Abstract: The present invention provides novel compounds useful as proteasome inhibitors. The invention also provides pharmaceutical compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various diseases.

Title: PROTEASOME INHIBITORS
PROTEASOME INHIBITORS

Field of the Invention

[001] The present invention relates to boronic acid and boronic ester compounds useful as proteasome inhibitors. The invention also provides pharmaceutical compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various diseases.

Background of the Invention


[003] Boronic acid and ester compounds hold particular promise as inhibitors of the proteasome, a multicatalytic protease responsible for the majority of intracellular protein turnover. Adams et al., U.S. Patent No. 5,780,454 (1998), describes peptide boronic ester and acid compounds useful as proteasome inhibitors. The reference also describes the use of boronic ester and acid compounds to reduce the rate of muscle protein degradation, to reduce the activity of NF-κB in a cell, to reduce the rate of degradation of p53 protein in a cell, to inhibit cydin degradation in a cell, to inhibit the growth of a cancer cell, and to inhibit NF-κB-dependent cell adhesion. Furet et al., WO 02/096933, Chatterjee et al., WO 05/016859, and Bernadini et al. WO 05/021558 and WO 06/08660, disclose additional boronic ester and acid compounds that are reported to have proteasome inhibitory activity.

[004] Ciechanover, Cell, 79: 13-21 (1994), discloses that the proteasome is the proteolytic component of the ubiquitin-proteasome pathway, in which proteins are targeted for degradation by conjugation to multiple molecules of ubiquitin. Ciechanover also discloses that the ubiquitin-proteasome pathway plays a key role in a variety of important physiological processes. Rivett et al., Biochem. J. 291:1 (1993) discloses that the proteasome displays trypsin-, chymotryptic-, and peptidylglutamyl- peptidase activities. Constituting the catalytic core of the 26S proteasome is the 20S proteasome. McCormack et al,
Biochemistry 37:7792 (1998), teaches that a variety of peptide substrates, including Suc-Leu-Leu-Val-Tyr-AMC, Z-Leu-Leu-Arg-AMC, and Z-Leu-Leu-Glu-2NA, wherein Sue is N-succinyl, AMC is 7-amino-4-methylcoumarin, and 2NA is 2-naphthylamine, are cleaved by the 20S proteasome.

[005] Proteasome inhibition represents an important new strategy in cancer treatment. King et al, Science 274:1652-1659 (1996), describes an essential role for the ubiquitin-proteasome pathway in regulating cell cycle, neoplastic growth and metastasis. The authors teach that a number of key regulatory proteins, including, cyclins, and the cyclin-dependent kinases p21 and p27KIP1, are temporally degraded during the cell cycle by the ubiquitin-proteasome pathway. The ordered degradation of these proteins is required for the cell to progress through the cell cycle and to undergo mitosis.

[006] Furthermore, the ubiquitin-proteasome pathway is required for transcriptional regulation. Palombella et al, Cell, 78:773 (1994), teaches that the activation of the transcription factor NF-κB is regulated by proteasome-mediated degradation of the inhibitor protein IκB. In turn, NF-κB plays a central role in the regulation of genes involved in the immune and inflammatory responses. Read et al., Immunity 2:493-506 (1995), teaches that the ubiquitin-proteasome pathway is required for expression of cell adhesion molecules, such as E-selectin, ICAM-I, and VCAM-I. Zetter, Seminars in Cancer Biology 4:219-229 (1993), teaches that cell adhesion molecules are involved in tumor metastasis and angiogenesis in vivo, by directing the adhesion and extravasation of tumor cells to and from the vasculature to distant tissue sites within the body. Moreover, Beg and Baltimore, Science 274:782 (1996), teaches that NF-κB is an anti-apoptotic controlling factor, and inhibition of NF-κB activation makes cells more sensitive to environmental stress and cytotoxic agents.

