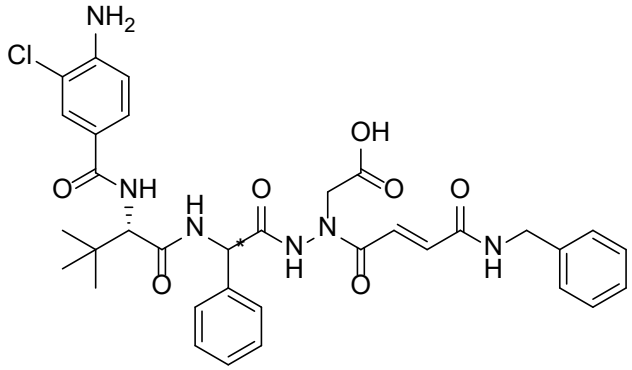
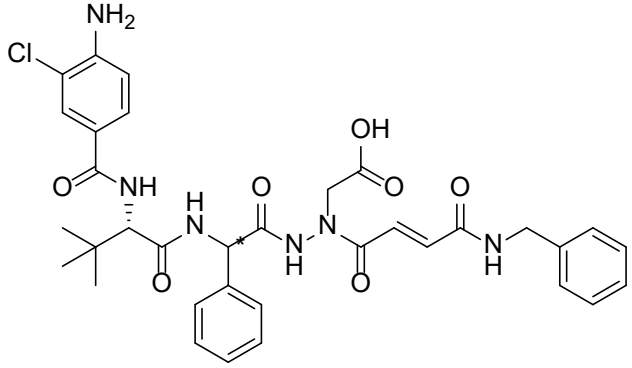
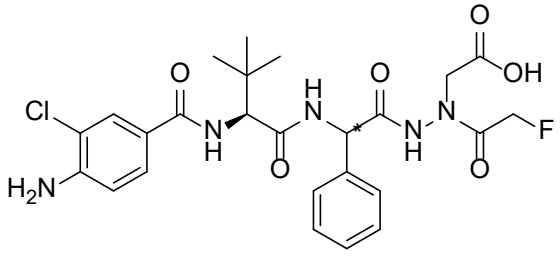
[0105] In certain embodiments, provided is a compound selected from Table 1, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

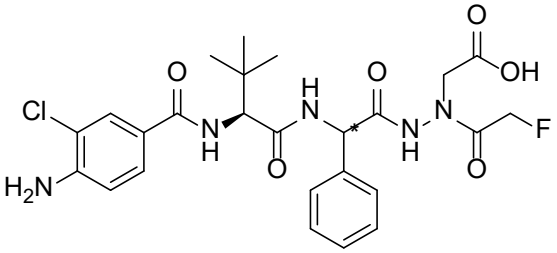
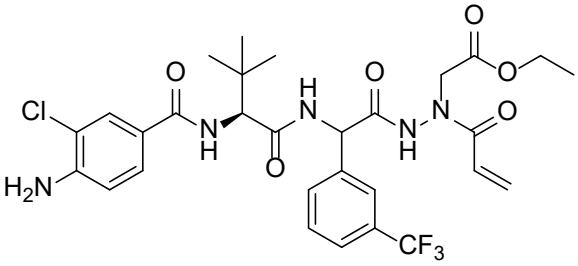
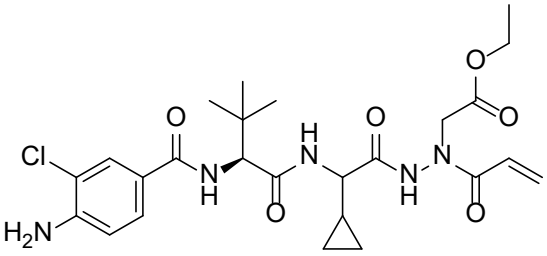
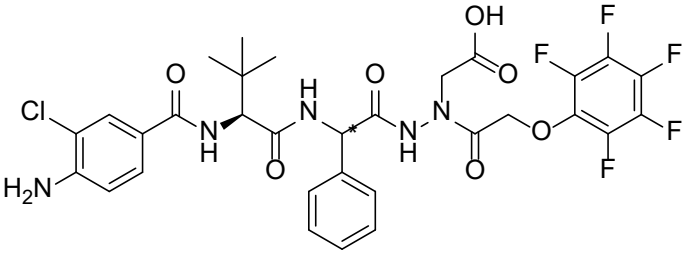
Table 1

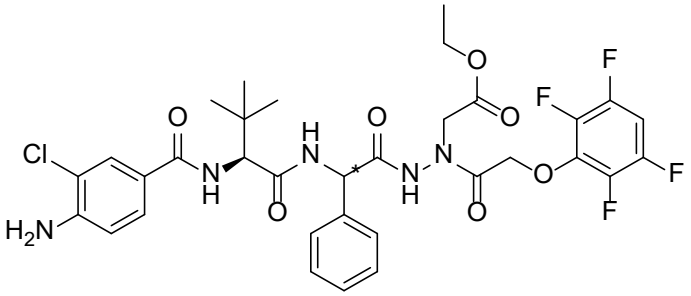
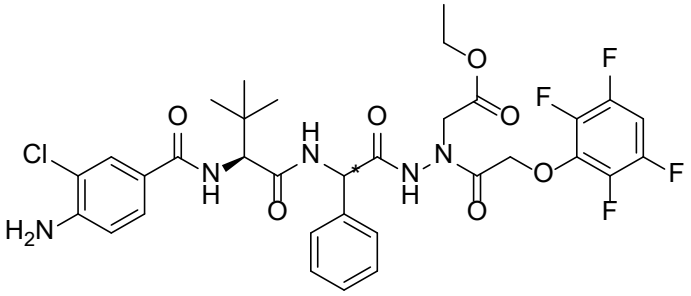
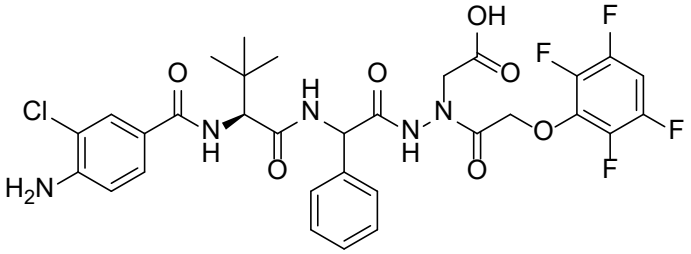
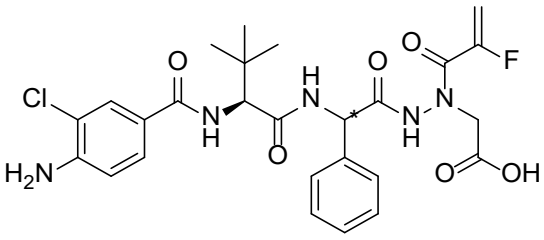
No.	Compound
1	
2	
3	 Single enantiomer
4	 Single enantiomer

No.	Compound
5	 Single enantiomer
6	 Single enantiomer
7	 Single enantiomer

No.	Compound
8	 Single enantiomer
9	
10	 Single enantiomer
11	 Single enantiomer

No.	Compound
12	 Single enantiomer
13	 Single enantiomer
14	 Single enantiomer

No.	Compound
15	 Single enantiomer
16	
17	
18	 Single enantiomer

No.	Compound
19	 Single enantiomer
20	 Single enantiomer
21	
22	 Single enantiomer

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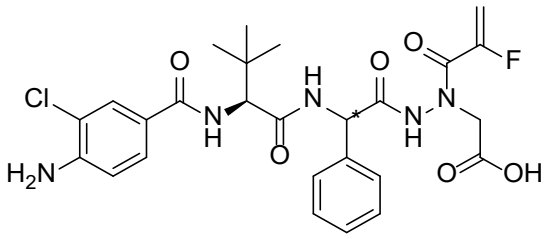
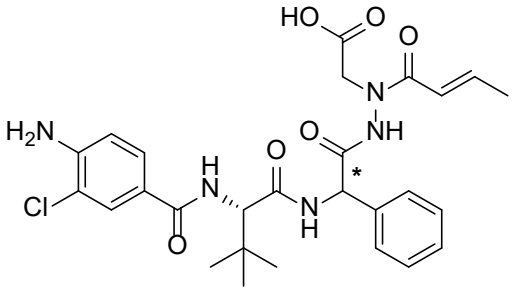
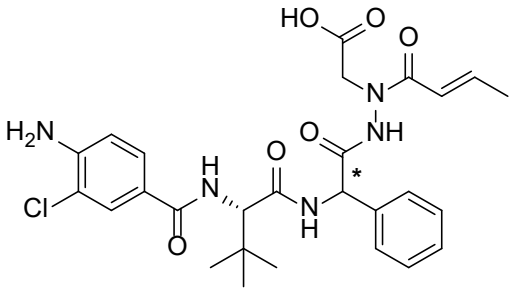
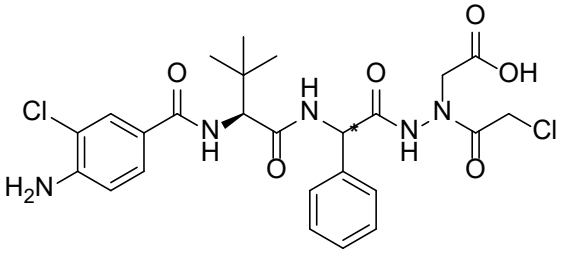
23	 Single enantiomer
24	 Single enantiomer
25	 Single enantiomer
26	 Single enantiomer

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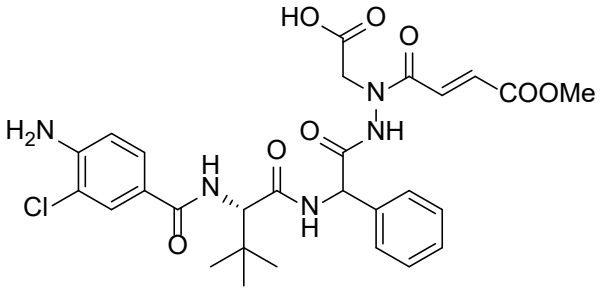
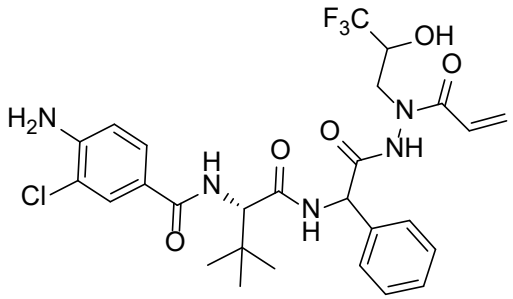
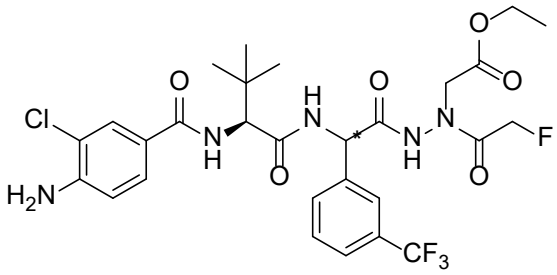
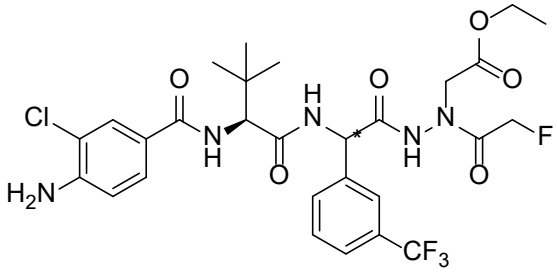
28	
29	
30	 Single enantiomer
31	 Single enantiomer

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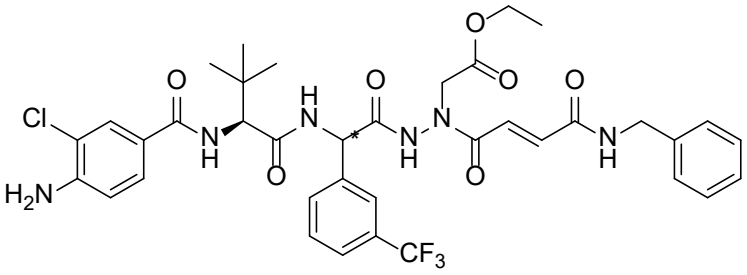
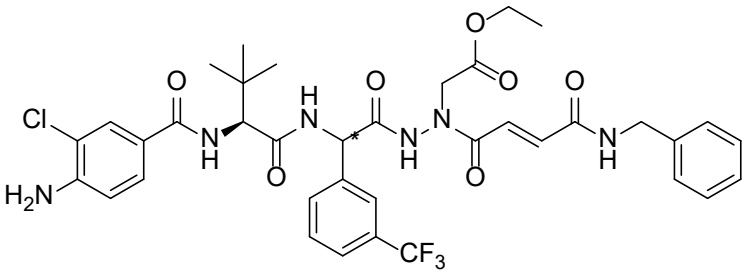
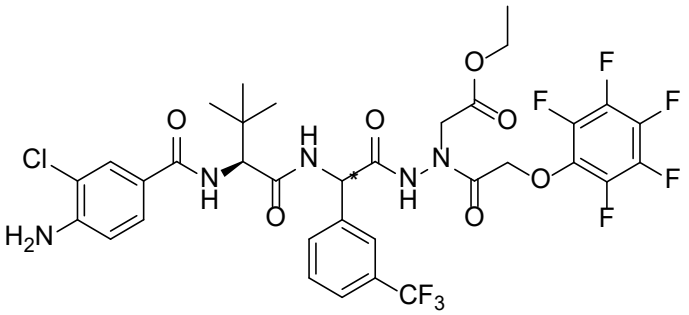
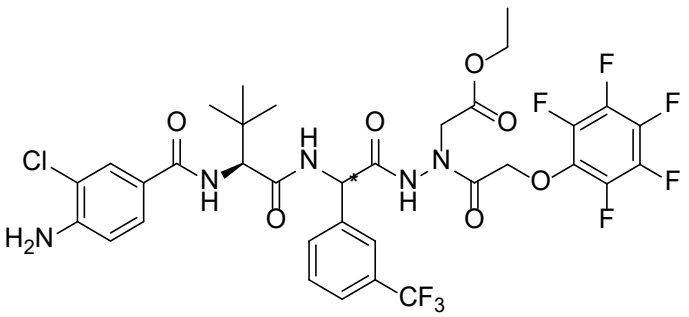
32	 Single enantiomer
33	 Single enantiomer
34	 Single enantiomer
35	 Single enantiomer

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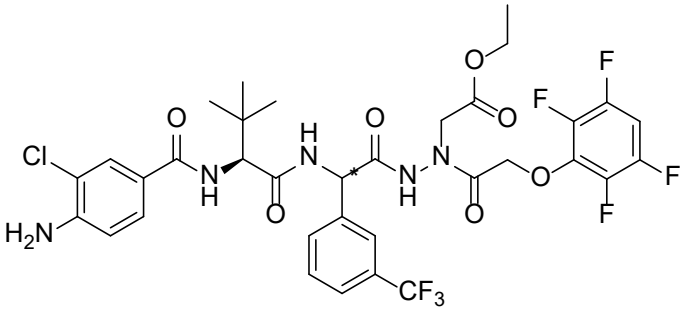
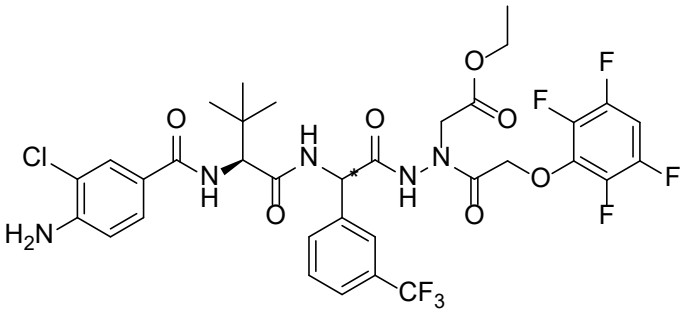
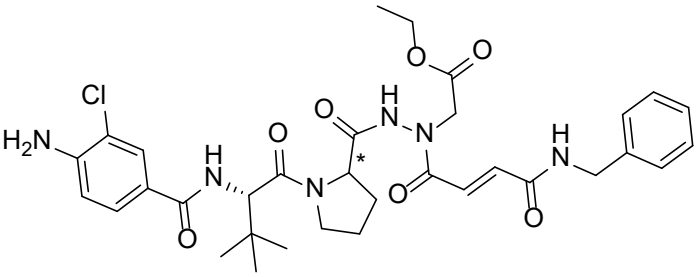
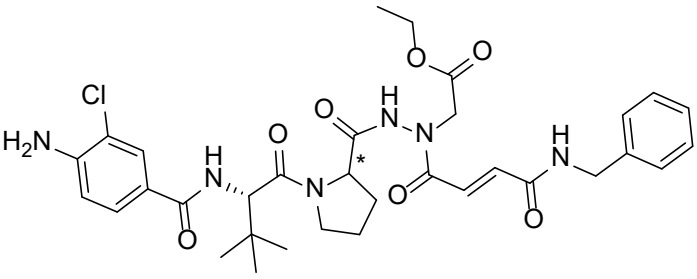
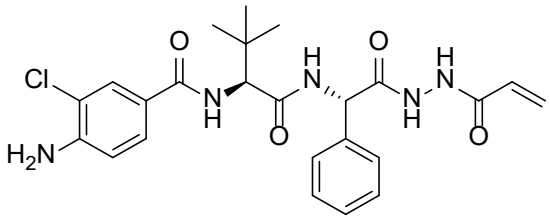
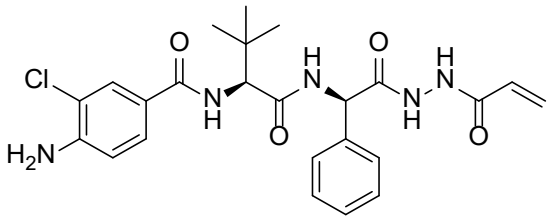
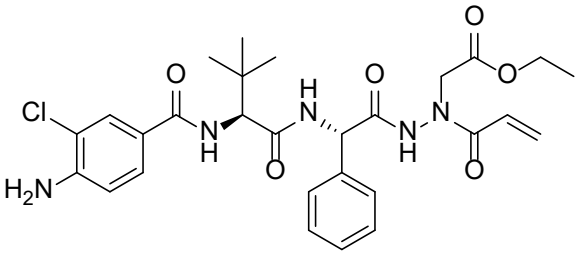
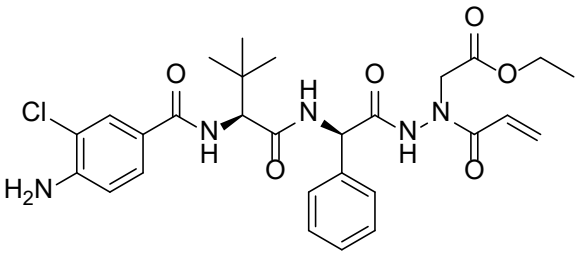
36	 Single enantiomer
37	 Single enantiomer
38	 Single enantiomer
39	 Single enantiomer

[0106] In certain embodiments, provided is a compound selected from Table 2, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

Table 2

Compound





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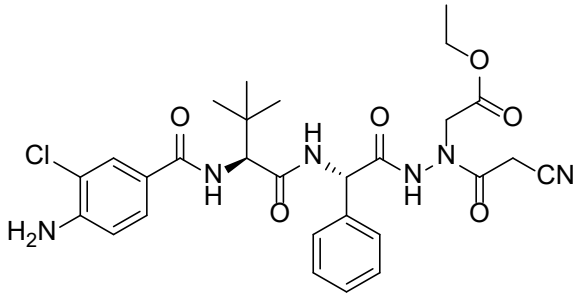
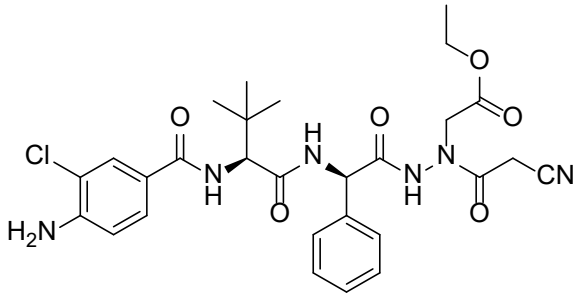
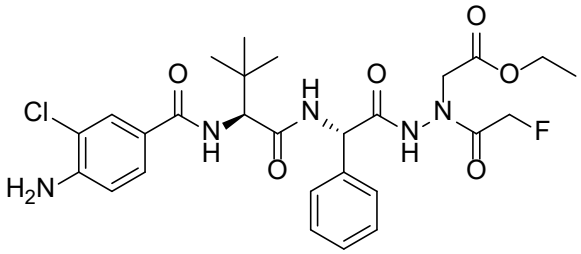
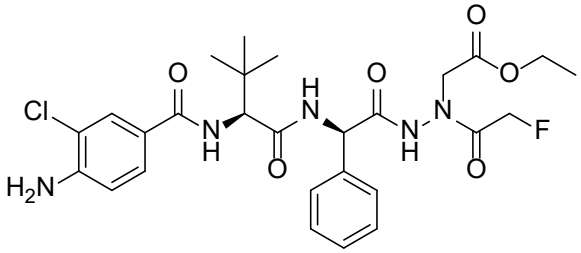

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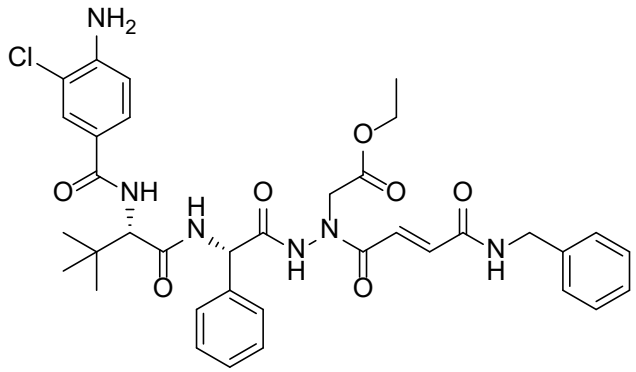
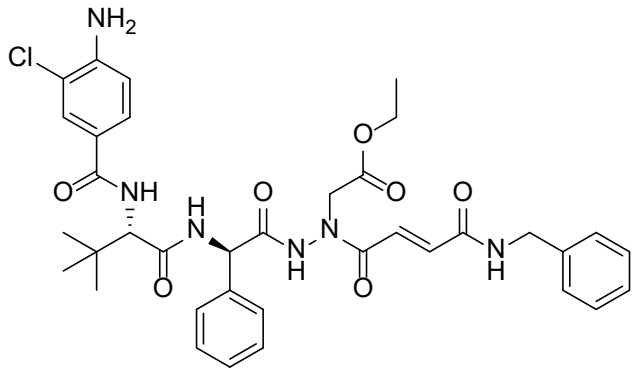
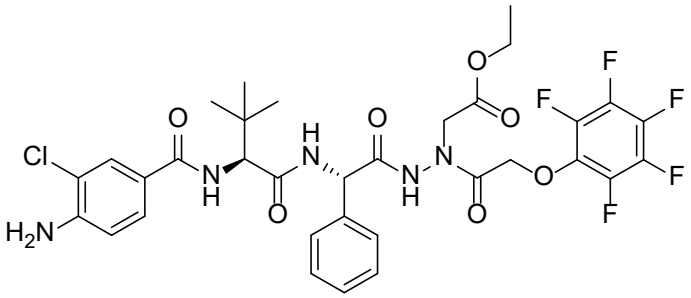
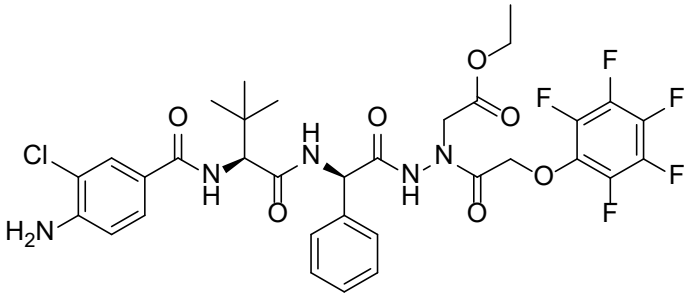