Structural analysis reported by Voges et al., Annu. Rev. Biochem., 68:1015 (1999) reveals that the 20S proteasome comprises 28 subunits, with the catalytic subunits \( \beta_1 \), \( \beta_2 \), and \( \beta_5 \) being responsible for peptidylglutamyl, trypic, and chymotryptic peptidase activity, respectively. Rivett et al., Curr. Protein Pept. Sci., 5:153 (2004) discloses that when the proteasome is exposed to certain cytokines, including IFN-\( \gamma \) and TNF-\( \alpha \), the \( \beta_1 \), \( \beta_2 \), and \( \beta_5 \) subunits are replaced with alternate catalytic subunits, \( \beta_{1i} \), \( \beta_{2i} \), and \( \beta_{5i} \), to form a variant form of the proteasome known as the immunoproteasome.

Orlowski, Hematology (Am. Soc. Hematol. Educ. Program) 220 (2005), discloses that the immunoproteasome also is expressed constitutively in some cells derived from hematopoietic precursors. The author suggests that inhibitors specific for the immunoproteasome may allow for targeted therapy against cancers arising from hematologic origins, thereby potentially sparing normal tissues, such as gastrointestinal and neurological tissues, from side effects.

As evidenced by the above references, the proteasome represents an important target for therapeutic intervention. There is thus a continuing need for new and/or improved proteasome inhibitors.

Description of the Invention

The present invention provides compounds that are effective inhibitors of one or more peptidase activities of the proteasome. These compounds are useful for inhibiting proteasome activity in vitro and in vivo, and are especially useful for the treatment of various cell proliferative diseases.

Compounds of the invention are of the general formula (I):

![Chemical Structure](image)

or a pharmaceutically acceptable salt or boronic acid anhydride thereof, wherein:

- \( P \) is hydrogen or an amino-group-blocking moiety;
- \( R^a \) is a \( C_{1-4} \) aliphatic or \( C_{1-4} \) fluoroaliphatic group that is substituted with 0-1 \( R^A \) or \( R^a \) and \( R^b \) taken together with the carbon atom to which they are attached, form a substituted or unsubstituted 3- to 6-membered cycloaliphatic group;
R\(^A\) is a substituted or unsubstituted aromatic or cycloaliphatic ring;

R\(^b\) is a C\(_{1,4}\) aliphatic or C\(_{1,4}\) fluoroaliphatic group; or R\(^a\) and R\(^b\), taken together with the carbon atom to which they are attached, form a substituted or unsubstituted 3- to 6-membered cycloaliphatic group;

R\(^c\) is a C\(_{1,4}\) aliphatic or C\(_{1,4}\) fluoroaliphatic group that is substituted with 0-1 R\(^c\);

R\(^c\) is a substituted or unsubstituted aromatic or cycloaliphatic ring; and

Z\(^1\) and Z\(^2\) are each independently hydroxy, alkoxy, aryloxy, or aralkoxy; or Z\(^1\) and Z\(^2\) together form a moiety derived from a boronic acid complexing agent.

[013] Unless otherwise explicitly stated, the term "proteasome" is intended to refer to both constitutive proteasome and immunoproteasome.

[014] The term "aliphatic" or "aliphatic group", as used herein, means a substituted or unsubstituted straight-chain, branched, or cyclic C\(_{1,4}\) hydrocarbon, which is completely saturated or which contains one or more units of unsaturation, but which is not aromatic. For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl, or alkynyl groups and hybrids thereof, such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl. In various embodiments, the aliphatic group has 1 to 12, 1 to 8, 1 to 6, 1 to 4, or 1 to 3 carbons.

[015] The terms "alkyl", "alkenyl", and "alkynyl", used alone or as part of a larger moiety, refer to a straight or branched chain aliphatic group having from 1 to 12 carbon atoms. For purposes of the present invention, the term "alkyl" will be used when the carbon atom attaching the aliphatic group to the rest of the molecule is a saturated carbon atom. However, an alkyl group may include unsaturation at other carbon atoms. Thus, alkyl groups include, without limitation, methyl, ethyl, propyl, allyl, propargyl, butyl, pentyl, and hexyl.

[016] For purposes of the present invention, the term "alkenyl" will be used when the carbon atom attaching the aliphatic group to the rest of the molecule forms part of a carbon-carbon double bond. Alkenyl groups include, without limitation, vinyl, 1-propenyl, 1-butynyl, 1-pentenyl, and 1-hexenyl.