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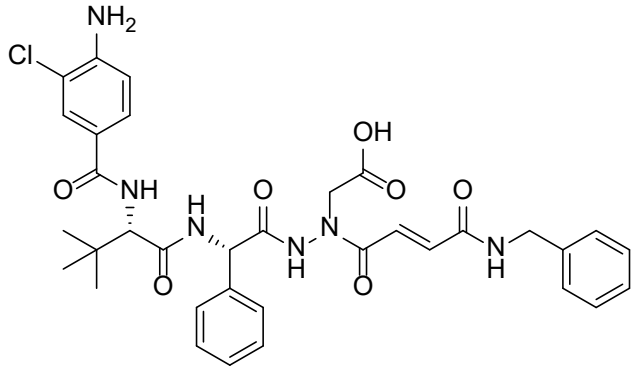
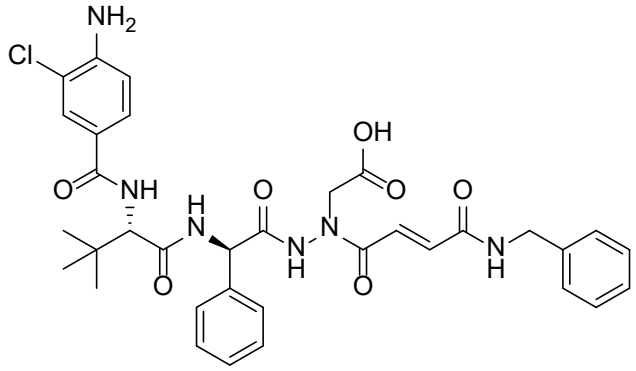
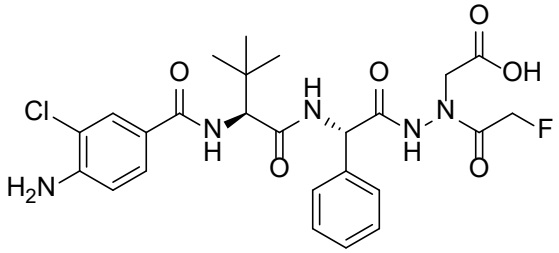
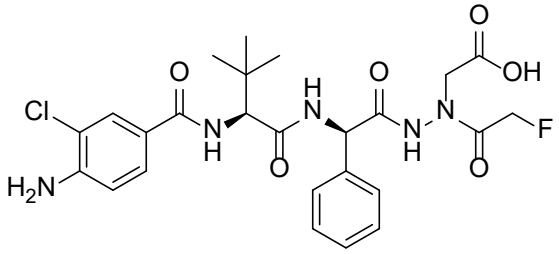

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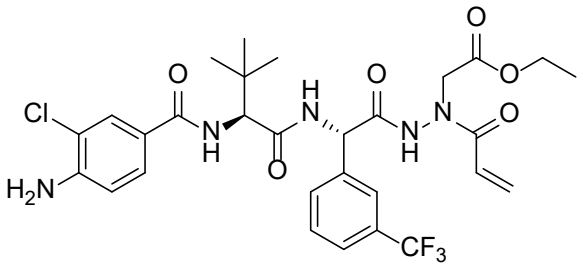
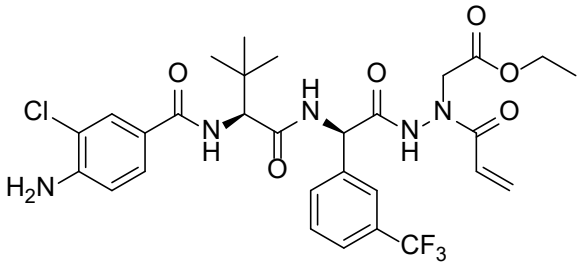
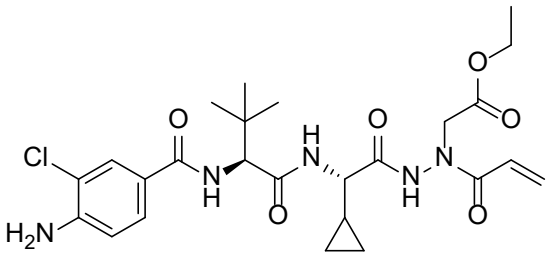
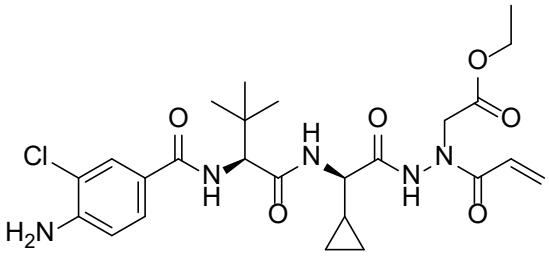
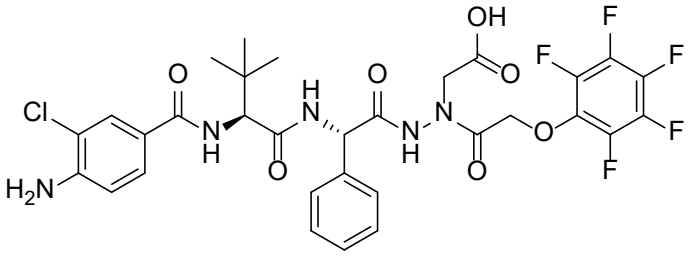

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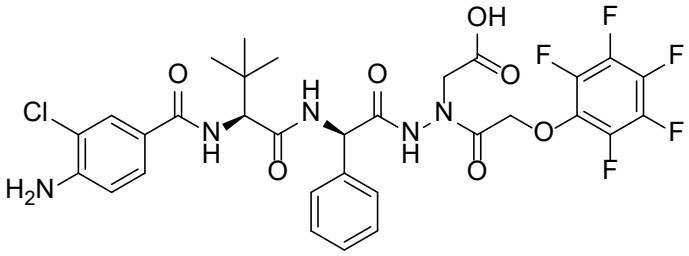
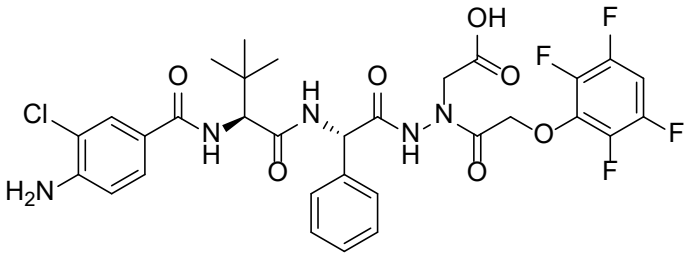
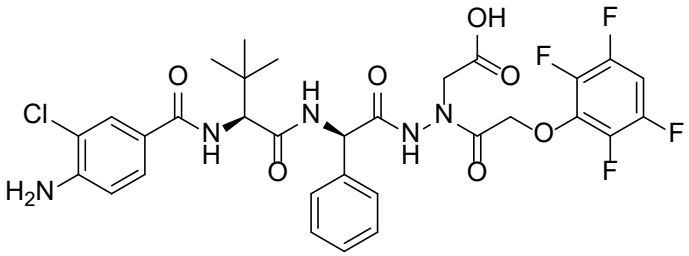
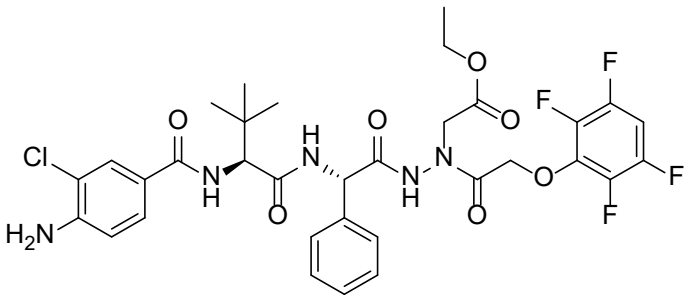
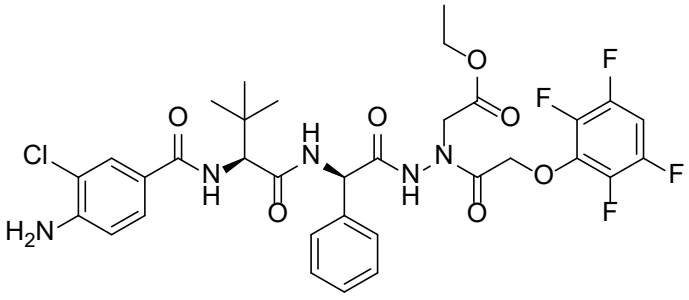

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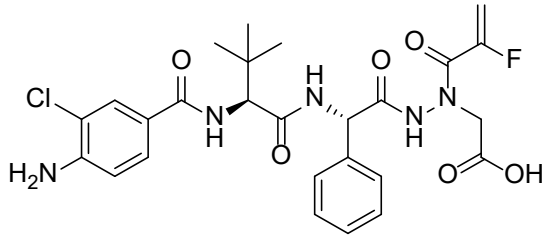
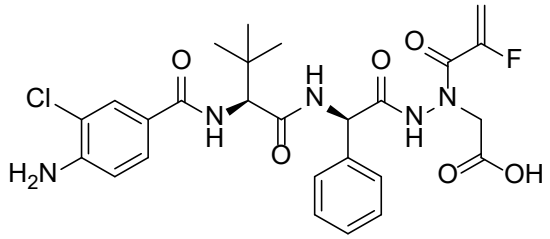
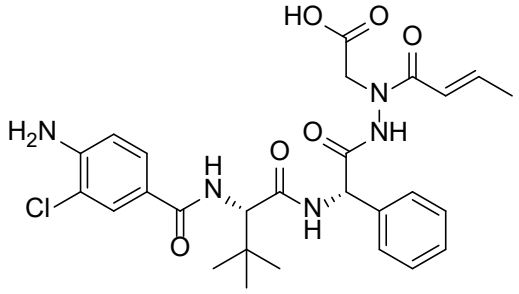
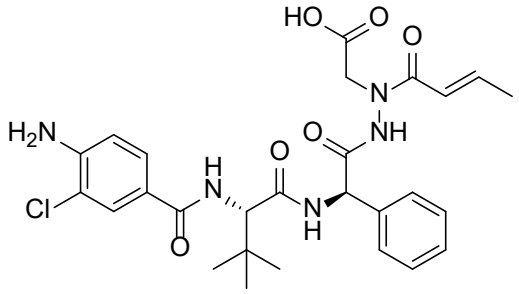
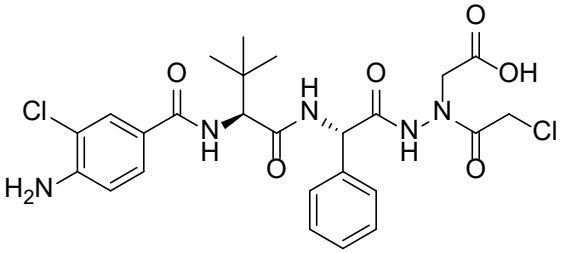

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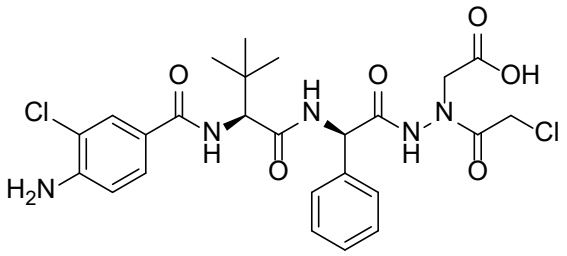
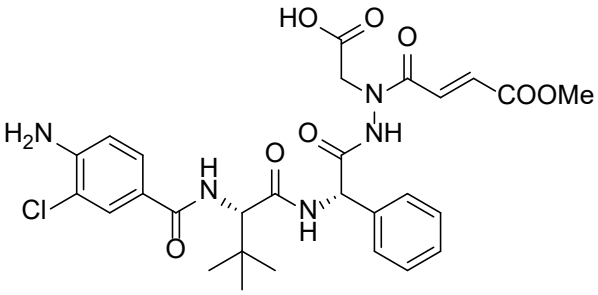
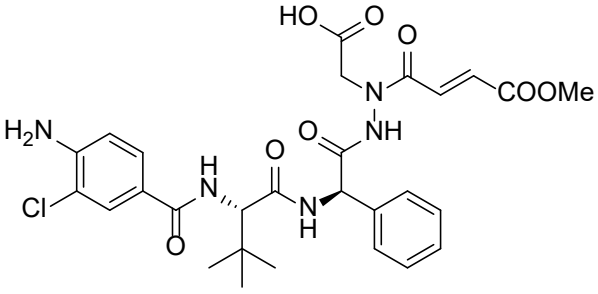
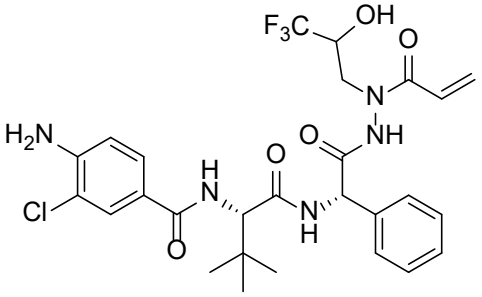

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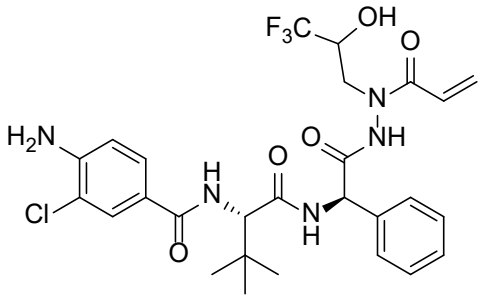
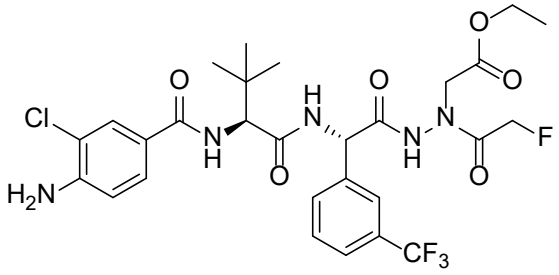
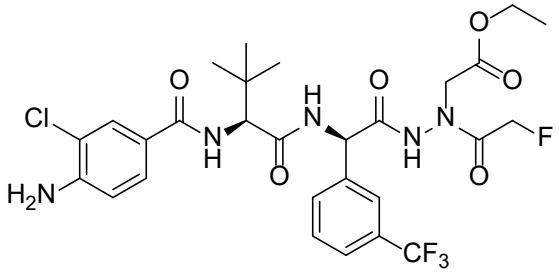
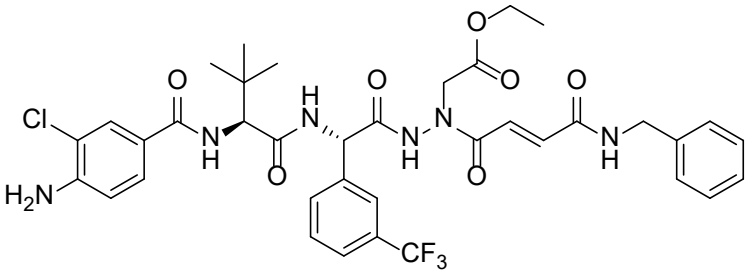
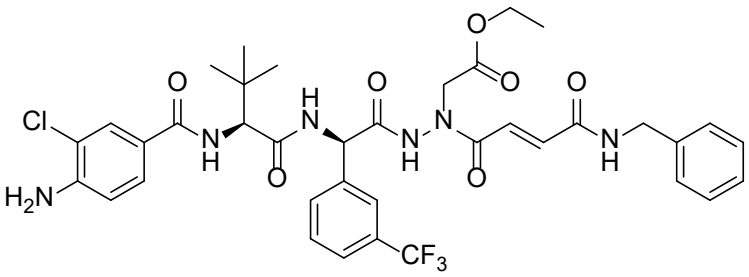

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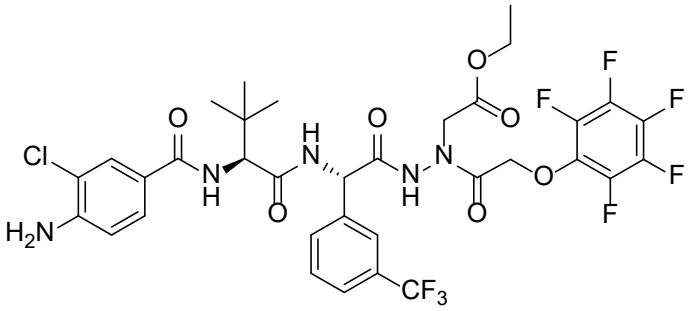
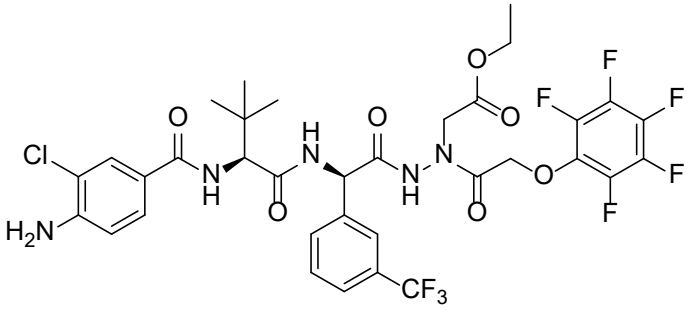
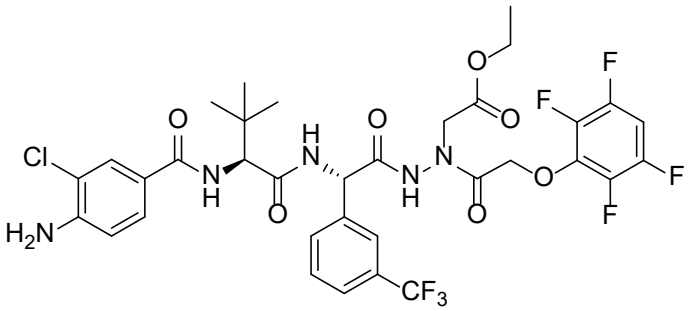
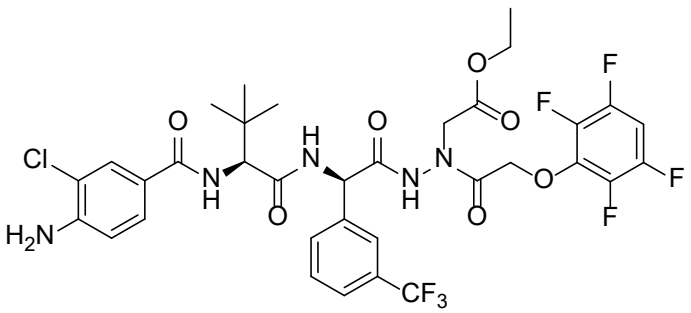

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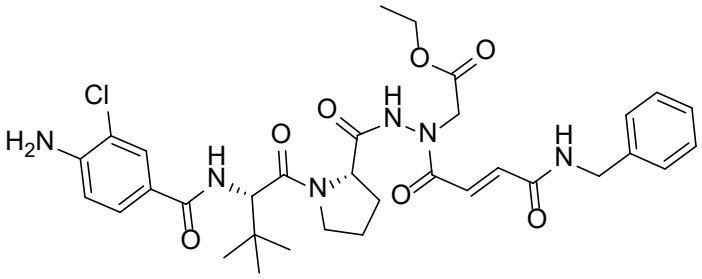
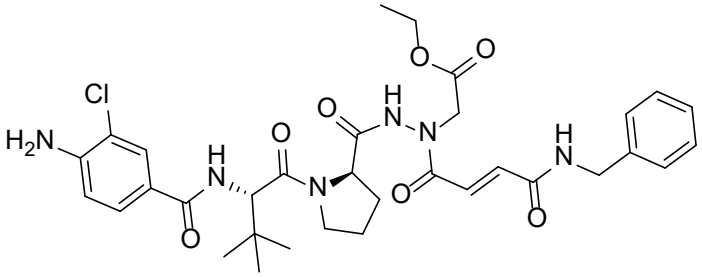



3. Methods

[0107] "Treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired clinical results may include one or more of the following: a) inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more clinical symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition, and/or preventing or delaying the spread (e.g., metastasis) of the disease or condition); and/or c) relieving the disease, that is, causing the regression of clinical symptoms (e.g., ameliorating the disease state, providing partial or total remission of the disease or condition, enhancing effect of another medication, delaying the progression of the disease, increasing the quality of life and/or prolonging survival. In one embodiment, treating does not encompass preventing.

[0108] "Prevention" or "preventing" means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0109] "Subject" refers to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal. In certain embodiments, the subject is a human.

[0110] The term "therapeutically effective amount" or "effective amount" of a compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof means an amount sufficient to effect treatment when administered to a subject, to provide a therapeutic benefit such as amelioration of symptoms or slowing of disease progression. For example, a therapeutically effective amount may be an amount sufficient to decrease a symptom of a disease or condition of as described herein. The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one of ordinary skill in the art.

[0111] The methods described herein may be applied to cell populations *in vivo* or *ex vivo*. "*In vivo*" means within a living individual, as within an animal or human. In this context, the methods described herein may be used therapeutically in an individual. "*Ex vivo*" means outside of a living individual. Examples of ex vivo cell populations include in vitro cell cultures and biological samples including fluid or tissue samples obtained from individuals. Such samples may be obtained by methods well known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine and saliva. In this context, the compounds and compositions described herein may be used for a variety of purposes, including therapeutic and experimental purposes. For example, the compounds and compositions described herein may be used *ex vivo* to determine the optimal schedule and/or dosing of administration of a compound of the present disclosure for a given indication, cell type, individual, and other parameters. Information gleaned from such use may be used for experimental purposes or in the clinic to set protocols for *in vivo* treatment. Other *ex vivo* uses for which the compounds and compositions described herein may be suited are described below or will become apparent to those skilled in the art. The selected compounds may be further characterized to examine the safety or tolerance dosage in human or non-human subjects. Such properties may be examined using commonly known methods to those skilled in the art.

[0112] In certain embodiments, a compound disclosed herein can be used to treat or lessen a disease or condition mediated, at least in part, by caspase-1, by administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, to a subject in need thereof.

[0113] In certain embodiments, the disease or condition includes a chronic or acute form of a IL-1beta apoptosis-, IL-18-, or IFN-γ-mediated disease, or an inflammatory, autoimmune, destructive bone, proliferative, infectious, or degenerative disease. Exemplary diseases include, but are not limited to, chronic kidney disease, diabetic nephropathy, IgA nephropathy, uveitis, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, an excess dietary alcohol intake disease, necrotic diseases, a viral mediated disease, inflammatory peritonitis, osteoarthritis, pancreatitis (e.g., acute pancreatitis or chronic pancreatitis), asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes (e.g., juvenile diabetes, insulin-dependent diabetes mellitus (Type I)), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, atopic dermatitis, scarring, graft vs. host disease, organ transplant rejection, osteoporosis, multiple myeloma-related bone disorder, leukemias and related disorders, myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, hemorrhagic shock, sepsis, septic shock, burns, Shigellosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, Kennedy's disease, prion disease, cerebral ischemia, epilepsy, myocardial ischemia, acute or chronic heart disease, myocardial infarction, congestive heart failure, atherosclerosis, coronary artery bypass graft, spinal muscular atrophy, amyotrophic lateral sclerosis, multiple sclerosis, HIV- or AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, neurological damage due to stroke, ulcerative colitis, traumatic brain injury, spinal cord injury, various forms of liver disease, infectious hepatitis, hepatitis-B, hepatitis-C, hepatitis-G, yellow fever, dengue fever, Japanese encephalitis, lichenplanus, acute dermatomyositis, eczema, primary cirrhosis, Behcet's disease, atopic skin disease, pure red cell aplasia, aplastic anemia, nephrotic syndrome, renal disease, renal tubulointerstitial fibrosis, neointimal hyperplasia (NH) in the arteries, polyaptic kidney disease, H. pylori-associated gastric and duodenal ulcer disease, HIV infection, tuberculosis, or meningitis.

[0114] In certain embodiments, the IL-1 or apoptosis mediated inflammatory disease which may be treated includes, but is not limited to osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, or adult respiratory distress syndrome.

[0115] In certain embodiments, the IL-1 or apoptosis mediated autoimmune disease which may be treated includes, but is not limited to, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia,

chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, Crohn's disease, psoriasis, atopic dermatitis, or graft vs. host disease.

[0116] In certain embodiments, the IL-1 or apoptosis mediated destructive bone disorders which may be treated include, but are not limited to, osteoporosis and multiple myeloma-related bone disorder.

[0117] In certain embodiments, the IL-1 or apoptosis mediated proliferative diseases which may be treated include, but are not limited to, leukemias and related disorders, such as myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

[0118] In certain embodiments, the IL-1 or apoptosis mediated infectious diseases which may be treated include, but are not limited to, sepsis, septic shock, or Shigellosis.

[0119] In certain embodiments, the IL-1 or apoptosis mediated degenerative or necrotic diseases which may be treated include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, and myocardial ischemia. Preferably, the degenerative disease is Alzheimer's disease.

[0120] In certain embodiments, the IL-1 or apoptosis-mediated degenerative diseases which may be treated include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, or neurological damage due to stroke.

[0121] Other diseases having an inflammatory or apoptotic component may be treated by the disclosed compounds. Such diseases may be systemic diseases or diseases with effects localized in the liver or other organs and may be caused by, for example, excess dietary alcohol intake or viruses, such as HBV, HCV, HGV, yellow fever virus, dengue fever virus, or Japanese encephalitis virus.

[0122] In certain embodiments, the IL-18- or IFN-γ-mediated diseases which may be treated include, but are not limited to, inflammatory, infectious, autoimmune, proliferative, neurodegenerative and necrotic conditions.

[0123] In certain embodiments, the IL-18- or IFN-γ-mediated inflammatory diseases which may be treated include, but are not limited to osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, cerebral ischemia, myocardial ischemia and adult respiratory distress syndrome.

[0124] In certain embodiments, the IL-18- or IFN-γ-mediated infectious diseases which may be treated include, but are not limited to infectious hepatitis, sepsis, septic shock and Shigellosis.

[0125] In certain embodiments, the IL-18- or IFN-γ-mediated autoimmune diseases which may be treated include, but are not limited to glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis and nephrotic syndrome.