[017] For purposes of the present invention, the term "alkynyl" will be used when the carbon atom attaching the aliphatic group to the rest of the molecule forms part of a
carbon-carbon triple bond. Alkynyl groups include, without limitation, ethynyl, 1-propynyl, 1-butynyl, 1-pentynyl, and 1-hexynyl.

[018] The term "cycloaliphatic", used alone or as part of a larger moiety, refers to a saturated or partially unsaturated cyclic aliphatic ring system having from 3 to about 14 members, wherein the aliphatic ring system is optionally substituted. In some embodiments, the cycloaliphatic is a monocyclic hydrocarbon having 3-8 or 3-6 ring carbon atoms. Nonlimiting examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, and cyclooctadienyl. In some embodiments, the cycloaliphatic is a bridged or fused bicyclic hydrocarbon having 6-12, 6-10, or 6-8 ring carbon atoms, wherein any individual ring in the bicyclic ring system has 3-8 members.

[019] In some embodiments, two adjacent substituents on the cycloaliphatic ring, taken together with the intervening ring atoms, form an optionally substituted fused 5- to 6-membered aromatic or 3- to 8-membered non-aromatic ring having 0-3 ring heteroatoms selected from the group consisting of O, N, and S. Thus, the term "cycloaliphatic" includes aliphatic rings that are fused to one or more aryl, heteroaryl, or heterocyclyl rings. Nonlimiting examples include indanyl, 5,6,7,8-tetrahydroquinoxalinyl, decahydroporphathyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aliphatic ring.

[020] The terms "aryl" and "ar-", used alone or as part of a larger moiety, e.g., "aralkyl", "aralkoxy", or "aryloxyalkyl", refer to a C₆ to C₁₄ aromatic hydrocarbon, comprising one to three rings, each of which is optionally substituted. Preferably, the aryl group is a C₅₋₁₀ aryl group. Aryl groups include, without limitation, phenyl, naphthyl, and anthracenyl. In some embodiments, two adjacent substituents on the aryl ring, taken together with the intervening ring atoms, form an optionally substituted fused 5- to 6-membered aromatic or 4- to 8-membered non-aromatic ring having 0-3 ring heteroatoms selected from the group consisting of O, N, and S. Thus, the term "aryl", as used herein, includes groups in which an aryl ring is fused to one or more heteroaryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the aromatic ring. Nonlimiting examples of such fused ring systems include indolyl, isoindolyl, benzothienyl, benzo[f]urananyl, dibenzofurananyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cirtmolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, fluorenyl, indanyl, phenanthridinyl, tetrahydroporphathyl, indolinyl, phenoazinyl,
benzodioxanyl, and benzodioxolyl. An aryl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term "aryl" may be used interchangeably with the terms "aryl group", "aryl moiety", and "aryl ring".

An "aralkyl" or "arylalkyl" group comprises an aryl group covalently attached to an alkyl group, either of which independently is optionally substituted. Preferably, the aralkyl group is C₆₋₁₀ aryl(C₃₋₁₀alkyl, C₆₋₁₀ aryl(C₄₋₁₀alkyl, or C₆₋₁₀ aryl(C₅₋₁₀alkyl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

The terms "heteroaryl" and "heteroar-", used alone or as part of a larger moiety, e.g., heteroaralkyl, or "heteroaralkoxy", refer to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to four heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Thus, when used in reference to a ring atom of a heteroaryl, the term "nitrogen" includes an oxidized nitrogen (as in pyridine N-oxide). Certain nitrogen atoms of 5-membered heteroaryl groups also are substitutable, as further defined below. Heteroaryl groups include, without limitation, radicals derived from thiophene, furan, pyrrole, imidazole, pyrazole, triazole, tetrazole, oxazole, isoxazole, oxadiazole, thiazole, isothiazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, indolizine, naphthyridine, pteridine, pyrrolopyridine, imidazopyridine, oxazolopyridine, thiazolopyridine, triazolopyridine, pyrrolopyrimidine, purine, and triazolopyrimidine. As used herein, the phrase "radical derived from" means a monovalent radical produced by removal of a hydrogen radical from the parent heteroaromatic ring system. The radical (i.e., the point of attachment of the heteroaryl to the rest of the molecule) may be created at any substitutable position on any ring of the parent heteroaryl ring system.

In some embodiments, two adjacent substituents on the heteroaryl, taken together with the intervening ring atoms, form an optionally substituted fused 5- to 6-membered aromatic or 4- to 8-membered non-aromatic ring having 0-3 ring heteroatoms selected from the group consisting of O, N, and S. Thus, the terms "heteroaryl" and "heteroar-", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, benzoazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-
quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-b]-1,4-oxazin-3(4H)-one. A heteroaryl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", or "heteroaryl group", any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[024] As used herein, the terms "aromatic ring" and "aromatic ring system" refer to an optionally substituted mono-, bi-, or tricyclic group having 0-6, preferably 0-4 ring heteroatoms, and having 6, 10, or 14 π electrons shared in a cyclic array. Thus, the terms "aromatic ring" and "aromatic ring system" encompass both aryl and heteroaryl groups.

[025] As used herein, the terms "heterocycle", "heterocyclyl", "heterocyclic radical", and "heterocyclic ring" are used interchangeably and refer to a stable 3- to 7-membered monocyclic, or to a fused 7- to 10-membered or bridged 6- to 10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a heterocyclyl ring having 1-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl), or +NR (as in N-substituted pyrrolidinyl). A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure, and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl.

[026] In some embodiments, two adjacent substituents on a heterocyclic ring, taken together with the intervening ring atoms, form an optionally substituted fused 5- to 6-membered aromatic or 3- to 8-membered non-aromatic ring having 0-3 ring heteroatoms selected from the group consisting of O, N, and S. Thus, the terms "heterocycle", "heterocyclyl", "heterocyclic ring", "heterocyclic group", "heterocyclic moiety", and "heterocyclic radical", are used interchangeably herein, and include groups in which a heterocyclic ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as
indolinyl, 3H-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the heterocycl ring. A heterocycl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocycl, wherein the alkyl and heterocycl portions independently are optionally substituted.

[027] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond between ring atoms. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[028] The terms "haloaliphatic", "haloalkyl", "haloalkenyl" and "haloalkoxy" refer to an aliphatic, alkyl, alkenyl or alkoxy group, as the case may be, which is substituted with one or more halogen atoms. As used herein, the term "halogen" or "halo" means F, Cl, Br, or I. The term "fluoroaliphatic" refers to a haloaliphatic wherein the halogen is fluoro, including perfluorinated aliphatic groups. Examples of fluoroaliphatic groups include, without limitation, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1,1,2-trifluoroethyl, 1,2,2-trifluoroethyl, and pentafluoroethyl.

[029] The term "linker group" or "linker" means an organic moiety that connects two parts of a compound. Linkers typically comprise an atom such as oxygen or sulfur, a unit such as -NH-, -CH₂-, -C(O)-, -C(O)NH-, or a chain of atoms, such as an alkylene chain. The molecular mass of a linker is typically in the range of about 14 to 200, preferably in the range of 14 to 96 with a length of up to about six atoms. In some embodiments, the linker is a C₁₆ alkylene chain.

[030] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., -(CH₂)ₙ-, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms is replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group. An alkylene chain also may be substituted at one or more positions with an aliphatic group or a substituted aliphatic group.

[031] An alkylene chain also can be optionally interrupted by a functional group. An alkylene chain is "interrupted" by a functional group when an internal methylene unit is replaced with the functional group. Examples of suitable "interrupting functional groups" include -C(R*)=C(R*)-, -C≡C-, -O-, -S-, -S(O)₂-, -S(O)₂N(R⁺)-, -N(R⁺)-, -N(R⁺)CO-,
-N(R⁺)C(O)N(R⁺)-, -N(R⁺)C(=NR⁺)-N(R⁺)-, -N(R⁺)-C(=NR⁺), -N(R⁺)CO₂⁻, -N(R⁺)SO₂⁻, -N(R⁺)-SO₂N(R⁺)-, -OC(O)-, -OC(O)O-, -OC(O)N(R⁺)-, -C(O)-, -CO₂⁻, -C(O)N(R⁺)-, -C(O)-C(O)-, -C(=NR⁺)N(R⁺)-, -C(NR>)-N-, -C(=NR⁺)=O-, -C(OR⁺)=N-, -C(R°)=N-O, or -N(R⁺)N(R⁺)-.