[0126] In certain embodiments, provided is a method of treating diabetic nephropathy comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, to a subject in need thereof.

[0127] In certain embodiments, provided is a method of treating IgA nephropathy comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, to a subject in need thereof.

[0128] In certain embodiments, provided is a method of treating a renal disease comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, to a subject in need thereof.

[0129] In certain embodiments, provided is a method of treating chronic kidney disease (CKD), comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, to a subject in need thereof.

[0130] Chronic kidney disease (CKD) ultimately progresses to renal failure and the need for dialysis or renal transplantation. As such, also provided are methods for treating a patient in need of dialysis or renal transplantation comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, to a subject in need thereof.

[0131] Many factors are involved in the onset and progression of CKD. Renal tubulointerstitial fibrosis. characterized by ECM deposition, interstitial myofibroblast proliferation, and the infiltration of

inflammatory mononuclear cells, is thought to play an important role in the pathogenesis of CKD. Therefore, preventing renal tubulointerstitial fibrosis remains a major target for clinicians.

[0132] In certain embodiments, provided is a method of treating or preventing renal tubulointerstitial fibrosis, comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, to a subject in need thereof.

[0133] In certain embodiments, provided is a method of treating or preventing neointimal hyperplasia (NH) in the arteries, comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, to a subject in need thereof.

[0134] One aspect of the present disclosure includes methods for treating a caspase-mediated disorder by administering a therapeutically effective amount of the disclosed compounds to a subject determined to be in need thereof.

[0135] In certain embodiments, the compounds and compositions described herein may also be useful in treating complications associated with coronary artery bypass grafts and as a component of immunotherapy for the treatment of various forms of cancer.

4. Kits

[0136] Provided herein are also kits that include a compound of the disclosure, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, and suitable packaging. In certain embodiments, a kit further includes instructions for use. In one aspect, a kit includes a compound of the disclosure, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, and a label and/or instructions for use of the compounds in the treatment of the indications, including the diseases or conditions, described herein.

[0137] Provided herein are also articles of manufacture that include a compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof in a suitable container. The container may be a vial, jar, ampoule, preloaded syringe and intravenous bag.

5. Pharmaceutical Compositions and Modes of Administration

[0138] Compounds provided herein are usually administered in the form of pharmaceutical compositions. Thus, provided herein are also pharmaceutical compositions that contain one or more of the compounds described herein a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or prodrug thereof and one or more pharmaceutically acceptable vehicles selected from carriers, adjuvants and excipients. Suitable pharmaceutically acceptable vehicles may include, for example, inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art. See, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0139] The pharmaceutical compositions may be administered in either single or multiple doses. The pharmaceutical composition may be administered by various methods including, for example, rectal, buccal, intranasal and transdermal routes. In certain embodiments, the pharmaceutical composition may be administered by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[0140] One mode for administration is parenteral, for example, by injection. The forms in which the pharmaceutical compositions described herein may be incorporated for administration by injection include, for example, aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[0141] Oral administration may be another route for administration of the compounds described herein. Administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0142] Some examples of suitable excipients include, e.g., lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0143] The compositions that include at least one compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Another formulation for use in the methods disclosed herein employ transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds described herein in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0144] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0145] The tablets or pills of the compounds described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

[0146] Compositions for inhalation or insufflation may include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described herein. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. In other embodiments, compositions in pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

6. Dosing

[0147] The specific dose level of a compound of the present application for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the subject undergoing therapy. For example, a dosage may be expressed as a number of milligrams of a compound described herein per kilogram of the subject's body weight (mg/kg). Dosages of between about 0.1 and 150 mg/kg may be appropriate. In some embodiments, about 0.1 and 100 mg/kg may be appropriate. In other embodiments a dosage of between 0.5 and 60 mg/kg may be appropriate. In some embodiments, a dosage of from about 0.0001 to about 100 mg per kg of body weight per day, from about 0.001 to about 50 mg of compound per kg of body weight, or from about 0.01 to about 10 mg of compound per kg of body weight may be appropriate. Normalizing according to the subject's body weight is particularly useful when adjusting dosages between subjects of widely disparate size, such as occurs when using the drug in both children and adult humans or when converting an effective dosage in a non-human subject such as dog to a dosage suitable for a human subject.

7. Synthesis of the Compounds

[0148] The compounds may be prepared using the methods disclosed herein and routine modifications thereof, which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. The synthesis of typical compounds described herein may be accomplished as described in the following examples. If available, reagents and starting materials may be purchased commercially, e.g., from Sigma Aldrich or other chemical suppliers.

[0149] It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[0150] Additionally, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in Wuts, P. G. M., Greene, T. W., & Greene, T. W. (2006). Greene's protective groups in organic synthesis. Hoboken, N.J., Wiley-Interscience, and references cited therein.

[0151] Furthermore, the compounds of this disclosure may contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this disclosure, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents, and the like.

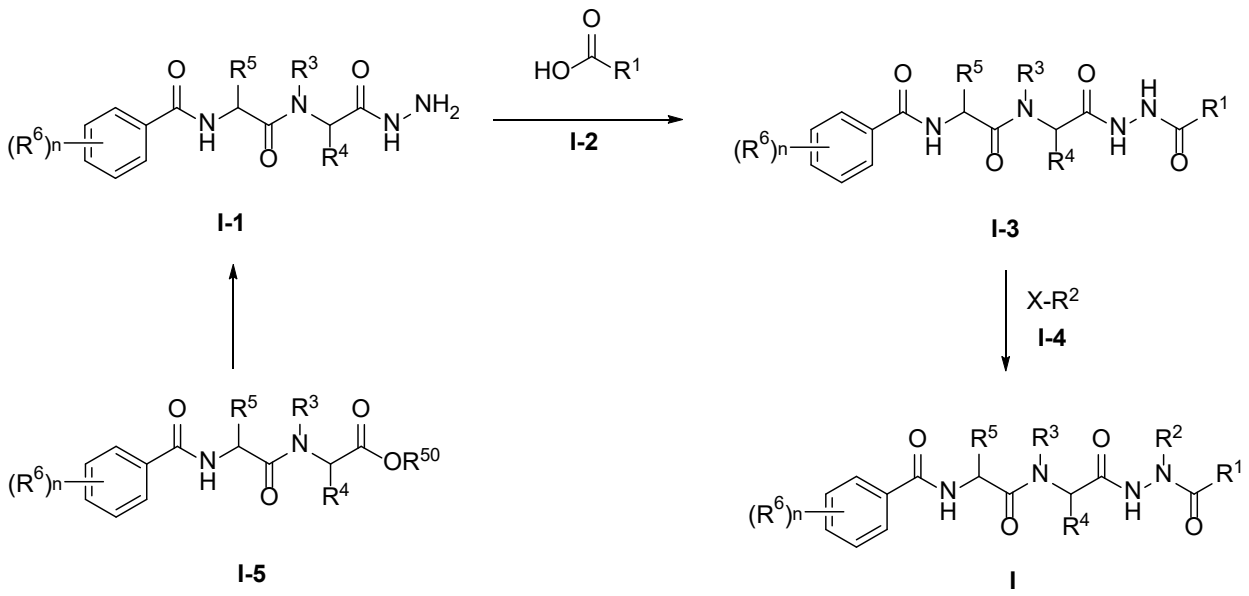
[0152] The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemce or Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989) organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

General Synthesis Method I

[0153] The following reaction shown in Scheme I illustrates a general method which can be employed for the synthesis of compounds disclosed herein. In Scheme I, each n, R^1, R^2, R^3, R^4, R^5, R^6, m, and t are

independently as defined herein, X is a leaving group (e.g., halo, such as bromo), and R^{50} is an alkyl group (e.g., ethyl).

Scheme I



[0154] Referring to Scheme I, compound I-3 (e.g., compounds of Formula I where R^2 is H) can be provided by contacting hydrazone compound I-1 with compound I-2 under standard amide coupling conditions. Coupling of compound I-3 with compound I-4 under standard nucleophilic substitution conditions provides compounds of Formula I. Compound I-1 can be prepared from the corresponding ester compounds I-5 using hydrazine hydrate under standard reaction conditions.

[0155] Appropriate starting materials and reagents for the reactions shown in Scheme I can be purchased or prepared by methods known to one of skill in the art (e.g., see Examples below). For any compound shown in Scheme I, it should be understood that various derivatives can be provided by functional group interconversion at any step. In some embodiments, the various substituents of Formula I-1, I-2, I-3, I-4, or I-5 are as defined herein. However, derivatization of compounds I-1, I-2, I-3, I-4, or I-5 prior to reacting in any step, and/or further derivatization of the resulting reaction product, provides various compounds of Formula I. Appropriate starting materials and reagents can be purchased or prepared by methods known to one of skill in the art. Upon each reaction completion, each of the intermediate or final compounds can be recovered, and optionally purified, by conventional techniques such as neutralization, extraction, precipitation, chromatography, filtration, and the like. Other modifications to arrive at compounds of this disclosure are within the skill of the art.

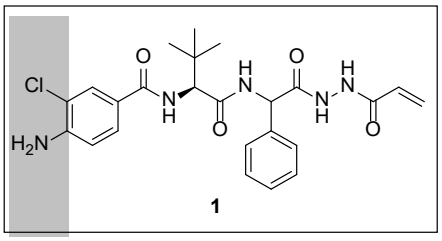
[0156] Furthermore, the compounds of this disclosure may contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this disclosure, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents, and the like. It should be appreciated that various isomers of Formula I can be separated as well.

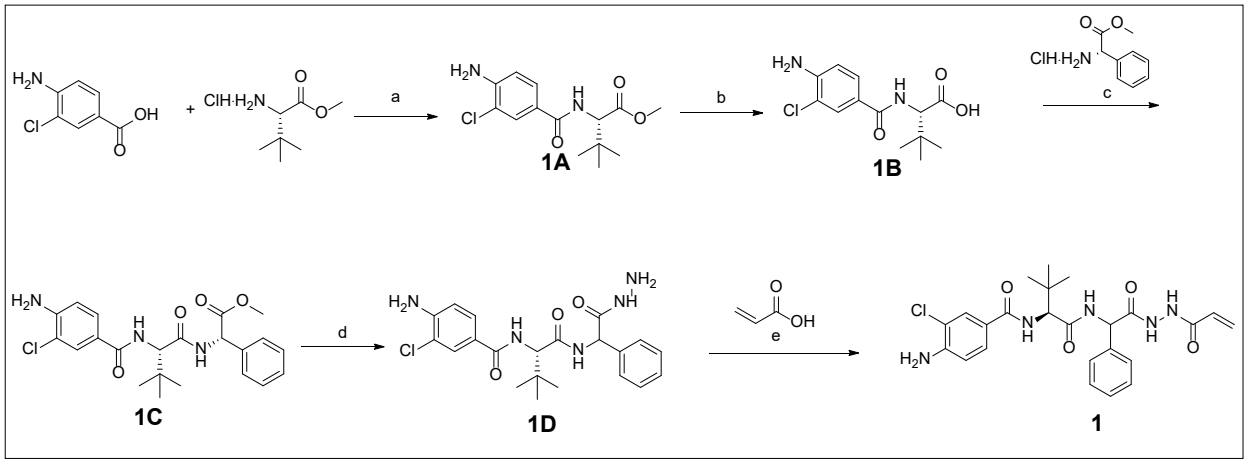
EXAMPLES

[0157] The following examples are included to demonstrate specific embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques to function well in the practice of the disclosure, and thus can be considered to constitute specific modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

EXAMPLE 1

N-((2S)-1-((2-(2-acryloylhydrazineyl)-2-oxo-1-phenylethyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-4-amino-3-chlorobenzamide





[0158] Reagents and conditions: (a) Isobutyl chloroformate, NMM, CH_2C_2, 0 ºC-rt, 18 h; (b) LiOH, THF/H_2O (5:1), rt, 8 h; (c) T3P, DIPEA, DMF, 0 ºC-rt, 14 h; (d) Hydrazine hydrate, EtOH, 80 ºC, 14 h; (e) T3P, DIPEA, DMF, 0 ºC-RT, 18 h.

EXAMPLE 1A

Methyl (S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanoate

[0159] To a stirred solution of 4-amino-3-chlorobenzoic acid (4.0 g, 23.3 mmol) in CH_2CL_2 (40 mL) at 0 °C was added NMM (10.3 mL, 93.3 mmol). Subsequently after 10 minutes, isobutyl chloroformate (5.4 mL, 46.6 mmol) was added. The reaction mixture was allowed to come to ambient temperature while stirring and finally (2S)-2-amino-3,3-dimethylbutanoate hydrochloride (8.4, 46.6 mmol) was added to the reaction mixture. Reaction was continued until both the starting materials were consumed and upon completion the reaction mixture was diluted CH_2CL_2 (60 mL) and washed with water and brine (2×100 mL each). CH_2CL_2 layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material which was triturated and recrystallized from hexane to afford the title compound (3.2 g).

EXAMPLE 1B

(S)-2-(4-Amino-3-chlorobenzamido)-3,3-dimethylbutanoic acid

[0160] To a stirred solution of Example 1A (3.2 g, 10.4 mmol) in THF (25 mL) and water (5 mL) was added lithium hydroxide (0.51 g, 20.8 mmol). The reaction mixture was stirred at an ambient temperature for overnight, concentrated to a minimum volume, and the residue was diluted with water (10 mL). The pH of the aqueous phase was adjusted to 1 by the addition of HCl (aq) (1.0 M) resulting in a thick precipitate that was collected by filtration and dried to afford the title compound (2.8 g).

EXAMPLE 1C

Methyl (S)-2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetate

[0161] To a stirred solution of Example of 1B (2.5 g, 9.8 mmol) at 0 ºC in DMF (20 mL) was added propylphosphonic anhydride (50% wt solution in ethyl acetate) (5.2 mL, 19.6 mmol) and DIPEA (3.2 mL, 30.0 mmol). The reaction mixture was allowed to come to ambient temperature while stirring and finally methyl (S)-2-amino-2-phenylacetate hydrochloride (1.8 g, 9.8 mmol) was added to. After overnight stirring, the reaction mixture was diluted with ethyl acetate (50 mL) and washed consecutively with ice-cold water and brine (2×100 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by flash chromatography on silica gel (40% ethyl acetate in hexane) afforded the title compound (3.8 g).

EXAMPLE 1D

4-Amino-3-chloro-N-((2S)-1-((2-hydrazineyl-2-oxo-1-phenylethyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)benzamide

[0162] To a suspension of 1C (30 g, 54,6 mmol) in ethanol (240 mL) was added hydrazine hydrate (100 mL). The mixture was allowed to reflux for overnight. Upon reaction completion, ethanol was removed under vacuum and precipitated by cold water (300 mL). Thus obtained white precipitate was filtered, washed with water (3×100 mL) and dried to afford the title compound (26.4 g).

EXAMPLE 1D

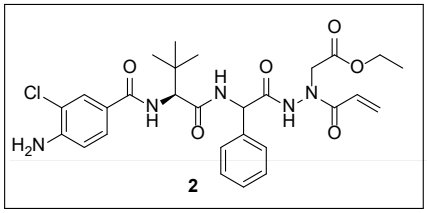
N-((2S)-1-((2-(2-acryloylhydrazineyl)-2-oxo-1-phenylethyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-4-amino-3-chlorobenzamide (1)

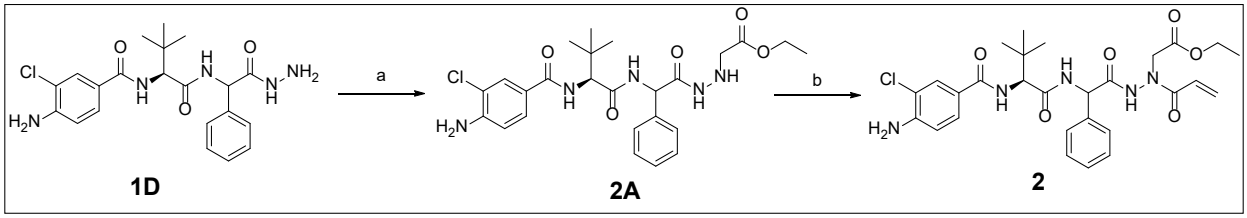
[0163] To a stirred solution of Example of 1D (0.15 g, 0.3 mmol) at 0 ºC in DMF (5 mL) was added propylphosphonic anhydride (50% wt solution in ethyl acetate) (0.1 mL, 0.4 mmol) and DIPEA (0.18 mL, 1.0 mmol). The reaction mixture was allowed to come to ambient temperature while stirring and finally acrylic acid (0.02 mL, 0.3 mmol) was added to. After overnight stirring, the reaction mixture was diluted

with ethyl acetate (15 mL) and washed consecutively with ice-cold water and brine (2×10 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by prep-HPLC using Sunfire C18 (19 X 250) mm; 5 µM column and water and MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.008 g) at RT 23.40 min.

EXAMPLE 2

Ethyl N-acryloyl-N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)glycinate





[0164] Reagents and conditions: (a) Ethyl 2-bromoacetate, NMM, DMF, 0 °C-rt, 16 h; (b) acryloyl chloride, Et_3N, THF, 0 °C-rt, 1 h.

EXAMPLE 2A

Ethyl (2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)glycinate

[0165] To a stirred solution of Example 1D (3.0 g, 7.0 mmol) in DMF (30 mL) was added 4-methylmorpholine (2.3 mL, 20.0 mmol). Reaction mixture was cooled to 0 °C and ethyl 2-bromoacetate (3.0 mL, 20.0 mmol) was added slowly. After stirring the reaction mixture for overnight in an ambient temperature, it was diluted with ethyl acetate (50 mL) and washed consecutively with ice-cold water and brine (2×100 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by flash chromatography on silica gel (50-90% ethyl acetate in hexane) afforded the title compound (2.5 g).

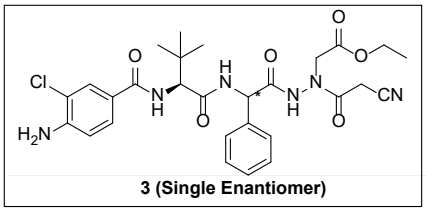
EXAMPLE 2B

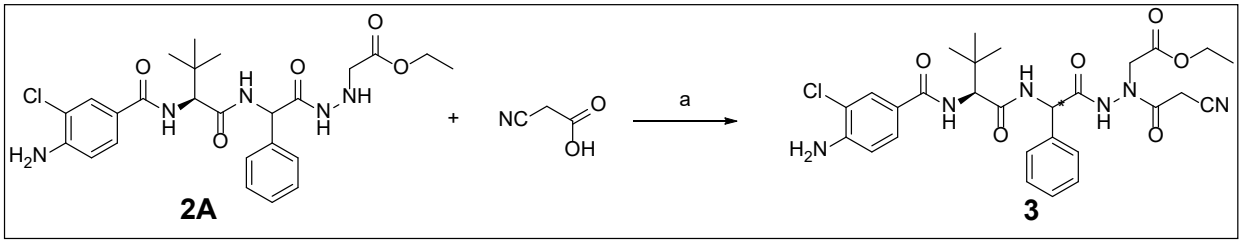
Ethyl N-acryloyl-N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)glycinate (2)

[0166] To a stirred solution of Example 2A (0.5 g, 0.9 mmol) in THF (10 mL) at 0 ºC was successively added triethyl amine (0.4 mL, 2.9 mmol) and acryloyl chloride (0.08 mL, 0.9 mmol). Reaction mixture was stirred and allowed to come to room temperature over a period of one hour. After this time, it was concentrated under reduced pressure to get the crude. Purification of the residue by prep-HPLC using XBridge C18 (19 X 250) mm; 5 µM column and water and MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.015 g) at RT 17.50 min.

EXAMPLE 3

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-cyanoacetyl)glycinate



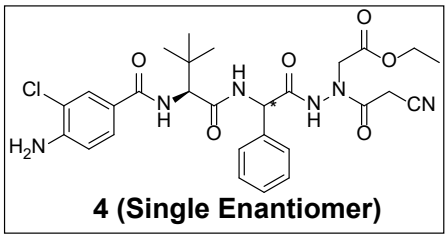


[0167] Reagents and conditions: (a) EDCl, HOBt, DIPEA, DMF, 0 ºC-rt, 18 h.

[0168] To a solution of 2-cyanoacetic acid (0.12 g, 1.5 mmol) in DMF (10 mL) at 0 ºC was added EDCl (0.4 g, 2.1 mmol), HOBt (0.2 g, 1.5 mmol) and DIPEA (0.8 mL, 4.5 mmol). After 10 minutes Example 2A (0.5 g, 1.0 mmol) was added to it. After overnight stirring, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with ice-cold water and brine (2×25 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by prep-HPLC using XSelect CSH C18 (4.6 X 250) mm; 5 µM column and water and MeCN as mobile phase (1 mL/ min flow rate) afforded the title compound (0.01 g) at RT 18.61 min.

EXAMPLE 4

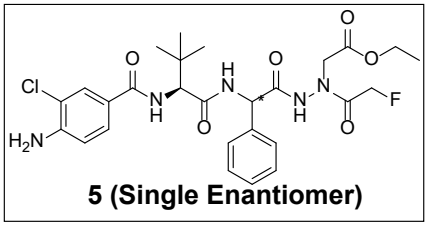
Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-cyanoacetyl)glycinate

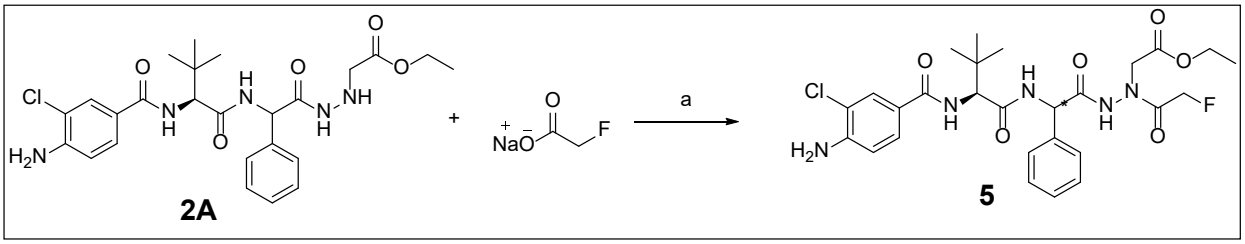


[0169] During the preparative HPLC purification of Example 3, the title compound (0.008 g) was isolated at RT 20.24 min.

EXAMPLE 5

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-fluoroacetyl)glycinate





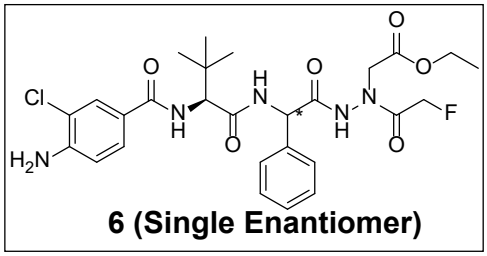
[0170] Reagents and conditions: (a) HATU, DIPEA, DMF, 0 ºC-rt, 4 h.

[0171] To a mixture of Example 2A (0.12 g, 0.2 mmol) and sodium 2-fluoroacetate (0.034 g, 0.3 mmol) in DMF (5 mL) at 0 ºC was consecutively added HATU (0.1 g, 0.3 mmol) and DIPEA (0.1 mL, 0.7 mmol). Reaction mixture was stirred and allowed to come to room temperature over a period of four hours. Upon completion, it was diluted with ethyl acetate (15 mL) and washed with ice-cold water and brine (2×20 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by prep-HPLC using XBridge C18 (19 X 250) mm; 5

μM column and 0.1% ammonia in water and MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.02 g) at RT 18.44 min.

EXAMPLE 6

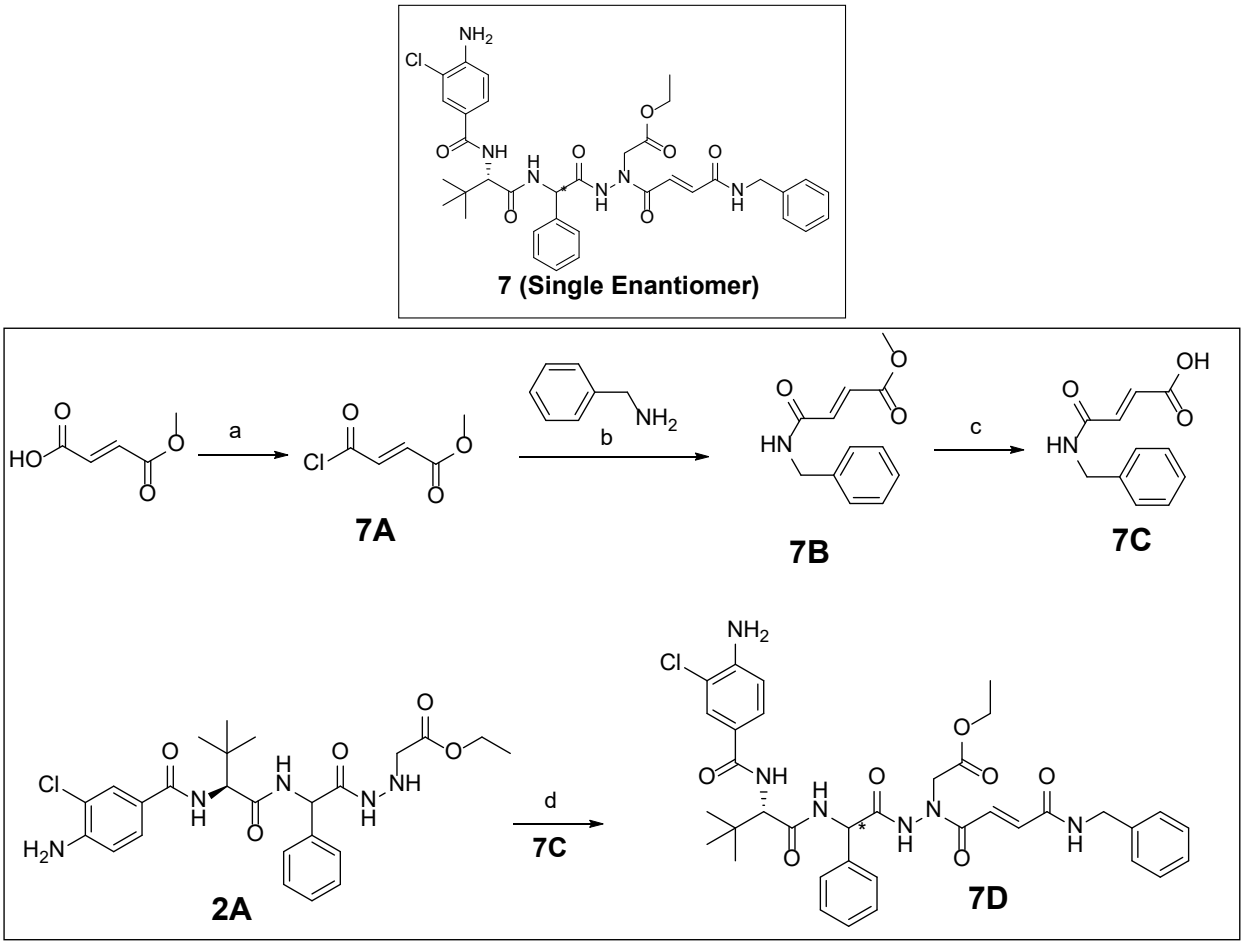
Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-fluoroacetyl)glycinate



[0172] During the preparative HPLC purification of Example 5, the title compound (0.018 g) was isolated at RT 19.73 min.

EXAMPLE 7

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-4-(benzylamino)-4-oxobut-2-enoyl)glycinate



[0173] Reagents and conditions: (a) $(CO)_2Cl_2$, CH_2Cl_2, 0 °C-rt, 4 h, (b) Et_3N, CH_2Cl_2, rt, 2 h, (c) LiOH, THF/H_2O (5:1), rt, 8 h; (d) EDCl, HOBt, DIPEA, DMF, 0 °C-rt, 14 h.

EXAMPLE 7A

Methyl (E)-4-chloro-4-oxobut-2-enoate

[0174] To a stirred solution of (E)-4-methoxy-4-oxobut-2-enoic acid (10 g, 76.9 mmol) in dichloromethane (100 mL) was added oxalyl chloride (13.2 mL, 154.0 mmol) dropwise at 0 °C. then reaction was allowed to continue for 4 h. After this time a small fraction of the reaction mixture was quenched with methanol and TLC was checked, which showed the formation of a nonpolar ester spot. The whole reaction mixture was concentrated to dryness under nitrogen atmosphere to get methyl (E)-4-

chloro-4-oxobut-2-enoate (11.0 g) in the crude form, which was directly used in the next step without further purification.

EXAMPLE 7B

methyl (E)-4-(benzylamino)-4-oxobut-2-enoate

[0175] To a stirred solution of 1-phenylmethanamine (5.1 mL, 46.7 mmol) in dichloromethane (100 mL) was added triethylamine (13.0 mL, 93 mmol) and the reaction mixture was stirred for 10 mins. After this time, Example 7A (11.0 g, 74.7 mmol) was added to the reaction mixture and the reaction was continued for 2 hours at an ambient temperature. Upon completion, reaction mixture was diluted with DCM (100 mL) and washed with water (2×150 mL). Organic layer was separated, dried with sodium sulphate and concentrated *in vacuo* to get the crude, which was then purified by flash column chromatography using 40% ethyl acetate in hexane to get Methyl (E)-4-(benzylamino)-4-oxobut-2-enoate (9.2 g).

EXAMPLE 7C

(E)-4-(benzylamino)-4-oxobut-2-enoic acid

[0176] The title compound (7.0 g) was prepared using the procedure described in Example 1B, using Example 51B (9.2 g, 42.0 mmol) in place of Example 1A.

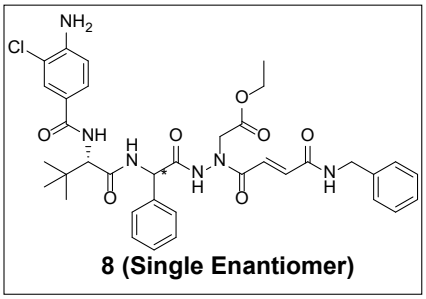
EXAMPLE 7D

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-4-(benzylamino)-4-oxobut-2-enoyl)glycinate (7)

[0177] To a stirred solution of Example 7C (0.15 g, 0.7 mmol) in N,N dimethyl formamide (10 mL) at 0 °C was added EDCl (0.3 g, 1.5 mmol) and HOBt (0.1 g, 0.7 mmol). Subsequently after 10 minutes, DIPEA (0.4 mL, 2.4 mmol) and Example 2A (0.25 g, 0.5 mmol) were added. Reaction was continued for overnight at an ambient temperature until both the starting materials were consumed and upon completion the reaction mixture was diluted ethyl acetate (50 mL) and washed with water and brine (2×100 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by prep-HPLC using Inertsil ODS C18 (250x20) mm; 5 µM column and 5mM ammonium acetate in water and MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.013 g) at RT 22.60 min.

EXAMPLE 8

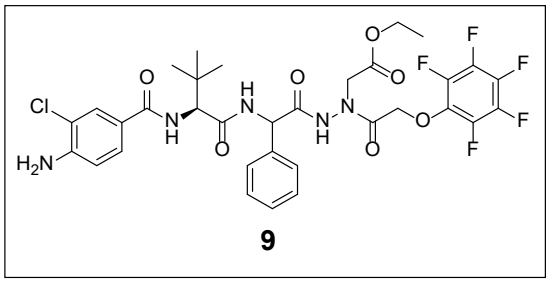
Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-4-(benzylamino)-4-oxobut-2-enoyl)glycinate

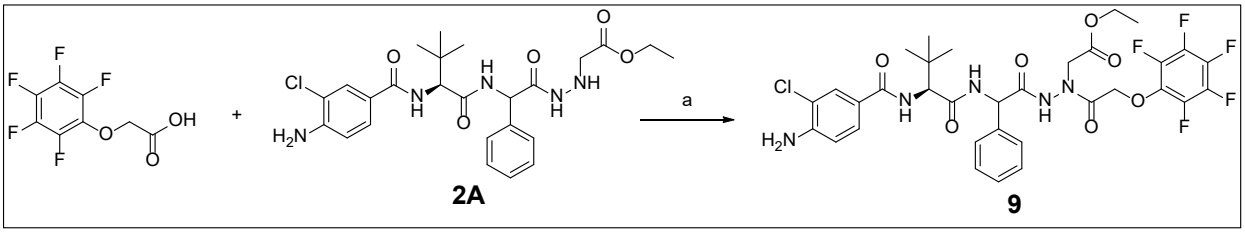


[0178] During the preparative HPLC purification of Example 7D, the title compound (0.008 g) was isolated at RT 24.06 min.

EXAMPLE 9

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-(perfluorophenoxy)acetyl)glycinate





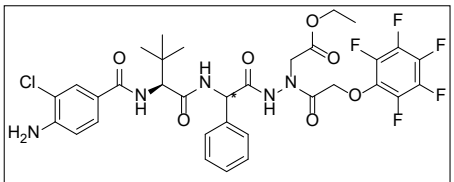
[0179] Reagents and conditions: (a) (i) $SOCl_2$, dioxane, 105 °C, 1 h, (ii) Et_3N, CH_2Cl_2, rt, 16 h.

[0180] To a stirred solution of 2-(perfluorophenoxy)acetic acid (0.2 g, 0.8 mmol) in dioxane (8 mL) was added thionyl chloride (0.3 mL, 4.0 mmol) dropwise at 0 °C. then reaction was allowed to reflux for 1 h. The whole reaction mixture was concentrated to dryness under nitrogen atmosphere. Separately, to a stirred solution of Example 2A (0.2 g, 0.4 mmol) in DCM (10 mL) was added triethyl amine (0.3 mL, 2.0 mmol) and after 15 minutes the crude 2-(perfluorophenoxy)acetyl chloride obtained from first reaction

mixture was added to it. Reaction was allowed to stir for overnight and then it was evaporated to dryness to get the crude. Purification of the residue by prep-HPLC using XBridge C18 (19 X 250) mm; 5 µM column and 5mM ammonium acetate in water and MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.06 g) at RT 17.30 min.

EXAMPLE 10

Ethyl N-((S)-2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-(perfluorophenoxy)acetyl)glycinate

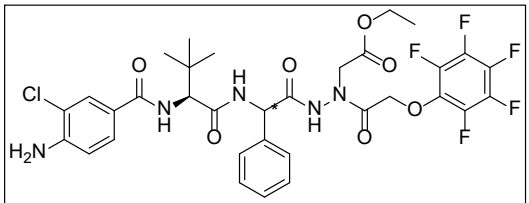


10 (Single Enantiomer)

and

EXAMPLE 11

Ethyl N-((R)-2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-(perfluorophenoxy)acetyl)glycinate

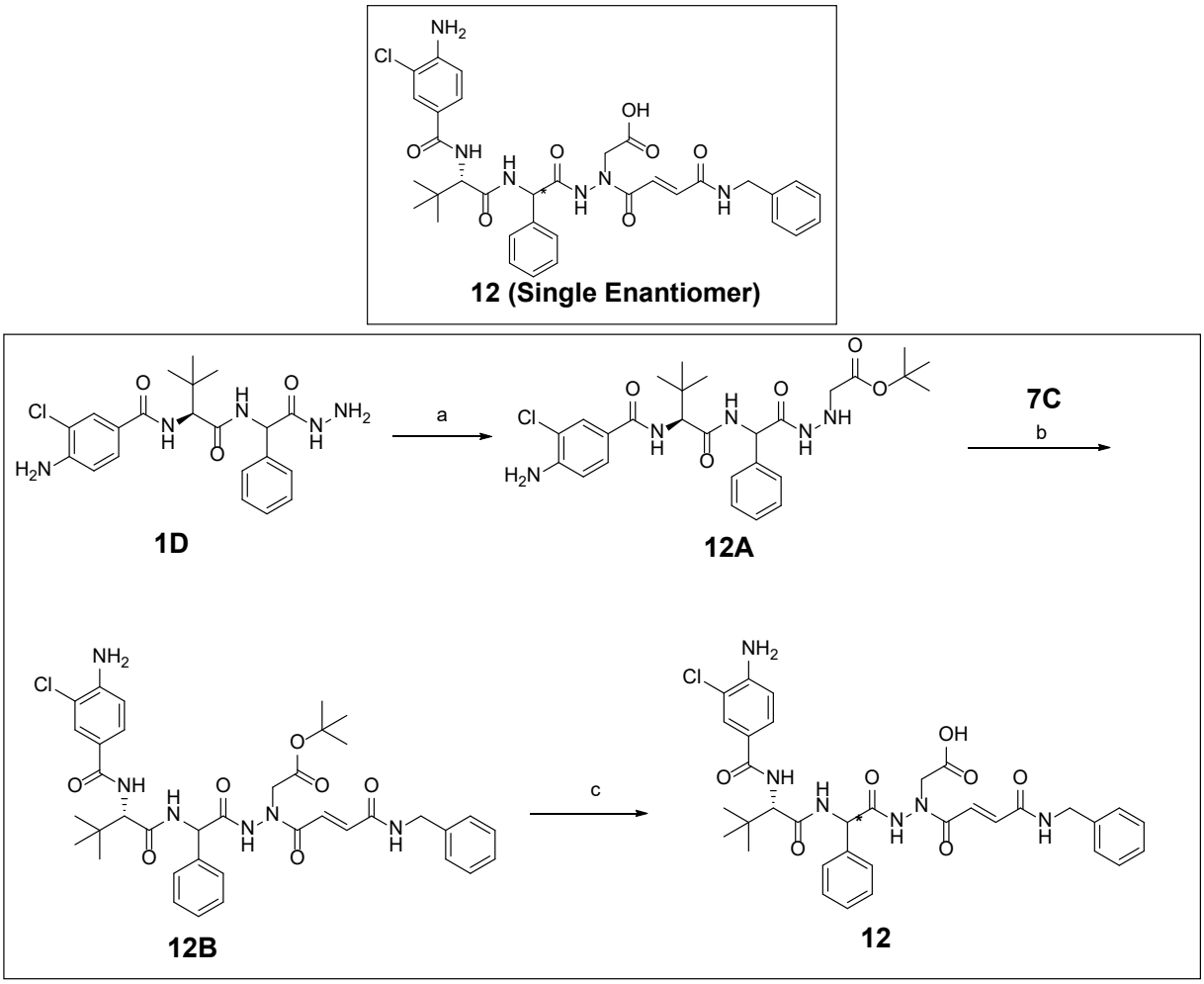


11 (Single Enantiomer)

[0181] Preparative HPLC purification of Example 9 by using XSELECT C18 (19 mm X 250 mm X 5 µM) and 5mM ammonium acetate in water and MeCN as mobile phase (19 mL/ min flow rate) and afforded the title compound (10) (0.02 g) at RT 29.74 min and title compound (11) (0.01 g) at RT 31.49 min.

EXAMPLE 12

N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-4-(benzylamino)-4-oxobut-2-enoyl)glycine



[0182] Reagents and conditions: (a) *t*-Butyl bromoacetate, DMF, rt, 2 h; (b) EDCl, HOBt, DIPEA, CH_2Cl_2, 0 ºC-rt, 14 h; (c) TFA, CH_2Cl_2, 0 ºC-rt, 2 h.

EXAMPLE 12A

tert-Butyl (2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)glycinate

[0183] To a stirred solution of Example 1D (10 g, 23.2 mmol) in N,N-dimethylformamide (50 mL) *tert*-butyl 2-bromoacetate (50 mL, 5 Vol) was added dropwise at room temperature and reaction mixture was allowed to stir for 2 hours. Upon completion, reaction was quenched with cold water (150 mL) and extracted with ethyl acetate (2×100 mL). Organic layer was washed with brine, separated, dried over

sodium sulphate and evaporated to dryness to get the crude. Purification of the residue by flash chromatography on silica gel (40-70% ethyl acetate in hexane) afforded the title compound (5.5 g).

EXAMPLE 12B

tert-Butyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-4-(benzylamino)-4-oxobut-2-enoyl)glycinate

[0184] To a stirred solution of Example 7C ((0.17 g, 0.8 mmol) in dichloromethane (10 mL) at 0 °C was added EDCl (0.3 g, 1.6 mmol) and HOBt (0.13 g, 0.8 mmol). Subsequently after 10 minutes, DIPEA (0.5 mL, 2.75 mmol) and Example 12A (0.3 g, 0.6 mmol) were added. Reaction was continued for overnight at an ambient temperature until both the starting materials were consumed and upon completion the reaction mixture was diluted DCM (20 mL) and washed with water and brine (2×50 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by flash chromatography on silica gel (0-50% ethyl acetate in hexane) afforded the title compound (0.25 g).

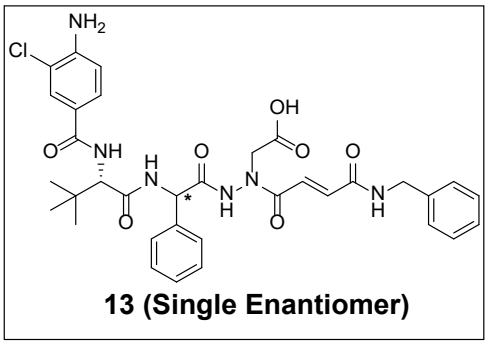
EXAMPLE 12C

N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-4-(benzylamino)-4-oxobut-2-enoyl)glycine (12)

[0185] To a stirred solution of Example 12B (0.25 g, 0.3 mmol) in dichloromethane at 0 °C was dropwise added trifluoroacetic acid (2.5 mL, 32.7 mmol). Reaction mixture was stirred for couple of hours while the reaction temperature was allowed to come to room temperature. Upon completion, reaction mixture was evaporated to dryness to get the crude. Purification of the residue by prep-HPLC using ZORBAX C18 (21.2 X 150) mm; 5 µM column and water and MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.017 g) at RT 13.65 min.

EXAMPLE 13

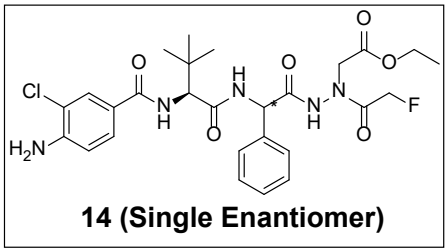
N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-4-(benzylamino)-4-oxobut-2-enoyl)glycine

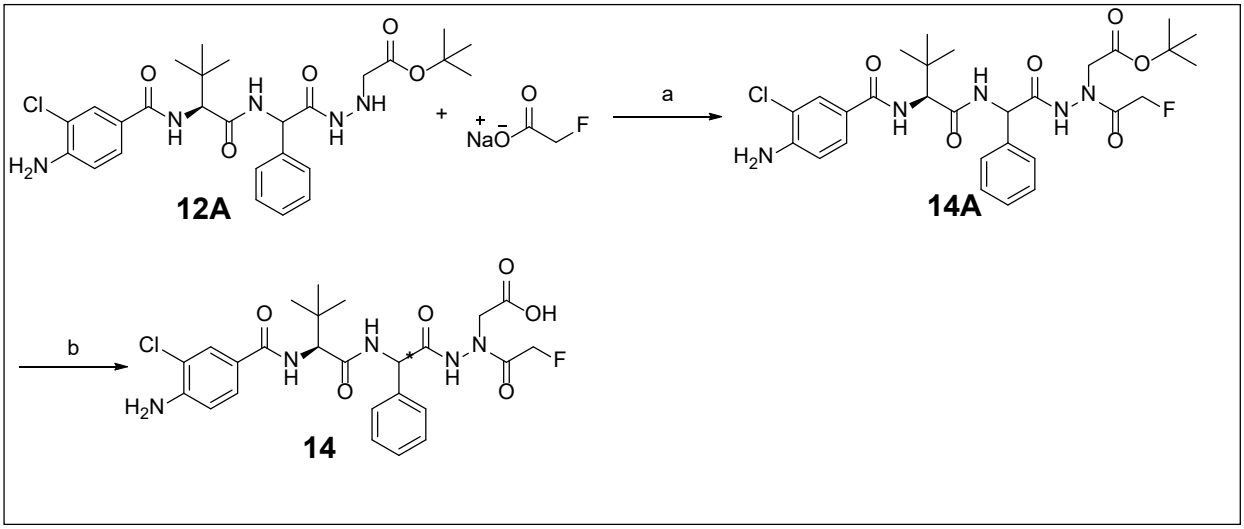


[0186] During the preparative HPLC purification of Example 12C, the title compound (0.02 g) was isolated at RT 14.12 min.

EXAMPLE 14

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-fluoroacetyl)glycinate





[0187] Reagents and conditions: (a) HATU, DIPEA, DMF, 0 ºC-rt, 4 h; (b) TFA, CH_2Cl_2, 0 ºC-rt, 2 h.

EXAMPLE 14A

tert-Butyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-fluoroacetyl)glycinate

[0188] The title compound (0.1 g) was prepared using the procedure described in Example 5, using Example 12A (0.2 g, 0.4 mmol) in place of Example 2A.

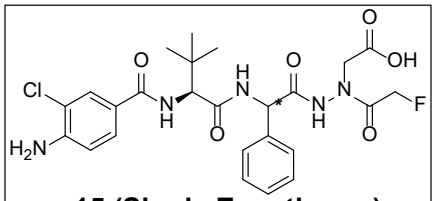
EXAMPLE 14B

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-fluoroacetyl)glycinate (14)

[0189] Following the procedure described in Example 12C and using Example 14A (0.1 g, 0.17 mmol) in place of 12B the crude product was obtained. Purification of the residue by prep-HPLC using XBridge C18 (19 X 250) mm; 5 µM column and 5% ammonium acetate in water; MeCN as mobile phase (17 mL/ min flow rate) afforded the title compound (0.01 g) at RT 11.90 min.

EXAMPLE 15

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-fluoroacetyl)glycinate

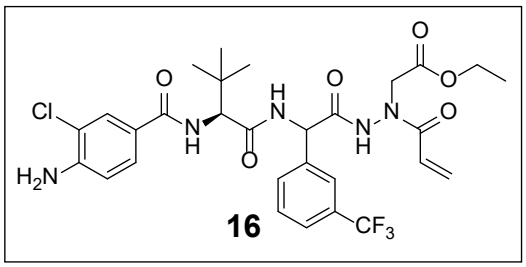


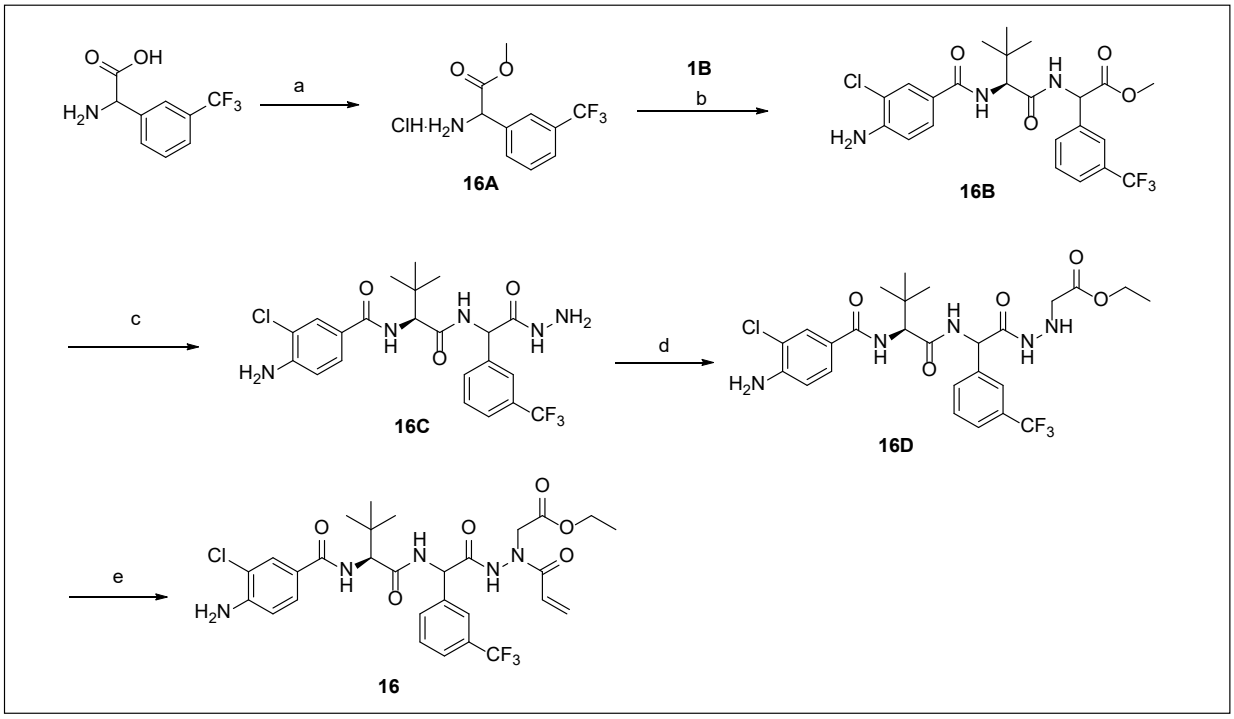
15 (Single Enantiomer)

[0190] During the preparative HPLC purification of Example 14B, the title compound (0.01 g) was isolated at RT 12.95 min.

EXAMPLE 16

Ethyl N-acryloyl-N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-(3-(trifluoromethyl)phenyl)acetamido)glycinate





[0191] Reagents and conditions: (a) $SOCl_2$, MeOH, 0 °C- rt, 16 h; (b) T3P, DIPEA, DMF, 0 °C-rt, 14 h; (c) Hydrazine hydrate, EtOH, 80 °C, 14 h; (d) Ethyl 2-bromoacetate, NMM, DMF, 0 °C-rt, 16 h; (e) acryloyl chloride, Et_3N, THF, 0 °C-rt, 1 h.

EXAMPLE 16A

Methyl 2-amino-2-(3-(trifluoromethyl)phenyl)acetate hydrochloride

[0192] To a suspension of 2-amino-2-(3-(trifluoromethyl)phenyl)acetic acid (25.0 g, 114.0 mmol) in MeOH (250 mL) at 0 °C was slowly added thionyl chloride (16.5 mL, 228.0 mmol). The reaction mixture was the allowed stir for overnight at an ambient temperature. Upon completion reaction mixture was

concentrated to afford solid mass, which was then washed with diethyl ether to furnish the title compound (30.5 g).

EXAMPLE 16B

Methyl 2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-(3-(trifluoromethyl)phenyl)acetate

[0193] The title compound (15.0 g) was prepared using the procedure described in Example 1C, using Example 16A (10.1 g, 37.5 mmol) in place of methyl (S)-2-amino-2-phenylacetate hydrochloride.

EXAMPLE 16C

4-Amino-3-chloro-N-((2S)-1-((2-hydrazineyl-2-oxo-1-(3-(trifluoromethyl)phenyl)ethyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)benzamide

[0194] The title compound (13.4 g) was prepared using the procedure described in Example 45A, using Example 16B (25.0 g, 50.0 mmol) in place of Example 1C.

EXAMPLE 16D

Ethyl (2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-(3-(trifluoromethyl)phenyl)acetamido)glycinate

[0195] The title compound (7.4 g) was prepared using the procedure described in Example 2A, using Example 16C (13.0 g, 26.0 mmol) in place of Example 45A.

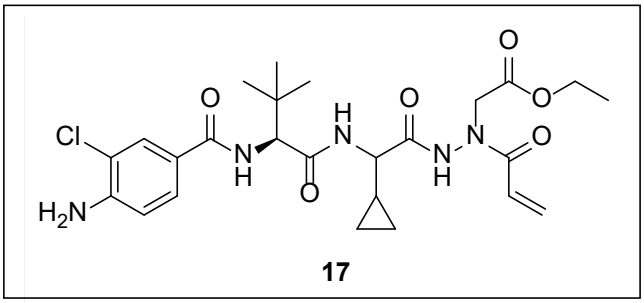
EXAMPLE 16E

Ethyl N-acryloyl-N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-(3-(trifluoromethyl)phenyl)acetamido)glycinate (16)

[0196] Following the procedure described in Example 2B and using Example 16D (0.1 g, 0.16 mmol) in place of 2A the crude product was obtained. Purification of the residue by prep-HPLC using XSelect C18 (19 X 250) mm; 5 µM column and 5mM ammonium acetate in water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.007 g) at RT 23.90 min.

EXAMPLE 17

Ethyl N-acryloyl-N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-cyclopropylacetamido)glycinate



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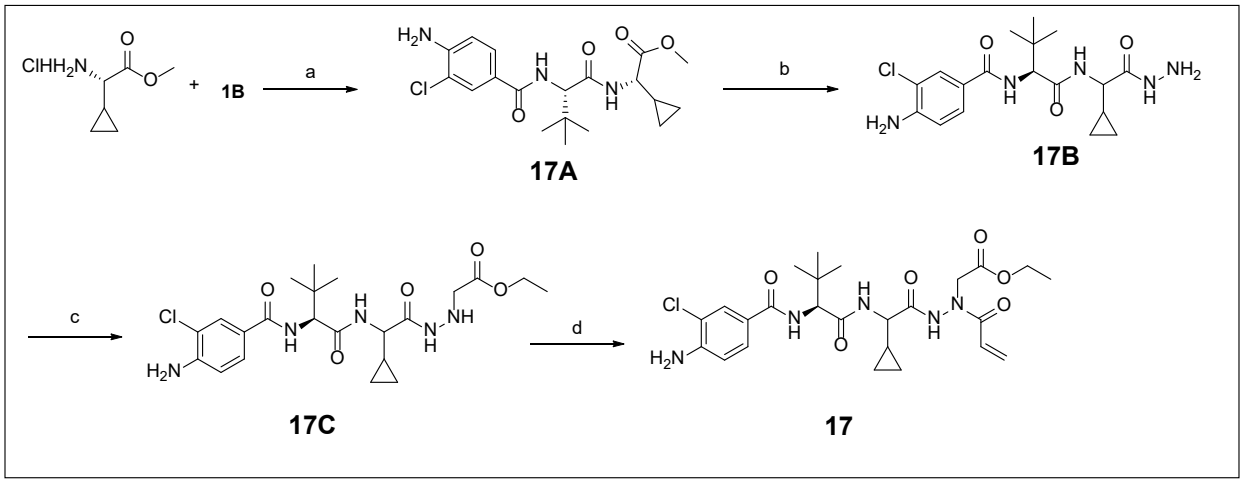


[0197] Reagents and conditions: (a) EDCl, HOBt, DIPEA, DMF, 0 ºC-rt, 14 h; (b) Hydrazine hydrate, EtOH, 80 ºC, 14 h; (c) Ethyl 2-bromoacetate, NMM, DMF, 0 ºC-rt, 16 h; (d) acryloyl chloride, Et_3N, THF, 0 ºC-rt, 1 h.

EXAMPLE 17A

Methyl (S)-2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-cyclopropylacetate

[0198] To a stirred solution of 1B (1.0 g, 3.5 mmol) in N,N dimethyl formamide (15 mL) at 0 °C was added EDCl (1.0 g, 5.3 mmol) and HOBt (0.52 g, 3.86 mmol). Subsequently after 10 minutes, DIPEA (1.8 mL, 10.5 mmol) and methyl (S)-2-amino-2-cyclopropylacetate hydrochloride (0.58 g, 3.5 mmol) were added. Reaction was continued for overnight at an ambient temperature until both the starting materials were consumed and upon completion the reaction mixture was diluted ethyl acetate (50 mL) and washed with water and brine (2×100 mL each). Organic layer was separated, dried over sodium sulfate

and concentrated *in vacuo* to get the crude material. Purification of the residue by flash chromatography on silica gel (0-60% ethyl acetate in hexane) afforded the title compound (0.9 g).

EXAMPLE 17B

4-Amino-3-chloro-N-((2S)-1-((1-cyclopropyl-2-hydrazineyl-2-oxoethyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)benzamide

[0199] The title compound (1.2 g) was prepared using the procedure described in Example 1D, using Example 17A (2.0 g, 5.1 mmol) in place of Example 1C.

EXAMPLE 17C

Ethyl (2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-cyclopropylacetamido)glycinate

[0200] The title compound (0.4 g) was prepared using the procedure described in Example 2A, using Example 17B (1.2 g, 2.5 mmol) in place of Example 1D.

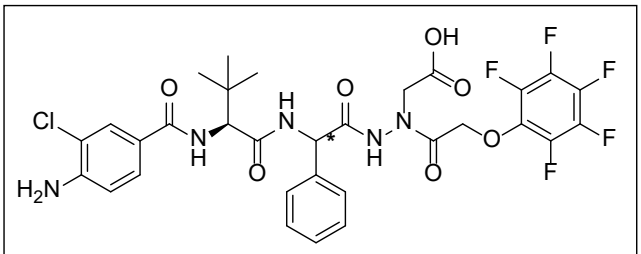
EXAMPLE 17D

Ethyl N-acryloyl-N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-cyclopropylacetamido)glycinate (17)

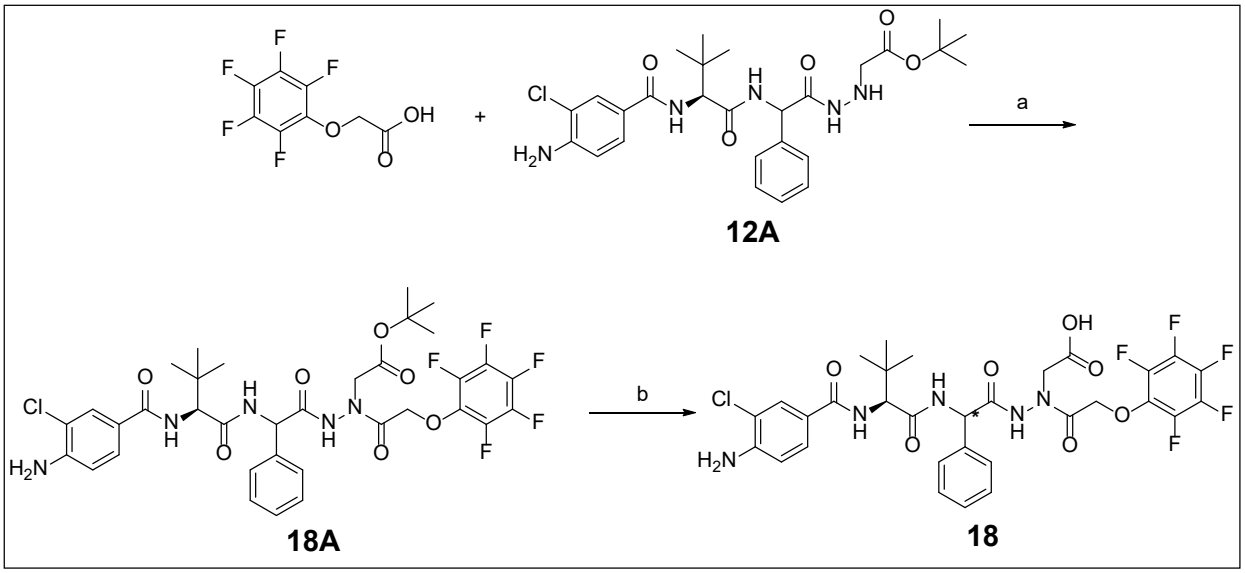
[0201] Following the procedure described in Example 2B and using Example 17C (0.2 g, 0.4 mmol) in place of 2A the crude product was obtained. Purification of the residue by prep-HPLC using XSelect C18 (19 X 250) mm; 5 µM column and 5mM ammonium acetate in water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.01 g) at RT 12.86 min.

EXAMPLE 18

N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-(perfluorophenoxy)acetyl)glycine



18 (Single Enantiomer)



[0202] Reagents and conditions: (a) (i) $SOCl_2$, dioxane, 105 °C, 1 h, (ii) Et_3N, CH_2Cl_2, rt, 16 h; (b) TFA, CH_2Cl_2, 0 ºC-rt, 2 h.

EXAMPLE 18A

tert-Butyl (2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)glycinate

[0203] The title compound (0.09 g) was prepared using the procedure described in Example 9, using Example 12A (0.3 g, 0.5 mmol) in place of Example 2A.

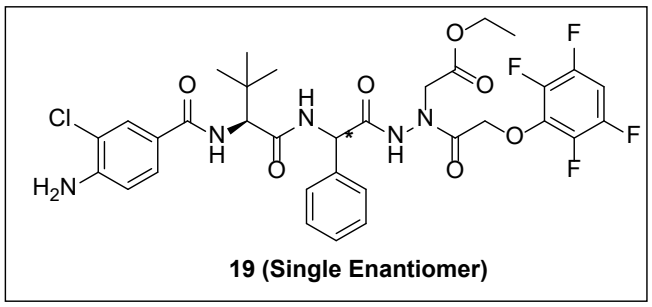
EXAMPLE 18B

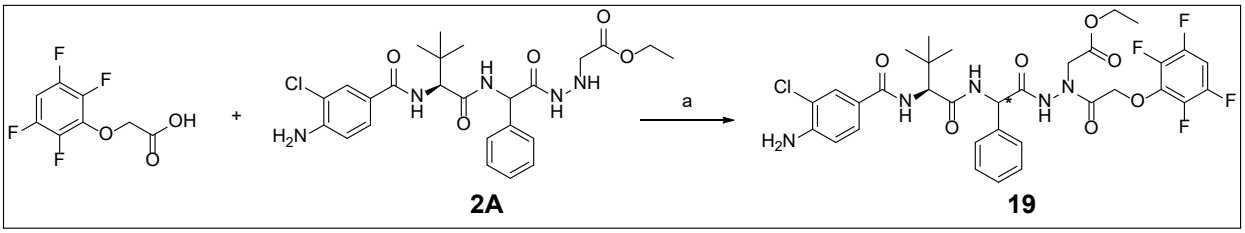
N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-(perfluorophenoxy)acetyl)glycine (18)

[0204] Following the procedure described in Example 12C and using Example 18A (0.08 g, 0.1 mmol) in place of 12B the crude product was obtained. Purification of the residue by prep-HPLC using SunFire C18 (19 X 250) mm; 5 µM column and water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.01 g) at RT 20.85 min.

EXAMPLE 19

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-(2,3,5,6-tetrafluorophenoxy)acetyl)glycinate



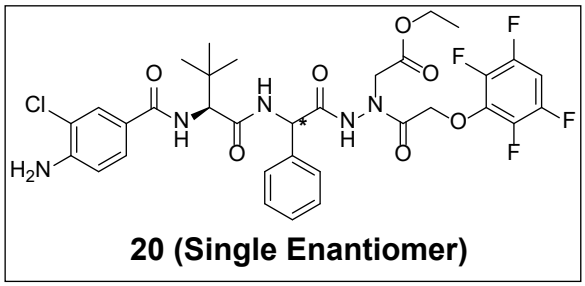


[0205] Reagents and conditions: (a) (i) $SOCl_2$, dioxane, 105 °C, 1 h, (ii) Et_3N, CH_2Cl_2, rt, 16 h.

[0206] Following the procedure described in Example 9 and using 2-(2,3,5,6-tetrafluorophenoxy)acetic acid (0.2 g, 0.8 mmol) in place of 2-(perfluorophenoxy)acetic acid and crude product was obtained. Purification of the residue by prep-HPLC using SunFire C18 (19 X 250) mm; 5 µM column and water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.008 g) at RT 30.58 min.

EXAMPLE 20

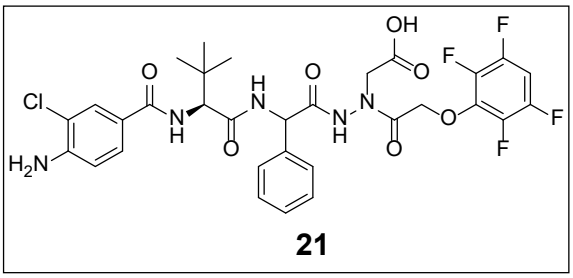
Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-(2,3,5,6-tetrafluorophenoxy)acetyl)glycinate



[0207] During the preparative HPLC purification of Example 19, the title compound (0.01 g) was isolated at RT 32.90 min.

EXAMPLE 21

N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-(2,3,5,6-tetrafluorophenoxy)acetyl)glycine



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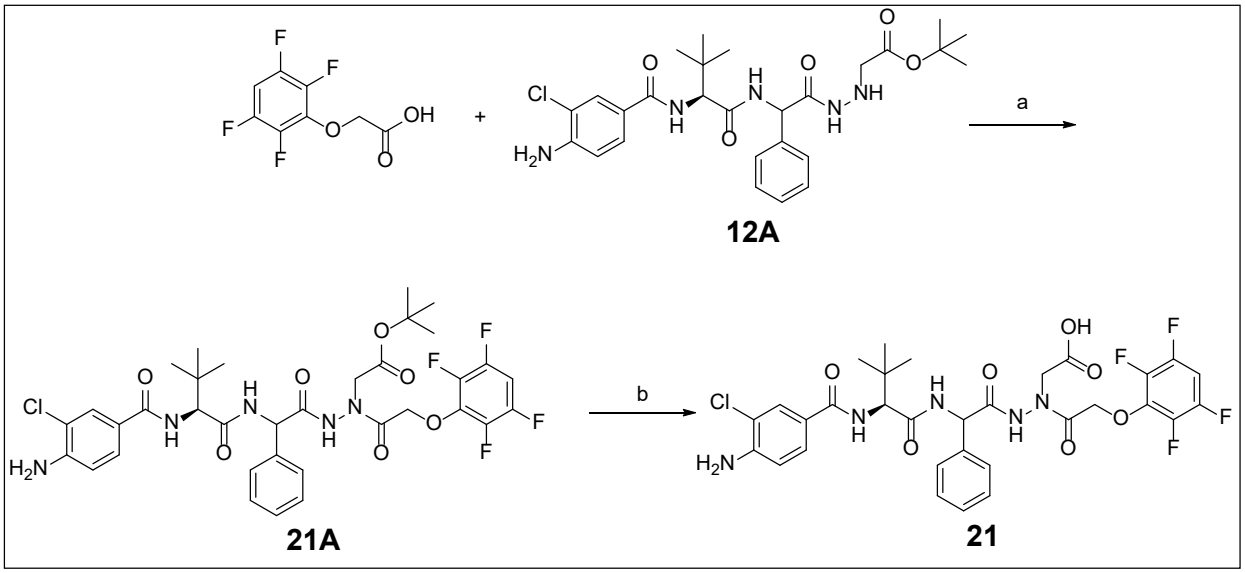


12A

21A

21

[0208] Reagents and conditions: (a) (i) $SOCl_2$, dioxane, 105 °C, 1 h, (ii) Et_3N, CH_2Cl_2, rt, 16 h; (b) TFA, CH_2Cl_2, 0 ºC-rt, 2 h.

EXAMPLE 21A

tert-Butyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-(2,3,5,6-tetrafluorophenoxy)acetyl)glycinate

[0209] The title compound (0.04 g) was prepared using the procedure described in Example 9, using Example 12A (0.1 g, 0.2 mmol) in place of Example 2A.

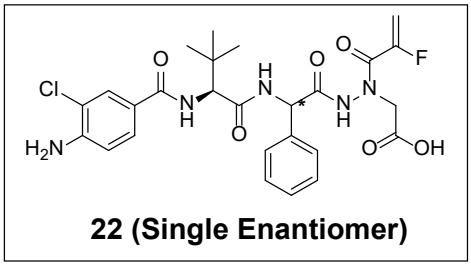
EXAMPLE 21B

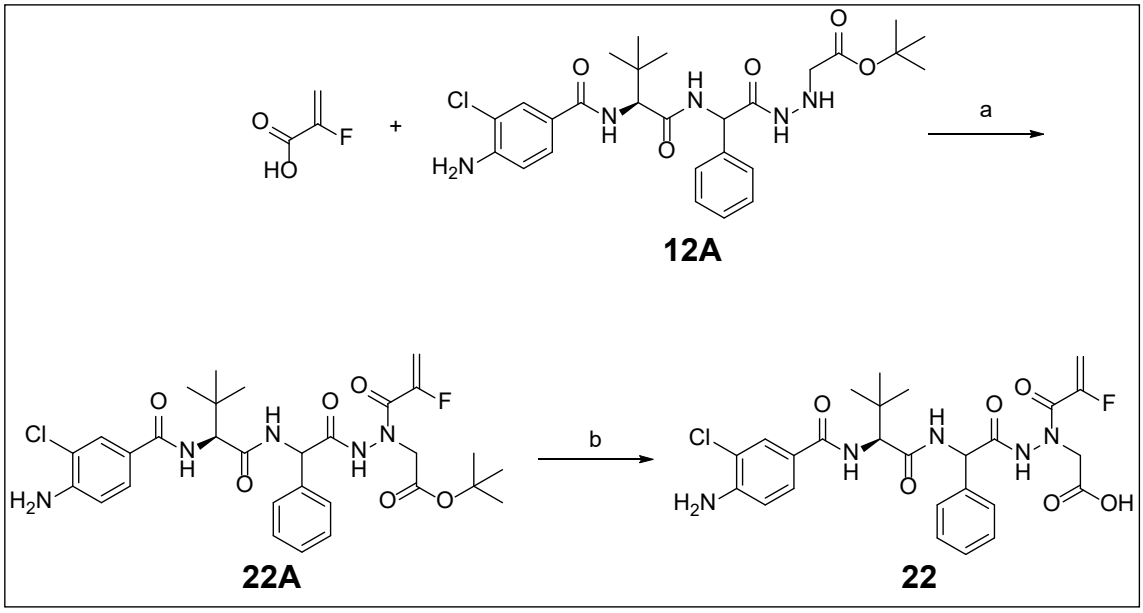
N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-(2,3,5,6-tetrafluorophenoxy)acetyl)glycine (21)

[0210] Following the procedure described in Example 12C and using Example 21A (0.04 g, 0.05 mmol) in place of 12B the crude product was obtained. Purification of the residue by prep-HPLC using SunFire C18 (19 X 250) mm; 5 µM column and 5 mM ammonium acetate in water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.005 g) at RT 26.81 min.

EXAMPLE 22

N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-fluoroacryloyl)glycine





[0211] Reagents and conditions: (a) BOP, DIPEA, DMF, 0 °C-rt, 14 h; (b) TFA, CH_2Cl_2, 0 °C-rt, 2 h.

EXAMPLE 22A

tert-Butyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-fluoroacryloyl)glycinate

[0212] To a stirred solution of Example 12A (0.35 g, 0.6 mmol) and 2-fluoroacrylic acid (0.09 g, 1.0 mmol) in DMF (10 mL) at 0 °C was subsequently added BOP (0.4 g, 1.0 mmol) and DIPEA (0.3 mL, 1.9 mmol). After overnight stirring, the reaction mixture was diluted with ethyl acetate (15 mL) and washed with ice-cold water and brine (2×10 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by flash chromatography on silica gel (0-50% ethyl acetate in hexane) afforded the title compound (0.15 g).

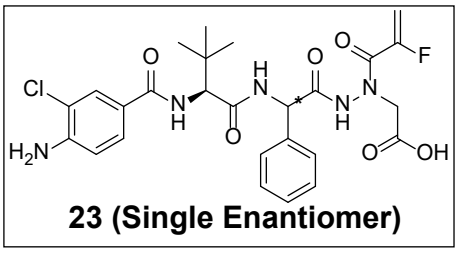
EXAMPLE 22B

N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-fluoroacryloyl)glycine (22)

[0213] Following the procedure described in Example 12C and using Example 22A (0.15 g, 0.2 mmol) in place of 12B the crude product was obtained. Purification of the residue by prep-HPLC using SunFire C18 (19 X 250) mm; 5 µM column and water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.008 g) at RT 17.25 min.

EXAMPLE 23

N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-fluoroacryloyl)glycine

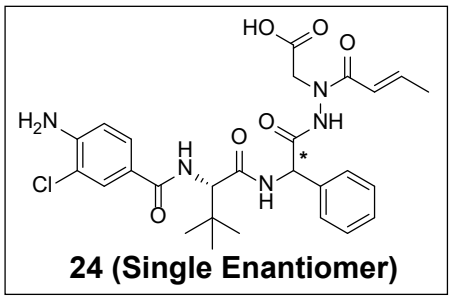


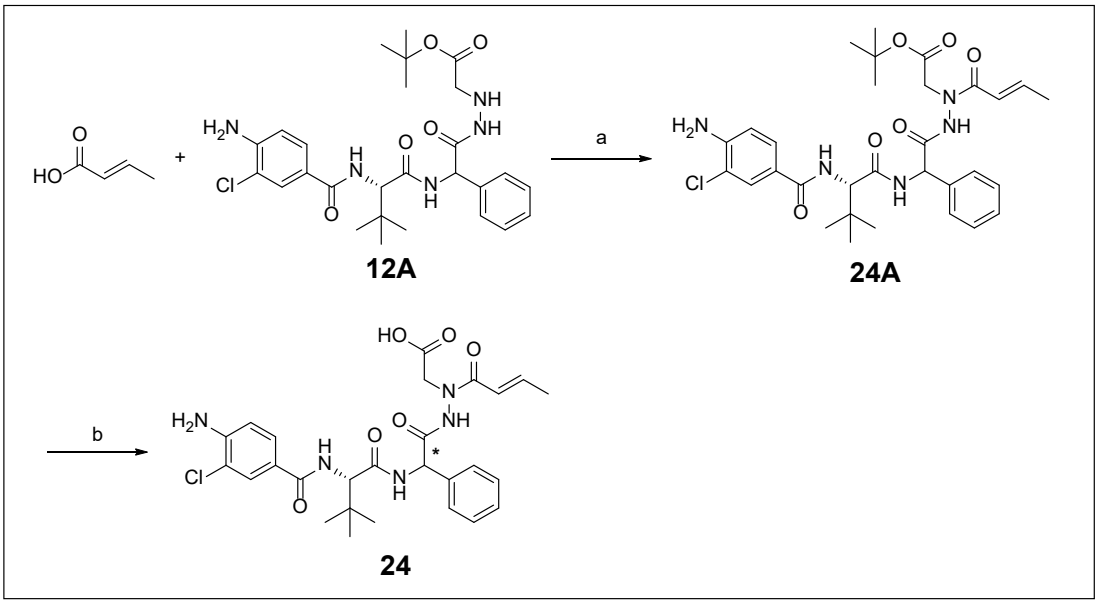
23 (Single Enantiomer)

[0214] During the preparative HPLC purification of Example 22B, the title compound (0.02 g) was isolated at RT 12.26 min.

EXAMPLE 24

N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-but-2-enoyl)glycine





[0215] Reagents and conditions: (a) EDCl, HOBt, DIPEA, DMF, 0 ºC-rt, 14 h; (b) TFA, CH_2Cl_2, 0 ºC-rt, 2 h.

EXAMPLE 24A

tert-Butyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-but-2-enoyl)glycinate

[0216] To a stirred solution of Example 12A (0.2 g, 0.4 mmol) and (2E)-but-2-enoic acid (0.05 g, 0.6 mmol) in DMF (10 mL) at 0 °C was subsequently added EDCl (0.1 g, 0.7 mmol), HOBt (0.1 g, 0.7 mmol) and DIPEA (0.3 mL, 1.9 mmol). After overnight stirring, the reaction mixture was diluted with ethyl acetate (15 mL) and washed with ice-cold water and brine (2×10 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue

by flash chromatography on silica gel (0-50% ethyl acetate in hexane) afforded the title compound (0.05 g).

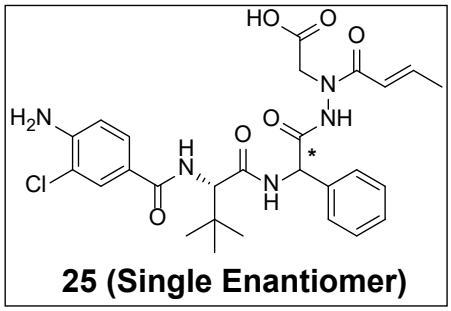
EXAMPLE 24B

N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-but-2-enoyl)glycine (24)

[0217] Following the procedure described in Example 12C and using Example 24A (0.05 g, 0.08 mmol) in place of 12B the crude product was obtained. Purification of the residue by prep-HPLC using ZORBAX C18 (19 X 250) mm; 5 µM column and 5 mM ammonium acetate in water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.004 g) at RT 17.57 min.

EXAMPLE 25

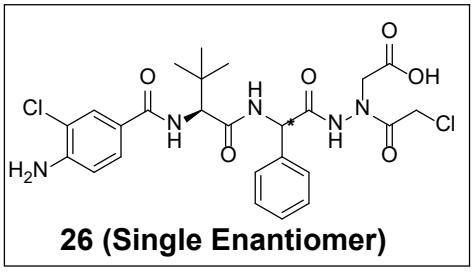
N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-but-2-enoyl)glycine

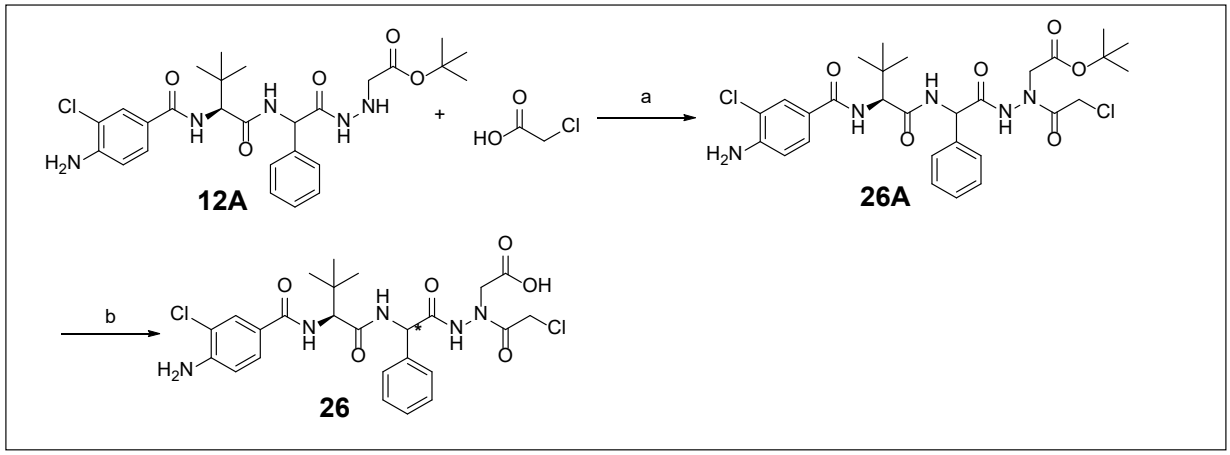


[0218] During the preparative HPLC purification of Example 24B, the title compound (0.015 g) was isolated at RT 19.70 min.

EXAMPLE 26

N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-chloroacetyl)glycine





[0219] Reagents and conditions: (a) EDCl, HOBt, DIPEA, DMF, 0 ºC-rt, 14 h; (b) TFA, CH_2Cl_2, 0 ºC-rt, 2 h.

EXAMPLE 26A

tert-Butyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-but-2-enoyl)glycinate

[0220] To a stirred solution of Example 12A (0.2 g, 0.4 mmol) and 2-chloroacetic acid (0.05 g, 0.5 mmol) in DMF (10 mL) at 0 °C was subsequently added EDCl (0.1 g, 0.7 mmol), HOBt (0.03 g, 0.2 mmol) and DIPEA (0.3 mL, 1.9 mmol). After overnight stirring, the reaction mixture was diluted with ethyl acetate (15 mL) and washed with ice-cold water and brine (2×10 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by flash chromatography on silica gel (0-50% ethyl acetate in hexane) afforded the title compound (0.06 g).

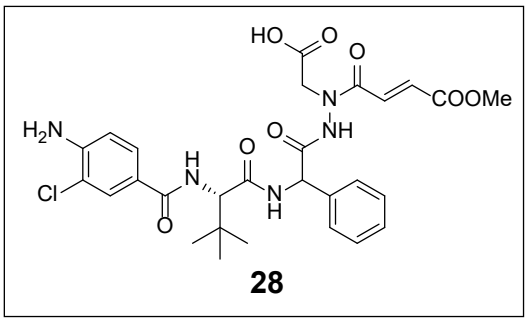
EXAMPLE 26B

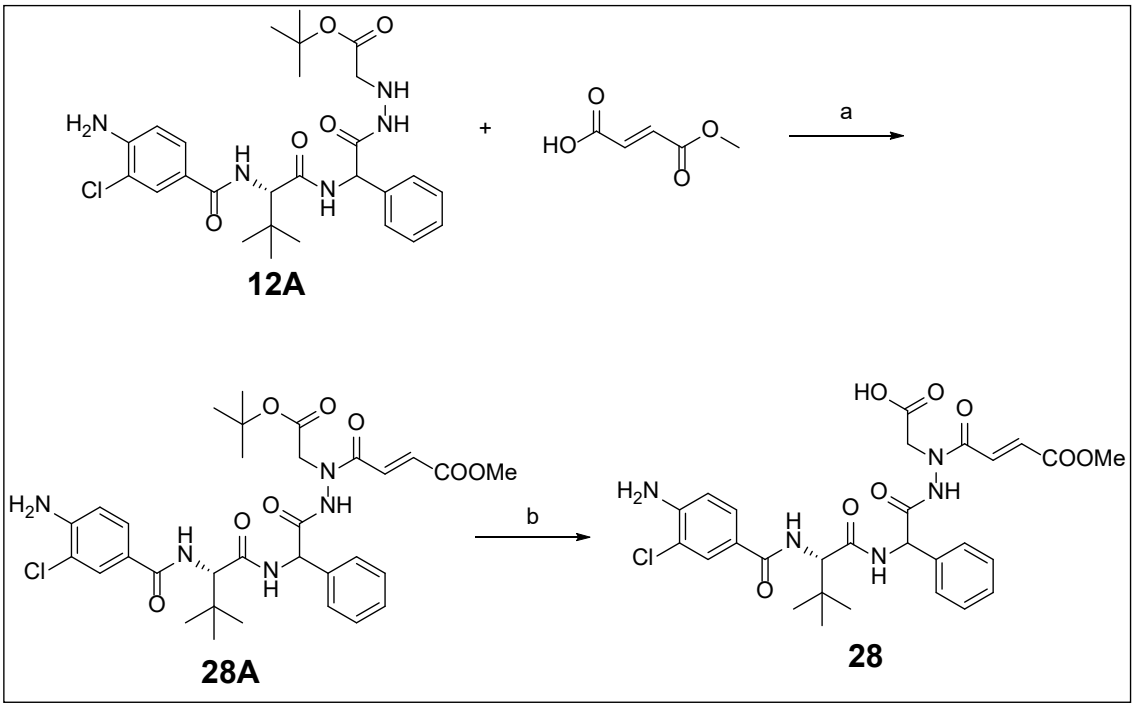
N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-(2-chloroacetyl)glycine (26)

[0221] Following the procedure described in Example 12C and using Example 26A (0.06 g, 0.08 mmol) in place of 12B the crude product was obtained. Purification of the residue by prep-HPLC using SunFire C18 (19 X 250) mm; 5 µM column and water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.025 g) at RT 15.96 min.

EXAMPLE 28

N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-4-methoxy-4-oxobut-2-enoyl)glycine





[0222] Reagents and conditions: (a) T3P, DIPEA, CH_2Cl_2, 0 °C-rt, 2 h; (b) TFA, CH_2Cl_2, 0 °C-rt, 2 h.

EXAMPLE 28A

Methyl (E)-4-((3S)-1-(4-amino-3-chlorophenyl)-3-(tert-butyl)-13,13-dimethyl-1,4,7,11-tetraoxo-6-phenyl-12-oxa-2,5,8,9-tetraazatetradecan-9-yl)-4-oxobut-2-enoate

[0223] To a stirred solution of Example 12A (0.2 g, 0.4 mmol) and (E)-4-methoxy-4-oxobut-2-enoic acid (0.05 g, 0.4 mmol) in DMF (10 mL) at 0 °C was added T3P (0.2 mL, 0.7 mmol) and DIPEA (0.3 mL, 1.6 mmol). Reaction mixture was allowed to stir for couple of hours while allowing to worm to room

temperature gradually. Upon completion, reaction mixture was diluted with ethyl acetate and washed with water and brine (2×20 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material which was purified by flash chromatography on silica gel (0-40% ethyl acetate in hexane) afforded the title compound (0.13 g).

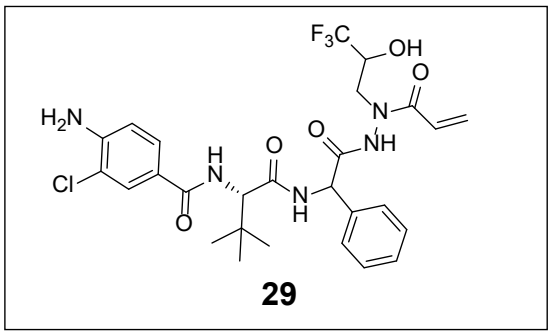
EXAMPLE 28B

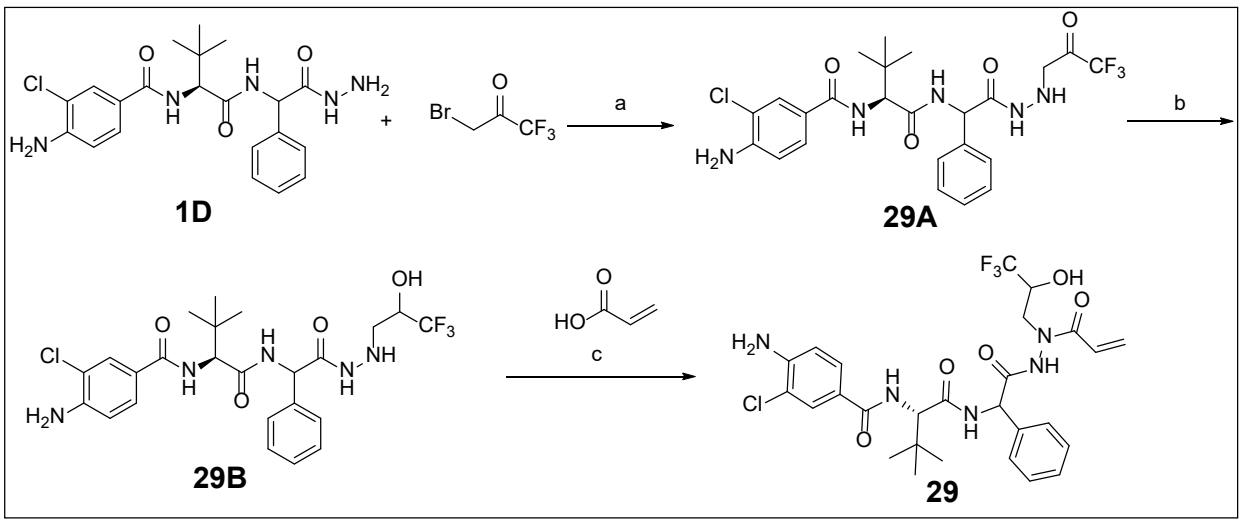
N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-phenylacetamido)-N-((E)-4-methoxy-4-oxobut-2-enoyl)glycine (28)

[0224] Following the procedure described in Example 12C and using Example 28A (0.13 g, 0.2 mmol) in place of 12B the crude product was obtained. Purification of the residue by prep-HPLC using SunFire C18 (19 X 250) mm; 5 µM column and water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.003 g) at RT 19.28 min.

EXAMPLE 29

N-((2S)-1-((2-(2-acryloyl-2-(3,3,3-trifluoro-2-hydroxypropyl)hydrazineyl)-2-oxo-1-phenylethyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-4-amino-3-chlorobenzamide





[0225] Reagents and conditions: (a) NMM, DMF, 100 ºC, 2 h; (b) $NaBH_4$, THF, MeOH, 50 ºC, 3 h; (c) EDC, HOBt, DMF, 0 ºC-rt, 6 h.

EXAMPLE 29A

4-Amino-3-chloro-N-((2S)-3,3-dimethyl-1-oxo-1-((2-oxo-1-phenyl-2-(2-(3,3,3-trifluoro-2-oxopropyl)hydrazineyl)ethyl)amino)butan-2-yl)benzamide

[0226] To a stirred solution of Example 1D (0.5 g, 1.2 mmol) in DMF (15 mL) was added 4-methylmorpholine (0.2 mL, 1.2 mmol). Reaction mixture was cooled to 0 ºC and 3-bromo-1,1,1-trifluoropropan-2-one (0.3 mg, 1.5 mmol) was added slowly. After stirring the reaction mixture for 2 hours at 100 ºC, it was diluted with ethyl acetate (25 mL) and washed consecutively with ice-cold water and brine (2×50 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by flash chromatography on silica gel (0-50% ethyl acetate in hexane) afforded the title compound (0.23 g).

EXAMPLE 29B

4-Amino-3-chloro-N-((2S)-3,3-dimethyl-1-oxo-1-((2-oxo-1-phenyl-2-(2-(3,3,3-trifluoro-2-hydroxypropyl)hydrazineyl)ethyl)amino)butan-2-yl)benzamide

[0227] To a stirred solution of Example 29A (0.23 g, 0.4 mmol) in THF (10 mL) was added sodium borohydride (0.03 g, 0.8 mmol). Reaction mixture was heated to 40 ºC and methanol (1 mL) was added. Reaction was continued at the same temperature for 3 hours and upon completion, it was quenched by adding water (15 mL) and extracted with ethyl acetate (2×20 mL). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by flash chromatography on silica gel (0-50% ethyl acetate in hexane) afforded the title compound (0.16 g).

EXAMPLE 29C

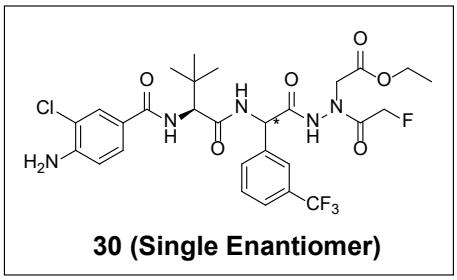
N-((2S)-1-((2-(2-acryloyl-2-(3,3,3-trifluoro-2-hydroxypropyl)hydrazineyl)-2-oxo-1-phenylethyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-4-amino-3-chlorobenzamide (29)

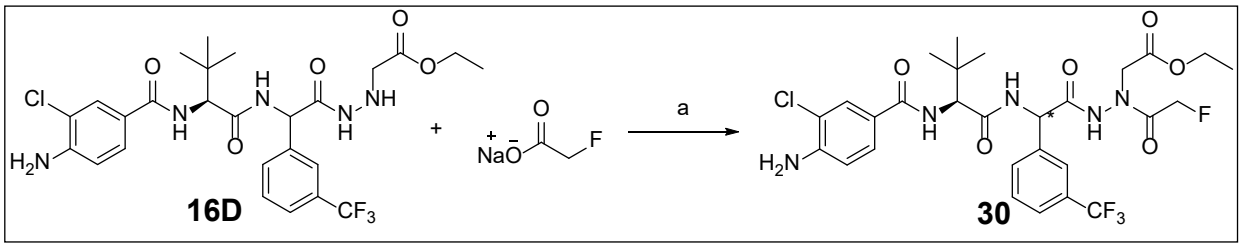
[0228] To a solution of prop-2-enoic acid (0.013 g, 0.2 mmol) in DMF (5 mL) at 0 ºC was added EDC (0.04 g, 0.2 mmol) and HOBt (0. 3 g, 0.16 mmol). After 10 minutes Example 29B (0.1 g, 0.16 mmol) was added to it. After 6 hours of stirring, the reaction mixture was diluted with ethyl acetate (10 mL) and washed with ice-cold water and brine (2×15 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by prep-HPLC

using XSelect C18 (19 X 250) mm; 5 µM column and 5mM ammonium acetate in water and MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.005 g) at RT 25.01 min.

EXAMPLE 30

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-(3-(trifluoromethyl)phenyl)acetamido)-N-(2-fluoroacetyl)glycinate



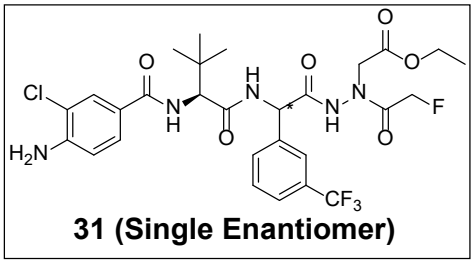


[0229] Reagents and conditions: (a) HATU, DIPEA, DMF, 0 ºC-rt, 4 h.

[0230] Following the procedure described in Example 5 and using Example 16D (0.3 g, 0.5 mmol) in place of 2B the crude product was obtained. Purification of the residue by prep-HPLC using X-Select C18 (19 X 250) mm; 5 µM column and 5 mM ammonium acetate in water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.022 g) at RT 19.34 min.

EXAMPLE 31

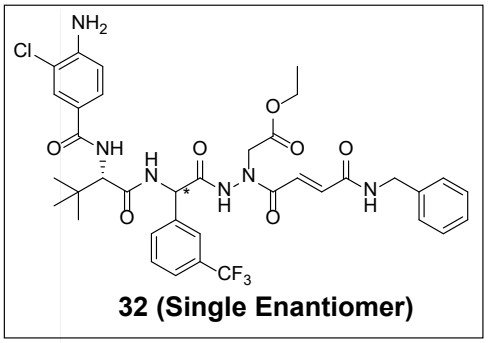
Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-(3-(trifluoromethyl)phenyl)acetamido)-N-(2-fluoroacetyl)glycinate

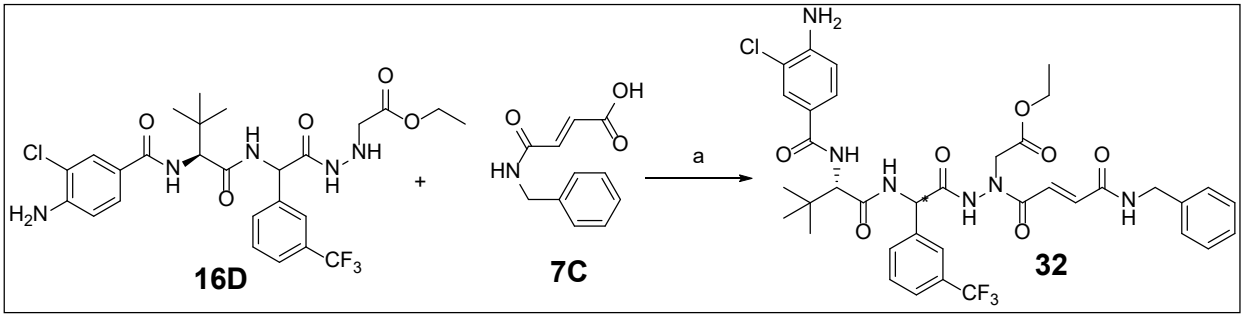


[0231] During the preparative HPLC purification of Example 30, the title compound (0.025 g) was isolated at RT 20.32 min.

EXAMPLE 32

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-(3-(trifluoromethyl)phenyl)acetamido)-N-((E)-4-(benzylamino)-4-oxobut-2-enoyl)glycinate



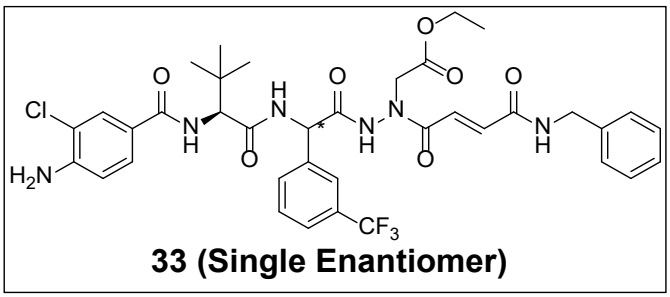


[0232] Reagents and conditions: (a) EDCl, HOBt, DIPEA, DMF, 0 ºC-rt, 14 h.

[0233] Following the procedure described in Example 7D and using Example 16D (0.3 g, 0.5 mmol) in place of 2A the crude product was obtained. Purification of the residue by prep-HPLC using X-Select C18 (19 X 250) mm; 5 µM column and water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.03 g) at RT 19.43 min.

EXAMPLE 33

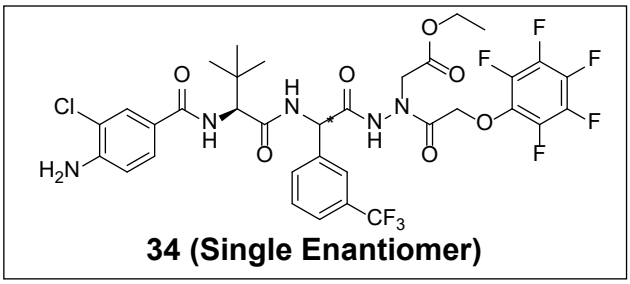
Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-(3-(trifluoromethyl)phenyl)acetamido)-N-((E)-4-(benzylamino)-4-oxobut-2-enoyl)glycinate

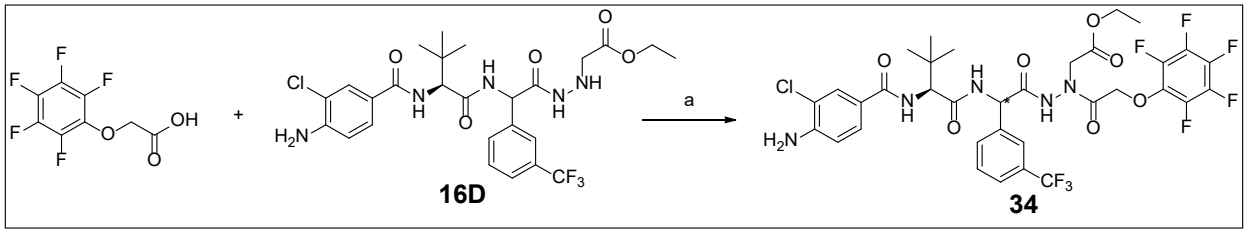


[0234] During the preparative HPLC purification of Example 32, the title compound (0.035 g) was isolated at RT 21.62 min.

EXAMPLE 34

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-(3-(trifluoromethyl)phenyl)acetamido)-N-(2-(perfluorophenoxy)acetyl)glycinate



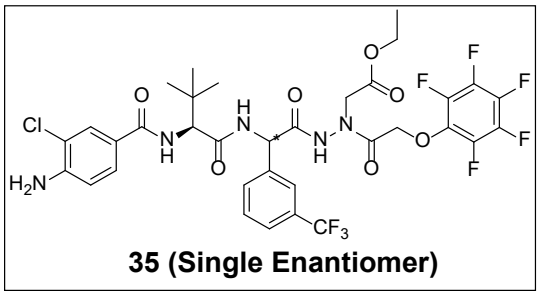


[0235] Reagents and conditions: (a) (i) $SOCl_2$, dioxane, 105 °C, 1 h, (ii) Et_3N, CH_2Cl_2, rt, 16 h.

[0236] Following the procedure described in Example 9 and using Example 16D (0.3 g, 0.5 mmol) in place of 2A the crude product was obtained. Purification of the residue by prep-HPLC using X-Select C18 (19 X 250) mm; 5 µM column and 5 mM ammonium acetate in water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.01 g) at RT 20.44 min.

EXAMPLE 35

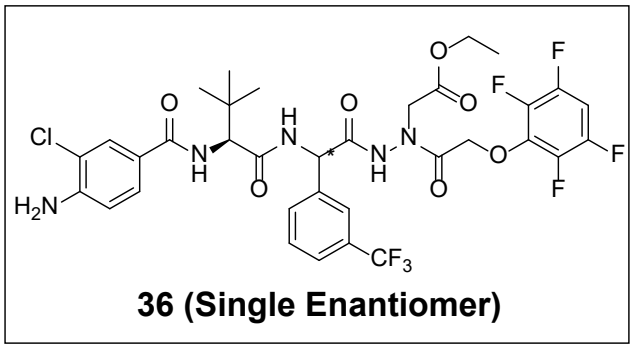
Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-(3-(trifluoromethyl)phenyl)acetamido)-N-(2-(perfluorophenoxy)acetyl)glycinate

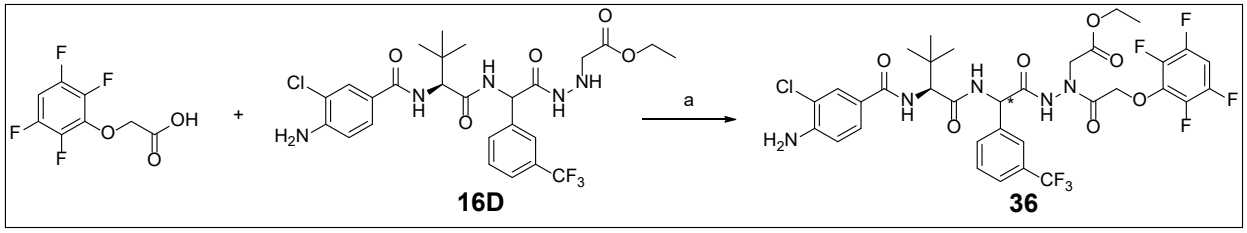


[0237] During the preparative HPLC purification of Example 34, the title compound (0.04 g) was isolated at RT 22.61 min.

EXAMPLE 36

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-(3-(trifluoromethyl)phenyl)acetamido)-N-(2-(2,3,5,6-tetrafluorophenoxy)acetyl)glycinate





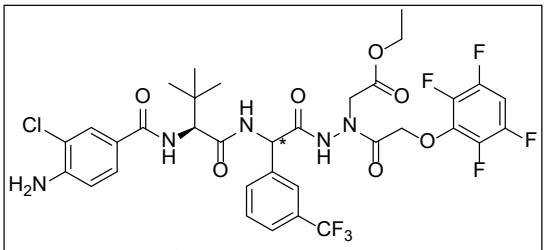
[0238] Reagents and conditions: (a) (i) $SOCl_2$, dioxane, 105 °C, 1 h, (ii) Et_3N, CH_2Cl_2, rt, 16 h.

[0239] Following the procedure described in Example 9 and using Example 16D (0.3 g, 0.5 mmol) in place of 2A the crude product was obtained. Purification of the residue by prep-HPLC using X-Select

C18 (19 X 250) mm; 5 µM column and 5 mM ammonium acetate in water; MeCN as mobile phase (19 mL/ min flow rate) afforded the title compound (0.01 g) at RT 16.70 min.

EXAMPLE 37

Ethyl N-(2-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanamido)-2-(3-(trifluoromethyl)phenyl)acetamido)-N-(2-(2,3,5,6-tetrafluorophenoxy)acetyl)glycinate

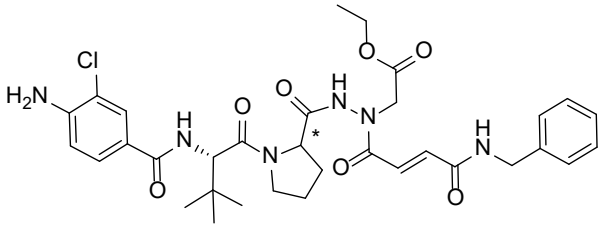


37 (Single Enantiomer)

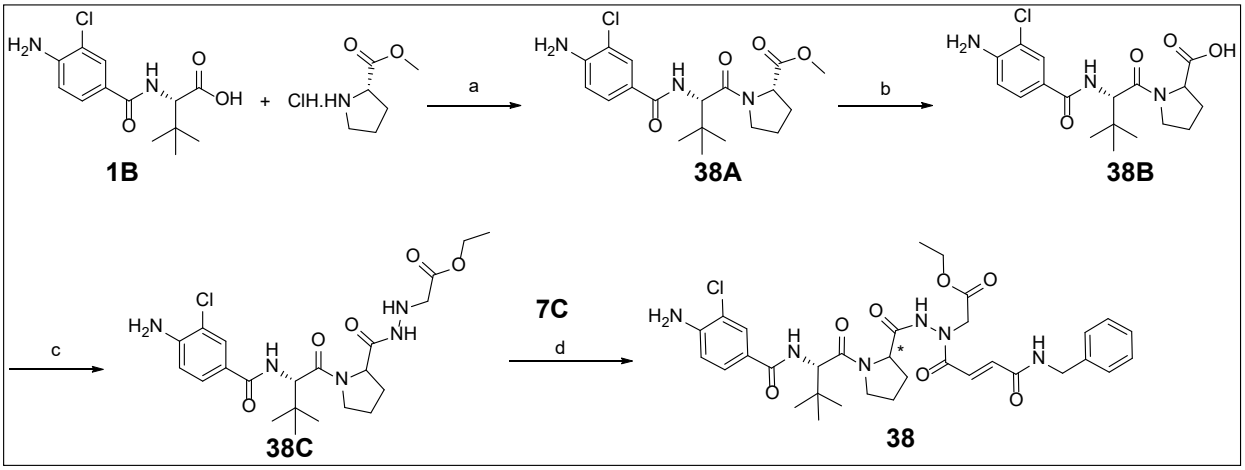
[0240] During the preparative HPLC purification of Example 36, the title compound (0.01 g) was isolated at RT 17.22 min.

EXAMPLE 38

Ethyl N-(1-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanoyl)pyrrolidine-2-carboxamido)-N-((E)-4-(benzylamino)-4-oxobut-2-enoyl)glycinate



38 (Single Enantiomer)



[0241] Reagents and conditions: (a) HATU, DIPEA, DMF, 0 °C-rt, 14 h; (b) LiOH, THF/H_2O (5:1), rt, 8 h; (c) Ethyl 2-hydrazinylacetate hydrochloride, HATU, DIPEA, DMF, 0 °C-rt, 14 h; (d) T3P, DIPEA, DMF, 0 °C-rt, 14 h.

EXAMPLE 38A

Methyl ((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanoyl)-L-prolinate

[0242] To a stirred solution of Example 1B (4.0 g, 14.0 mmol) in N,N dimethyl formamide (20 mL) at 0 °C was added HATU (7.0 g, 18.0 mmol) and DIPEA (7.3 mL, 42.0 mmol). Subsequently after 10 minutes, methyl L-prolinate hydrochloride (2.6 g, 15.0 mmol) was added. Reaction was continued overnight at an ambient temperature until both the starting materials were consumed and upon completion the reaction mixture was diluted ethyl acetate (40 mL) and washed with water and brine (2×100 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by flash chromatography on silica gel (0-40% ethyl acetate in hexane) afforded the title compound (5.0 g).

EXAMPLE 38B

((S)-2-(4-Amino-3-chlorobenzamido)-3,3-dimethylbutanoyl)proline

[0243] To a stirred solution of Example 38A (5.0 g, 12.6 mmol) in THF (50 mL) and water (10 mL) was added lithium hydroxide (1.1 g, 42.0 mmol). The reaction mixture was stirred at an ambient temperature for overnight, concentrated to a minimum volume, and the residue was diluted with water (10 mL). The pH of the aqueous phase was adjusted to 1 by the addition of HCl (aq) (1.0 M) resulting in a thick precipitate that was collected by filtration and dried to afford the title compound (4.0 g).

EXAMPLE 38C

Ethyl (1-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanoyl)pyrrolidine-2-carboxamido)glycinate

[0244] To a stirred solution of Example 38B (0.5 g, 1.3 mmol) in N,N dimethyl formamide (10 mL) at 0 °C was added HATU (0.75 g, 2.0 mmol) and DIPEA (0.7 mL, 4.0 mmol). Subsequently after 10 minutes, ethyl 2-hydrazinylacetate hydrochloride (0.3 g, 2.0 mmol) was added. Reaction was continued overnight at an ambient temperature until both the starting materials were consumed and upon completion the reaction mixture was diluted ethyl acetate (40 mL) and washed with water and brine (2×100 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by flash chromatography on silica gel (0-60% ethyl acetate in hexane) afforded the title compound (0.4 g).

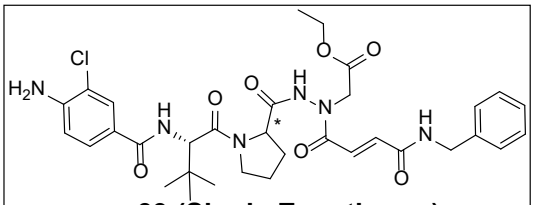
EXAMPLE 38D

Ethyl N-(1-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanoyl)pyrrolidine-2-carboxamido)-N-((E)-4-(benzylamino)-4-oxobut-2-enoyl)glycinate (38)

[0245] To a solution of Example 38C (0.3 g, 0.6 mmol) in DMF (10 mL) at 0 ºC was added propylphosphonic anhydride (50% wt solution in ethyl acetate) (0.8 mL, 1.2 mmol) and DIPEA (0.3 mL, 1.8 mmol). After 10 minutes, Example 7C (0.25 g, 1.2 mmol) was added to the solution. After overnight stirring, the reaction mixture was diluted with ethyl acetate (30.0 mL) and washed with ice-cold water and brine (2×50 mL each). Organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to get the crude material. Purification of the residue by prep-HPLC using X Select CSH C18 (19 X 250) mm; 5 µM column and 5 mM ammonium acetate in water and MeCN as mobile phase (19 mL/min flow rate) afforded the title compound (0.03 g) at RT 18.72 min.

EXAMPLE 39

Ethyl N-(1-((S)-2-(4-amino-3-chlorobenzamido)-3,3-dimethylbutanoyl)pyrrolidine-2-carboxamido)-N-((E)-4-(benzylamino)-4-oxobut-2-enoyl)glycinate



39 (Single Enantiomer)

[0246] During the preparative HPLC purification of Example 38D, the title compound (0.11 g) was isolated at RT 18.72 min.

[0247] Data for select compounds is provided in the Table below:

No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
1	10.23 (s, 1H), 10.12 (s, 1H), 8.56 (d, *J* = 8.0 Hz, 1H), 7.73-7.67 (m, 1H), 7.56-7.53 (m, 1H), 7.48-7.34 (m, 2H), 7.32-7.25 (m, 3H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.25-6.11 (m, 2H), 5.87 (s, 2H), 5.68-5.62 (m, 1H), 4.58 (d, *J* = 10 Hz, 1H), 3.24-3.19 (m, 1H), 0.95 (s, 9H)	486.2
2	11.1 (s, 1H), 8.78-8.77 (m, 1H), 8.00 (m, 1H), 7.78-7.76 (m, 1H), 7.72 (d, *J* = 9.2 Hz, 1H), 7.59-7.57 (m, 1H), 7.44-7.33 (m, 4H), 6.80-6.79 (d, *J* = 8.4 Hz, 1H), 6.15-6.11 (m, 1H), 5.89 (s, 2H), 5.56 (d, *J* = 6.8 Hz, 1H), 4.59 (d, *J* = 9.6 Hz, 1H), 4.09-4.02 (m, 2H), 3.20-3.17 (m, 2H), 1.17-1.14 (t, *J* = 6.8 Hz 3H), 0.94 (s, 9H)	572.3
3	11.19 (s, 1H), 8.83 (s, 1H), 7.77 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.39-7.35 (m, 4H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.88 (s, 2H), 5.23 (s, 1H), 4.57 (d, *J* = 8.8 Hz, 1H), 4.01 (m, 4H), 1.09 (m, 3H), 0.98 (s, 9H)	585.3
4	11.14 (s, 1H), 8.80 (s, 1H), 7.79-7.73 (m, 2H), 7.59- 7.57 (m, 1H), 7.41-7.34 (m, 5H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.94 (s, 2H), 5.42 (s, 1H), 4.55 (d, *J* = 9.2 Hz, 1H), 4.06-4.18 (m, 2H), 3.17-3.15 (m, 1H), 2.66-2.06 (m, 1H), 1.09 (m, 3H), 0.95 (s, 9H)	585.3
5	11.01 (bs, 1H), 8.80 (d, *J* = 4.8 Hz, 1H), 7.80 (d, J = 1.6 Hz, 1H), 7.65-7.58 (m, 2H), 7.42-7.35 (m, 5H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.90 (s, 2H), 5.27 (m, 2H), 4.61 (d, *J* = 9.2 Hz, 1H), 4.12- 4.05 (m, 2H), 1.13-1.06 (m, 3H), 1.0 (s, 9H).	578.3
6	11.01 (bs, 1H), 8.75 (s, 1H), 7.84-7.75 (m, 2H), 7.60-7.57 (m, 1H), 7.43-7.31 (m, 5H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.92 (s, 2H), 5.39 (d, J = 1.6 Hz, 2H), 4.86-4.76 (m, 1H), 4.57 (d, *J* = 9.2 Hz, 1H), 4.16- 4.06 (m, 2H), 1.15 (t, *J* = 5.6 Hz, 3H), 0.99 (s, 9H).	578.2

No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
7	11.22 (s, 1H), 8.89 (m, 1H), 8.74 (d, *J* = 6.4 Hz, 1H), 7.78 (d, *J* = 1.6 Hz, 1H), 7.61-7.56 (m, 2H), 7.42-7.40 (m, 2H), 7.37-7.31 (m, 6H), 7.26-7.24 (m, 3H), 6.96-6.92 (m, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.90 (s, 2H), 5.51 (d, *J* = 6.4 Hz, 1H), 4.59 (d, *J* = 9.2 Hz, 1H), 4.37 (m, 2H), 4.09 (m, 2H), 1.17-1.10 (m, 3H), 0.97 (s, 9H)	705.4
8	11.22 (s, 1H), 8.89 (m, 1H), 8.79 (d, *J* = 7.2 Hz, 1H), 7.78 (d, *J* = 2 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.59-7.57 (m, 1H), 7.40-7.38 (m, 2H), 7.35-7.25 (m, 8H), 6.94-6.90 (m, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.91 (s, 2H), 5.59 (d, *J* = 7.2 Hz, 1H), 4.59 (d, *J* = 9.2 Hz, 1H), 4.37-4.36 (m, 2H), 4.07-4.07 (m, 2H), 1.15 (t, *J* = 7.2 Hz, 3H), 0.97 (s, 9H)	705.4
9	11.01 (s, 1H), 8.78 (s, 1H), 7.77 (m, 1H), 7.68-7.55 (m, 2H), 7.43-7.34 (m, 5H), 6.79-6.74 (m, 1H), 5.88 (s, 2H), 5.45-5.30 (m,1H), 4.60-4.58 (m, 2H), 4.06-3.91 (m, 3H), 1.24-1.04 (m, 3H), 0.99-0.94 (m, 9H).	742.3
10	11.08 (s, 1H), 8.75 (s, 1H), 7.77 (m, 1H), 7.63-7.55 (m, 2H), 7.44-7.35 (m, 5H), 6.77 (d, *J* = 8.4, 1H), 5.90 (s, 2H), 5.27 (s,1H), 4.57 (d, *J* = 9.2 Hz, 1H), 4.04-3.91 (m, 3H), 1.24-1.04 (m, 3H), 0.99 (s, 9H)	742.3
11	10.91 (s, 1H), 8.79 (s, 1H), 7.76-7.68 (m, 2H), 7.57 (d, *J* = 8.4 Hz,1H), 7.43-7.29 (m, 5H), 6.75 (d, *J* = 8.4, 1H), 5.90 (s, 2H), 5.44 (s,1H), 4.59-4.57 (m, 3H), 4.06 (m, 2H), 1.20-1.14 (m, 3H), 0.98 (s, 9H)	742.3
12	12.91 (s, 1H), 11.20 (s, 1H), 8.86 (m, 1H), 8.71 (d, *J* = 6.4 Hz, 1H), 7.78 (s, 1H), 7.60-7.58 (m, 2H), 7.48-7.46 (m, 2H), 7.42-7.31 (m, 5H), 7.26-7.20 (m, 3H), 6.97-6.84 (m, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.88 (s, 2H), 5.53 (d, *J* = 6.4 Hz, 1H), 4.60 (d, *J* = 9.2 Hz, 1H), 4.37-4.26 (m, 2H), 0.93 (s, 9H)	677.4
13	12.90 (s, 1H), 11.21 (s, 1H), 8.86 (m, 1H), 8.73 (d, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.58 (dd, *J* = 1.6, 2.0 Hz, 1H), 7.44-7.38 (m, 2H), 7.35-7.31 (m, 5H), 6.29 -7.24 (m, 3H), 6.93-6.90 (m, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.89 (s, 2H), 5.60 (d, *J* = 7.2 Hz, 1H), 4.59 (d, *J* = 9.6 Hz, 1H), 4.41-4.31 (m, 2H), 0.93 (s, 9H)	677.4

No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
14	8.73 (d, *J* = 5.6 Hz, 1H), 7.80 (s, 1H), 7.63 - 7.58 (m, 3H), 7.44 - 7.35 (m, 6H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.87 (s, 2H), 5.34 (s, 1H), 4.99-4.70 (bs, 1H), 4.62 (d, *J* = 9.2 Hz, 1H), 1.01 (s, 9H)	548.2
15	10.90 (bs, 1H), 8.70-8.59 (m, 1H), 7.78 (s, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.42 - 7.33 (m, 5H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.89 (s, 2H), 5.46 (d, *J* = 5.6 Hz, 1H), 4.84-4.58 (bs, 1H), 4.45 (d, *J* = 9.6 Hz, 1H), 0.99 (s, 9H)	548.2
16	11.21 (bs, 1H), 8.92 (bs, 1H), 7.82-7.58 (m, 7H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.17-6.14 (m, 1H), 5.90 (s, 2H), 5.58-5.56 (m, 2H), 4.58 (d, *J* = 9.2 Hz, 1H), 4.12-4.05 (m, 2H), 3.18-3.16 (m, 1H), 1.15 (m, 3H), 0.99 (s, 9H)	640.3
17	10.78 (s, 1H), 8.57 (s, 1H), 7.80 (s , 1H), 7.60-7.56 (m, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.78-6.73 (m, 1H), 6.25-6.20 (m, 1H), 5.88 (s ,2H), 5.74-5.71 (m, 1H), 4.53 (d, *J* = 9.6 Hz, 1H), 4.17-.4.09 (m, 2H), 3.51-3.47 (m, 1H), 1.27-1.21 (m, 4H), 1.06-0.82 (m. 12H), 0.58-0.51 (m, 3H), 0.26 (m, 1H)	536.3
18	11.0 (bs, 1H), 8.75 (m, 1H), 7.77-7.68 (m, 2H), 7.58-7.55 (m, 1H), 7.45-7.40 (m, 2H), 7.38-7.29 (m, 3H), 6.77 (t, *J* = 8.4 Hz, 1H), 5.89 (s, 2H), 5.50-5.35 (m, 1H), 4.8-4.59 (m, 1H), 4.60 (d, *J* = 9.2 Hz), 1.0-0.94 (m, 9H)	714.2
19	11.08 (s, 1H), 8.82 (bs, 1H), 7.78 (d, *J*=2.0 Hz, 1H), 7.61-7.52 (m, 3H), 7.49-7.43 (m, 2H), 7.40-7.39 (m, 3H), 6.78 (d, *J*=7.6 Hz, 1H), 5.89 (s, 2H), 5.32 (bs, 1H), 4.61 (d, *J*=9.2 Hz, 1H), 4.06 (bs, 2H), 3.37-3.27 (m, 4H), 1.19-1.10 (m, 3H), 0.99 (s, 9H).	724.3
20	11.02 (bs, 1H), 8.79 (bs, 1H), 7.76 (bs, 1H), 7.68 (d, *J*=9.6 Hz, 1H), 7.58-7.50 (m, 2H), 7.49-7.41 (m, 2H), 7.35-7.31 (m, 3H), 7.76 (d, *J*=8.4 Hz, 1H), 5.89 (s, 2H), 5.47 (bs, 1H), 4.58 (d, *J*=9.2 Hz, 1H), 4.06 (bs, 2H), 3.30-3.22 (m, 2H), 2.42-2.35 (m, 2H), 1.19-1.10 (m, 3H), 0.94 (s, 9H).	724.3
21	10.97 (bs, 1H), 8.76 (d. *J* = 5.2 Hz 1H), 7.83-7.72 (m, 1H), 7.58-7.50 (m, 3H), 7.46-7.41 (m, 2H), 7.38-7.32 (m, 3H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.87 (s, 2H), 5.36 (s, 1H), 4.61 (d, *J* = 9.2 Hz, 1H), 1.00 (s, 9H)	696.3

No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
22	8.70 (s, 1H), 7.79 (d, *J* = 2 Hz, 1H), 7.73 -7.71 (m, 1H), 7.61-7.58 (m, 1H), 7.50- 7.40 (m, 2H), 7.32-7.27 (m, 5H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.89 (s, 2H), 5.71 (s, 1H), 4.64 (d, *J* = 9.6 Hz, 1H), 0.91 (s, 9H)	560.3
23	8.59 (s, 1H), 7.76 (d, *J* = 2 Hz, 1H), 7.64 -7.62 (m, 1H), 7.58-7.56 (m, 1H), 7.44- 7.42 (m, 2H), 7.35-7.29 (m, 3H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.88 (s, 2H), 5.58 (s, 1H), 4.59 (d, *J* = 9.6 Hz, 1H), 0.98 (s, 9H)	560.3
24	8.67 (d, J = 6.4 Hz, 1H), 7.77 (s, 1H), 7.61-7.49 (m, 4H), 7.41-7.31 (m, 3H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.61 (s, 1H), 5.88 (s, 2H), 5.54 (d, *J* = 6.4 Hz, 1H), 4.62 (d, *J* = 9.2 Hz, 1H), 3.01 (m, 1H), 1.76-1.58 (m, 3H), 1.0 (s, 9H)	558.3
25	8.70 (m, 1H), 7.79 (s, 1H), 7.59-7.48 (m, 4H), 7.38-7.37 (m, 3H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.61 (s, 1H), 5.89 (s, 2H), 5.62 (d, *J* = 6.4 Hz, 1H), 4.63 (d, *J* = 9.2 Hz, 1H), 3.01-2.94 (m, 2H), 1.76-1.58 (m, 3H), 0.93 (s, 9H)	558.3
26	8.80 - 8.78 (m, 1H), 7.68- 7.63 (m, 1H), 7.60-7.57 (m, 1H), 7.46-7.44 (m, 2H), 7.40-7.31 (m, 3H), 5.90-5.89 (m, 2H), 5.55-5.39 (m, 1H), 4.88 (s, 1H), 4.63- 4.58 (m, 1H), 4.30 (d, *J* = 3.2 Hz, 1H), 0.95 (s, 9H)	566.2
28	11.22 (s, 1H), 8.71 (s, 1H), 7.77-7.69 (m, 2H), 7.59-7.52 (m, 1H), 7.45-7.41 (m, 2H), 7.36-7.34 (m, 3H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.55-6.50 (m, 1H), 5.89 (s, 2H), 5.60 (d, *J* = 7.2 Hz, 1H), 4.61 (d, *J* = 9.6 Hz, 1H), 3.65 (s, 3H), 2.98-2.89 (m, 2H), 0.93 (s, 9H)	600.2
29	9.66-9.91 (m, 1H), 8.60-8.53 (s, 1H), 7.76 (d, *J* = 2 Hz, 1H), 7.71-7.65 (m, 1H), 7.58-7.55 (m, 1H), 7.43 - 7.38 (m, 2H), 7.35-7.26 (m, 3H), 6.80-6.78 (m, 1H), 6.39-6.33 (m, 1H), 6.17 - 6.08 (m, 1H), 5.98 - 5.95 (m, 1H), 5.89 (s, 2H), 5.70-5.66 (m, 1H), 5.47-5.43 (m, 1H), 4.60-4.57 (m, 1H), 4.33-4.26 (m, 1H), 3.74- 3.56 (m, 1H), 0.93 (s, 9H)	598.3
30	11.09 (bs, 1H), 8.97 (bs, 1H), 7.80-7.58 (m, 7H), 6.79-6.77 (d, *J*=8.4 Hz, 1H), 5.91 (s, 2H), 5.42 (bs, 1H), 5.20-4.77 (m, 1H), 4.58 (d, *J*=9.2 Hz, 1H), 4.08 - 4.02 (m, 2H), 3.16 - 3.08 (m, 1H), 1.18- -1.16 (m, 3H), 0.96 (s, 9H).	646.3

No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
31	10.38 (bs, 1H), 8.98 (bs, 1H), 7.82-7.79 (m, 2H), 7.73-7.71 (m, 3H), 7.65-7.58 (m, 2H), 6.79 (d, *J*=8.4 Hz, 1H), 5.92 (s, 2H), 5.58-5.54 (m, 1H), 4.87-4.77 (m, 1H), 4.57 (d, *J*=8.8 Hz, 1H), 4.18 - 4.05 (m, 2H), 3.22 - 3.16 (m, 2H), 1.15 -1.12 (t, *J*=6.6 Hz, 3H), 0.99 (s, 9H).	646.3
32	11.34 (s, 1H), 8.89-8.87 (m, 2H), 7.81-7.75 (m, 2H), 7.72-7.64 (m, 3H), 7.59-7.57 (m, 2H), 7.35-7.31 (m, 2H), 7.28-7.25 (m, 3H), 6.95-6.92 (m, 1H), 6.78 (d, *J*=8.4 Hz, 1H), 5.89 (s, 2H), 5.63 (d, *J*=6.0 Hz, 1H), 4.58 (d, *J*=8.8 Hz, 1H), 4.39-4.32 (m, 2H), 4.09-4.07 (m, 2H), 1.16 (t, *J*=6.8 Hz, 3H), 0.98 (s, 9H).	773.4
33	11.35 (s, 1H), 9.01 (d, *J*=5.2 Hz, 1H), 8.87 (bs, 1H), 7.81-7.78 (m, 2H), 7.72-7.65 (m, 3H), 7.61-7.55 (m, 2H), 7.35-7.25 (m, 5H), 7.00-6.94 (m, 1H), 6.78 (d, *J*=8.4 Hz, 1H), 5.90 (s, 2H), 5.74 (d, *J*=6.8 Hz, 1H), 4.62 (d, *J*=9.2 Hz, 1H), 4.47-4.35 (m, 2H), 4.08-4.06 (m, 2H), 1.14 (t, *J*=6.8 Hz, 3H), 0.92 (s, 9H).	773.4
34	11.20 (s, 1H), 8.90 (s. 1H), 7.81-7.78 (m, 2H), 7.75-7.73 (m, 1H), 7.70-7.56 (m, 4H), 6.77 (d, J = 8.4 Hz, 1H), 5.89 (s, 2H), 5.39 (s, 1H), 4.77 (s, 1H), 4.55 (d, J = 9.2 Hz, 1H), 4.10-3.98 (m, 2H), 1.13 (s, 3H), 0.99 (s, 9H)	810.3
35	11.13 (s, 1H), 9.02 (s. 1H), 7.84-7.78 (m, 3H), 7.70-7.57 (m, 4H), 6.76 (d, *J* = 8.8 Hz, 1H), 5.89 (s, 2H), 5.62 (s, 1H), 4.77 (s, 1H), 4.61-4.59 (m, 2H), 4.10-4.00 (m, 2H), 1.14 (s, 3H), 0.98 (s, 9H)	810.3
36	11.17 (s, 1H), 8.98 (s. 1H), 7.82-7.75 (m, 3H), 7.67-7.57 (m, 5H), 6.77 (d, *J* = 8.4 Hz, 1H), 5.90 (s, 2H), 5.45 (s, 1H), 4.58 (d, *J* = 9.2 Hz, 1H), 4.10-3.98 (m, 2H), 1.12 (s, 3H), 0.99 (s, 9H)	792.2
37	11.16 (s, 1H), 9.01 (s. 1H), 7.84-7.76 (m, 3H), 7.69-7.49 (m, 5H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.89 (s, 2H), 5.63-5.62 (m, 1H), 4.73 (s, 1H), 4.61 (d, *J* = 8.8 Hz, 1H), 4.06-4.01 (m, 2H), 1.08 (s, 3H), 0.92 (s, 9H)	792.2

No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
38	10.95 (s, 1H), 8.96 (bs, 1H), 7.83 (d, *J*=2.0 Hz, 1H), 7.68 (d, *J*=8.4 Hz, 1H), 7.60 (dd, *J*=8.4 Hz, 2.0 Hz, 1H), 7.34-7.24 (m, 5H), 7.20-7.10 (m, 1H), 6.98-6.94 (m, 1H), 6.76 (d, *J*=8.4 Hz, 1H), 5.90 (s, 2H), 6,64 (d, *J*=8.8 Hz, 1H), 4.40-4.29 (m, 3H), 4.15 (q, *J*=7.2 Hz, 2H), 3.83 (bs, 1H), 3.65-3.61 (m, 1H), 2.17-2.08 (m, 1H), 2.02-1.97 (m, 1H), 1.93-1.76 (m, 2H), 1.22 (t, *J*=7.2 Hz, 3H), 1.02 (s, 9H).	669.4
39	10.76 (s, 1H), 8.92 (t, *J*=6.0 Hz, 1H), 7.87-7.81 (m, 2H), 7.58 (dd, *J*=8.4 Hz, 1.6 Hz, 1H), 7.34-7.23 (m, 5H), 7.22-7.16 (m, 1H), 6.96-6.88 (m, 1H), 6.73 (d, *J*=8.8 Hz, 1H), 5.89 (s, 2H), 4.76 (d, *J*=11.6 Hz, 1H), 4.38-4.33 (m, 3H), 4.10 (q, *J*=6.8 Hz, 2H), 3.83-3.80 (m, 1H), 3.68-3.62 (m, 1H), 2.18-2.08 (m, 1H), 1.97-1.85 (m, 3H), 1.91 (t, *J*=6.8 Hz, 3H), 0.99 (s, 9H).	669.4

BIOLOGICAL EXAMPLES

[0248] IL-1, IL-18 and NLRP3 inflammasome activity regulates pyroptosis and promotes fibrosis. The IL-1β and IL-18 cause inflammation and kidney fibrosis. Inhibition of IL-1β and reversal of pyroptosis will block or reverse phenotypic changes associated with CKD. Direct correlation between inflammasome activation, including caspase-1, IL-1β and IL-18 and severity of proteinuria was observed in kidney patients. Pyroptosis is an inflammatory form of programmed cell death driven by inflammatory caspase-1, caspase-4 and caspase-5 in humans following infection or cellular damage.

Biological Example 1: Human IL-1β ELISA Assay

[0249] IL-1β release assay measures the levels of IL-1β secreted from the LPS and nigericin induced THP-1 cells. These inducers activate inflammasome pathway in THP-1 cells. Upon inflammasome activation, pro-caspase-1 is converted to caspase-1 which further processes pro-IL-1β to its bioactive IL-1β that is secreted out of the cells.

[0250] THP-1 cells stimulated with the LPS (Lipopolysaccharides from Escherichia coli O111:B4) and nigericin (Catalogue number N7143) were treated with compounds at various concentration doses and the inhibition of IL-1β levels secreted into the media supernatant is measured by ELISA (Human IL 1β ELISA kit Cat no: 557953; BD Biosciences). 20,000 cells per well of THP-1 were seeded in 35 µL RPMI media in a 384-well white plate. 5 µL of test compound was added and incubated for 1hour. 5 µL of LPS

(300 ng/mL) was added to the cells according to the plate map and the plate was incubated for 1 hour at 37 °C. 5 µL of Nigericin was added all the wells except control and blank wells, and it was incubated for 2 hours at 37°C. 25 µL of supernatant was transferred to 384 well plate. The plate was stored at -80 °C until further use. The absorbance was read at 450 nm within 30 minutes of stopping reaction.

Biological Example 2: Pyroptosis Assay

[0251] Pyroptosis assay measures the degree of Pyroptosis that occurs upon stimulation of THP-1 cells with LPS and nigercin. Pyroptosis is an inflammatory form of program cell death that depends on the formation of plasma membrane pores by members of the gasdermin (GSDM) protein family, as a consequence of caspase-1 activation via inflammasomes. Pyroptosis occurs as the result of membranous pore formation and cytoplasmic swelling, and leakage of cytosolic contents.

[0252] THP-1 cells stimulated with the LPS (Lipopolysaccharides from Escherichia coli O111:B4) and nigericin (Catalogue number N7143) are treated with compounds at various concentration doses and the inhibition of pyroptosis is measured by evaluation of levels of cellular ATP as an indirect measure of cell viability using Cell-Titer-gloTM reagent.

[0253] 20,000 cells per well of THP-1 were seeded in 35 µL RPMI media in a 384-well white plate. 5 µL of compound was added and incubated for 1 hour. 5 µL of LPS (300 ng/mL) was added to the cells according to the plate map and the plate was incubated for 1 hour at 37 °C. 5 µL of Nigericin was added all the wells except control and blank wells, and it was incubated for 2 hours at 37 °C. After incubation, plate was brought to room temperature for 5 minutes. 25 µL of CellTiter-Glo was added and the plate was incubated for 30 minutes on plate shaker covered with aluminium foil (protected from light). Luminescence was recorded on Tecan Spark. Assay buffer was thawed and aliquots of appropriate volumes was stored in -20 °C Freezer.

[0254] Activity of the tested compounds in the assays above is provided in Table 3 as follows: +++ = IC_{50} < 10 µM; ++ = IC_{50} 10 to < 30 µM; + = IC_{50} ≥ 30 µM; +* = IC_{50} > 11.

Table 3

No.	IL-1β Release	Inhibition of Pyroptosis
1	+	+
2	+++	+++
3	+	+
4	+	+

No.	IL-1β Release	Inhibition of Pyroptosis
5	+++	+
6	+++	+
7	+++	+
8	+++	++

No.	IL-1β Release	Inhibition of Pyroptosis
9	++	+
10	+++	+
11	+	+
12	+++	+
13	++	+
14	+++	+
15	+++	+
16	+++	+++
17	++	+
18	+	+
19	+++	+
20	++	+
21	+++	+
22	+	+
23	+	+

No.	IL-1β Release	Inhibition of Pyroptosis
24	+	+
25	+	+
26	+++	+
28	+	+
29	+++	+++
30	+++	+
31	+++	+
32	+++	+
33	+++	+*
34	+*	+
35	+*	+*
36	++	+
37	+++	+
38	+++	+
39	++	+

[0255] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0256] The inventions illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising”, “including,” “containing,” etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed.

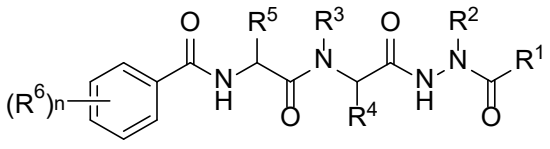
[0257] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

[0258] It is to be understood that while the disclosure has been described in conjunction with the above embodiments, that the foregoing description and examples are intended to illustrate and not limit the

scope of the disclosure. Other aspects, advantages and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure pertains.

What is claimed is:

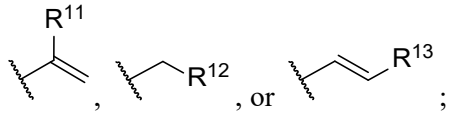
1. A compound of Formula I:



I

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

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

R^1 is  ;

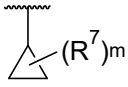
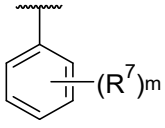
R^{11} is hydrogen, fluoro, chloro, cyano, $-CF_3$, or aryl; wherein the aryl is independently optionally substituted with one to five halo;

R^{12} is hydrogen, fluoro, chloro, cyano, $-CF_3$, aryl, or -O-aryl; wherein the aryl or -O-aryl is independently optionally substituted with one to five halo;

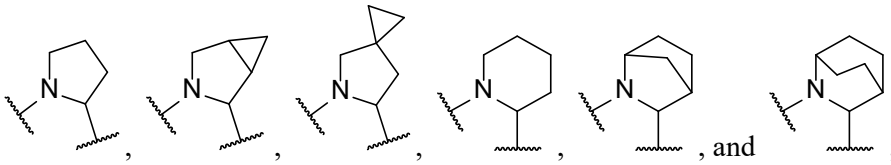
R^{13} is C_{1-6} alkyl, $-C(O)OR^8$, or $-C(O)N(R^8)_2$;

R^2 is hydrogen or C_{1-6} alkyl substituted with one to six substituents independently selected from halo, hydroxy, -C(O)OH, $-C(O)OC_{1-6}$ alkyl, and tetrazolyl, wherein each $-C(O)OC_{1-6}$ alkyl or tetrazolyl is independently optionally substituted with one to five Z^{1a};

R^3 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

R^4 is  or  , wherein m is 0, 1, 2, 3, 4, or 5;

or R^3 and R^4 together with the atoms to which they are attached form a ring selected from



; wherein each is optionally substituted by oxo or a C_{3-6} spirocycle;

R^5 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1b};

each R^6 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-C(O)N(R^{16})_2$, $-NR^{16}C(O)R^{16}$, $-OC(O)N(R^{16})_2$, $-NR^{16}C(O)OR^{16}$, $-S(O)_{0-2}R^{16}$, $-NR^{16}S(O)_{1-2}R^{16}$, $-NR^{16}C(O)N(R^{16})_2$, or $-NR^{16}S(O)_{1-2}N(R^{16})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a}; or two R^6 together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each R^7 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-OR^{17}$, $-N(R^{17})_2$, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-OC(O)R^{17}$, $-C(O)N(R^{17})_2$, $-NR^{17}C(O)R^{17}$, $-OC(O)N(R^{17})_2$, $-NR^{17}C(O)OR^{17}$, $-S(O)_{0-2}R^{17}$, $-NR^{17}S(O)_{1-2}R^{17}$, $-NR^{17}C(O)N(R^{17})_2$, or $-NR^{17}S(O)_{1-2}N(R^{17})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a}; or two R^5 together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each R^8 is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each R^{16} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each Z^{1a} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-C(O)N(R^{10})_2$, $-NR^{10}C(O)R^{10}$, $-OC(O)N(R^{10})_2$, $-NR^{10}C(O)OR^{10}$, $-S(O)_{0-2}R^{10}$, $-NR^{10}S(O)_{1-2}R^{10}$, $-NR^{10}C(O)N(R^{10})_2$, or $-NR^{10}S(O)_{1-2}N(R^{10})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1b};

each R^{10} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1b};

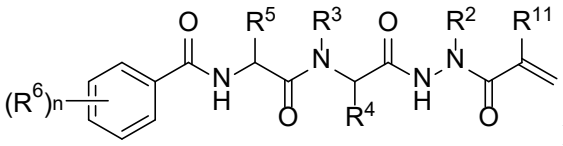
each R^{17} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each Z^{1b} is independently halo, cyano, -OH, -SH, $-NH_2$, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C_{1-6} alkyl, -L-C_{2-6} alkenyl, -L-C_{2-6} alkynyl, -L-C_{1-6} haloalkyl, -L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, $-S(O)_2-$, -N(C_{1-6} alkyl)-, -N(C_{2-6} alkenyl)-, -N(C_{2-6} alkynyl)-, -N(C_{1-6} haloalkyl)-, -N(C_{3-10} cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C_{1-6} alkyl)-, -C(O)N(C_{2-6} alkenyl)-, -C(O)N(C_{2-6} alkynyl)-, -C(O)N(C_{1-6} haloalkyl)-, -C(O)N(C_{3-10} cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -OC(O)NH-, -OC(O)N(C_{1-6} alkyl)-, -OC(O)N(C_{2-6} alkenyl)-, -OC(O)N(C_{2-6} alkynyl)-, -OC(O)N(C_{1-6} haloalkyl)-, -OC(O)N(C_{3-10} cycloalkyl)-, -OC(O)N(heterocyclyl)-, -OC(O)N(aryl)-, -OC(O)N(heteroaryl)-, -NHC(O)-, -N(C_{1-6} alkyl)C(O)-, -N(C_{2-6} alkenyl)C(O)-, -N(C_{2-6} alkynyl)C(O)-, -N(C_{1-6} haloalkyl)C(O)-, -N(C_{3-10} cycloalkyl)C(O)-, -N(heterocyclyl)C(O)-, -N(aryl)C(O)-, -N(heteroaryl)C(O)-, -NHC(O)O-, -N(C_{1-6} alkyl)C(O)O-, -N(C_{2-6} alkenyl)C(O)O-, -N(C_{2-6} alkynyl)C(O)O-, -N(C_{1-6} haloalkyl)C(O)O-, -N(C_{3-10} cycloalkyl)C(O)O-, -N(heterocyclyl)C(O)O-, -N(aryl)C(O)O-, -N(heteroaryl)C(O)O-, -NHC(O)NH-, -NHS(O)-, -S(O)NH-, $-S(O)_2NH-$, -NHS(O)NH-, or $-NHS(O)_2NH-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1b} and L is further independently optionally substituted with one to six halo, cyano, hydroxy, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl.

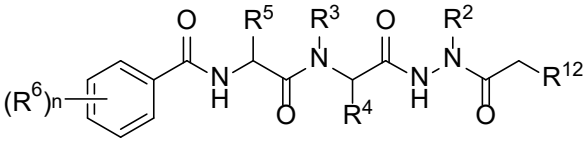
2. The compound of claim 1, wherein the compound is represented by Formula II:



II.

3. The compound of claim 1 or 2, wherein R^{11} is hydrogen or fluoro.

4. The compound of claim 1, wherein the compound is represented by Formula III:

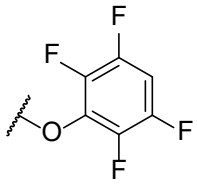
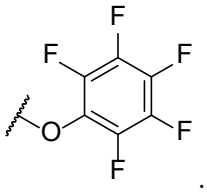


III.

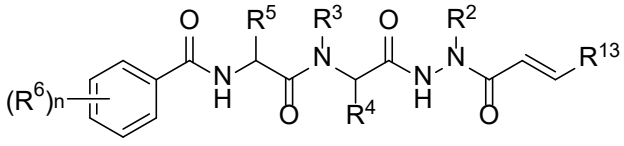
5. The compound of claim 1 or 4, wherein R^{12} is fluoro, chloro, cyano, or -O-aryl optionally substituted with one to five halo.

6. The compound of claim 1 or 4, wherein R^{12} is fluoro, chloro, or cyano.

7. The compound of claim 1 or 4, wherein R^{12} is -O-aryl optionally substituted with one to five halo.

8. The compound of claim 7, wherein R^{12} is  or  .

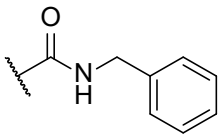
9. The compound of claim 1, wherein the compound is represented by Formula IV:



IV.

10. The compound of claim 1 or 9, wherein R^{13} is $-C(O)OR^8$ or $-C(O)N(R^8)_2$.

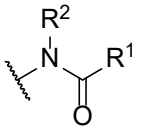
11. The compound of claim 1 or 9, wherein R^{13} is $-C(O)OR^8$ or $-C(O)NHR^8$.

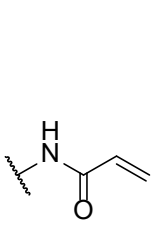
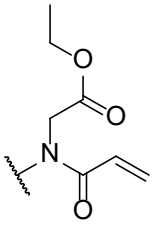
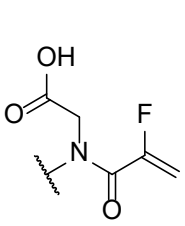
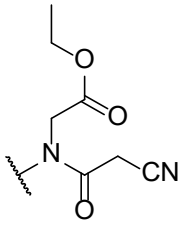
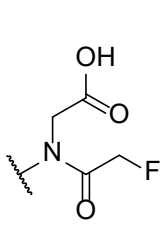
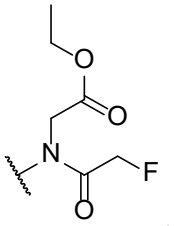
12. The compound of claim 11, wherein R^{13} is $-C(O)OCH_3$ or  .

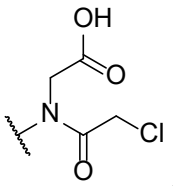
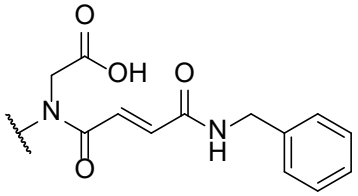
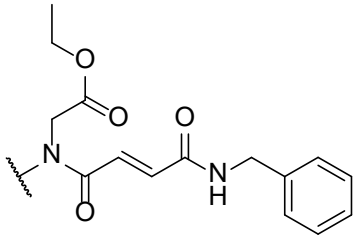
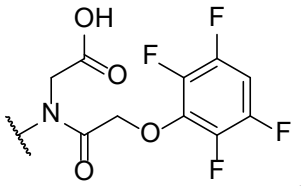
13. The compound of any preceding claim, wherein R^2 is hydrogen or C_{1-6} alkyl substituted with one to six substituents independently selected from halo, hydroxy, -C(O)OH, and $-C(O)OC_{1-6}$ alkyl.

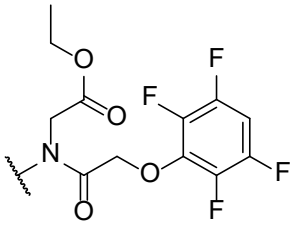
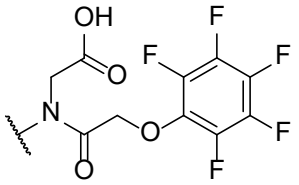
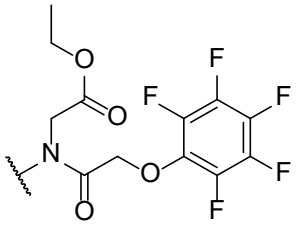
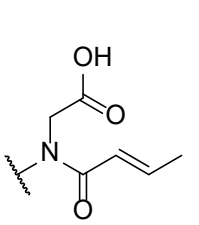
14. The compound of any preceding claim, wherein R^2 is hydrogen or C_{1-6} alkyl substituted with -CH(OH)(CF_3), -C(O)OH, or -C(O)OC_2 alkyl.

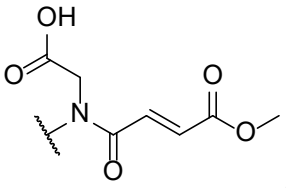
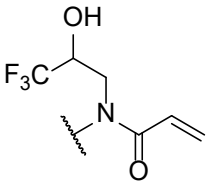
15. The compound of any preceding claim, wherein R^2 is hydrogen, -CH_2CH(OH)(CF_3), -CH_2C(O)OH, or -CH_2C(O)OC_2 alkyl.

16. The compound of any preceding claim, wherein the moiety  is:

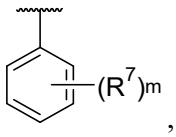
 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,

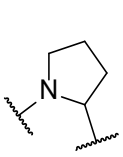
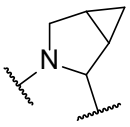
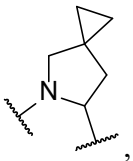
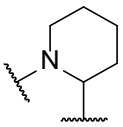
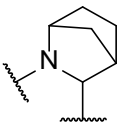
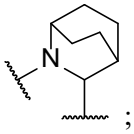
 ,  ,  ,  ,

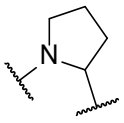
 ,  .

17. The compound of any preceding claim, wherein R^3 is hydrogen.

18. The compound of any preceding claim, wherein R^3 is hydrogen and R^4 is  or  , wherein m is 0 or 1.

19. The compound of any preceding claim, wherein m is 0 or 1, and R^7 is C_{1-6} haloalkyl.

20. The compound of any one of claims 1-16, wherein R^3 and R^4 together with the atoms to which they are attached form a ring selected from  ,  ,  ,  ,  , and  ; wherein each is optionally substituted by oxo or a C_{3-6} spirocycle.

21. The compound of claim 20, wherein R^3 and R^4 together with the atoms to which they are attached form a  .

22. The compound of any preceding claim, wherein n is 2.

23. The compound of any preceding claim, wherein each R^6 is independently halo or $-N(R^{16})_2$.

24. The compound of any preceding claim, wherein each R^6 is independently chloro or $-NH_2$.

25. The compound of any preceding claim, wherein R^5 is C_{1-6} alkyl.

26. The compound of any preceding claim, wherein R^5 is *tert*-butyl.

27. A compound of Table 1 or Table 2, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

28. A pharmaceutical composition comprising a compound of any preeding claim, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof and a pharmaceutically acceptable excipient.

29. A method for treating a disease or condition mediated, at least in part, by caspase-1, the method comprising administering an effective amount of a compound of any one of claims 1-27, or the pharmaceutical composition of claim 28 to a subject in need thereof.

30. A method for treating a chronic or acute form of an IL-1-mediated, apoptosis-mediated, IL-18-mediated, IFN-γ-mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disease, a proliferative disease, an infectious disease, or a degenerative disease, comprising administering an effective amount of a compound of any one of claims 1-27, or the pharmaceutical composition of claim 28 to a subject in need thereof.

31. The method of claim 29, wherein the disease is chronic kidney disease, diabetic nephropathy, IgA nephropathy, uveitis, an excess dietary alcohol intake disease, a necrotic disease, a viral mediated disease, inflammatory peritonitis, osteoarthritis, pancreatitis (e.g., acute pancreatitis or chronic pancreatitis), asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes (e.g., juvenile diabetes, insulin-dependent diabetes mellitus (Type I)), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, atopic dermatitis, scarring, graft vs. host disease, organ transplant rejection, osteoporosis, multiple myeloma-related bone disorder, leukemias and related disorders, myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, haemorrhagic shock, sepsis, septic shock, burns, Shigellosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, Kennedy's disease, prion disease, cerebral ischemia, epilepsy, myocardial ischemia, acute or chronic heart disease, myocardial infarction, congestive heart failure, atherosclerosis, coronary artery bypass graft, spinal muscular atrophy, amyotrophic lateral sclerosis, multiple sclerosis, HIV- or AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, neurological damage due to stroke, ulcerative collitis, traumatic brain injury, spinal cord injury, various forms of liver disease, infectious hepatitis, hepatitis-B, hepatitis-C, hepatitis-G, yellow fever, dengue fever, Japanese encephalitis, lichenplanus, acute dermatomyositis, eczema, primary cirrhosis, Behcet's disease, atopic skin disease, pure red cell aplasia, aplastic anemia, nephrotic syndrome, renal disease, renal tubulointerstitial fibrosis, neointimal hyperplasia (NH) in the arteries, polyaptic kidney disease, H. pylori-associated gastric and duodenal ulcer disease, HIV infection, tuberculosis, or meningitis.

32. The method of claim 29, wherein the disease is chronic kidney disease.

33. Use of a compound of any one of claims 1-27, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for treating a disease or condition mediated, at least in part, by caspase-1.

34. Use of a compound of any one of claims 1-27, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for treating chronic kidney disease.

35. A compound of any one of claims 1-27, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in therapy.

36. A compound of any one of claims 1-27, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in treating chronic kidney disease.

ABSTRACT

The present disclosure relates generally to small molecule modulators of caspase 1, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or prodrug thereof, and methods of making and using thereof.