Each R⁺ independently is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, or heterocyclyl group, or two R⁺ on the same nitrogen atom, taken together with the nitrogen atom, form a 5-8 membered aromatic or non-aromatic ring having, in addition to the nitrogen atom, 0-2 ring heteroatoms selected from N, O, and S. Each R⁺ independently is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, or heterocyclyl group.

[032] Examples of C₃₋₆ alkyene chains that have been "interrupted" with -O include -CH₂OCH₂-, -CH₂O(CH₂)₂-, -CH₂O(CH₂)₃-, -CH₂O(CH₂)V-, -(CH₂)PCH₂-, -(CH₂)P(CH₂)₂-, -(CH₂)P(CH₂)₃-, -(CH₂)₂O(CH₂)₂-, and -(CH₂)₂P(CH₂)₂-. Other examples of alkyene chains that are "interrupted" with functional groups include -CH₂ZCH₂-, -CH₂Z(CH₂)V-, -CH₂Z(CH₂)V-, -CH₂Z(CH₂)V-, -(CH₂)₂ZCH₂-, -(CHJ₂Z(CHJ₂)₂-, -(CH₂)₂Z(CH₂)V-, -(CH₂)Z(CH₂)₂-, and -(CH₂)₂Z(CH₂)₂-, wherein Z is one of the "interrupting" functional groups listed above.

[033] One of ordinary skill in the art will recognize that when an alkyene chain having an interruption is attached to a functional group, certain combinations would not be sufficiently stable for pharmaceutical use. Similarly, certain combinations of T¹ and R² would not be sufficiently stable for pharmaceutical use. Only stable or chemically feasible compounds are within the scope of the present invention. A stable or chemically feasible compound is one which maintains its integrity long enough to be useful for therapeutic or prophylactic administration to a patient. Preferably, the chemical structure is not substantially altered when kept at a temperature below -70 °C, below -50 °C, below -20 °C, below 0 °C, or below 20 °C, in the absence of moisture or other chemically reactive conditions for at least a week.

[034] The term "substituted", as used herein, means that a hydrogen radical of the designated moiety is replaced with the radical of a specified substituent, provided that the substitution results in a stable or chemically feasible compound. The term "substitutable", when used in reference to a designated atom, means that attached to the atom is a hydrogen radical, which can be replaced with the radical of a suitable substituent.

[035] The phrase "one or more substituents", as used herein, refers to a number of substituents that equals from one to the maximum number of substituents possible based on
the number of available bonding sites, provided that the above conditions of stability and chemical feasibility are met. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and the substituents may be either the same or different.

As used herein, the term "independently selected" means that the same or different values may be selected for multiple instances of a given variable in a single compound.

An aryl (including the aryl moiety in aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including the heteroaryl moiety in heteroaralkyl and heteroaralkoxy and the like) group may contain one or more substituents. Examples of suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group include -halo, -NO₂, -CN, -R⁺, -C(R⁺)=C(R⁺)₂, -C≡C-R⁺, -OR⁺, -S-R⁺, -SO₂-R⁺, -SO₃-R⁺, -SO₂N(R⁺)₂, -S(O)₂N(R⁺)₂, -NR⁺C(O)-R⁺, -NR⁺C(O)N(R⁺)₂, -N(R⁺)C(NR⁺)-N(R⁺)₂, -N(R⁺)C(=NR⁺)-R⁺, -NR⁺CO₂R⁺, -NR⁺SO₂R⁺, -NR⁺SO₂N(R⁺)₂, -O-C(O)R⁺, -OC(O)N(R⁺)₂, -C(O)R⁺, -CO₂R⁺, -C(O)-C(O)R⁺, -C(O)-N(R⁺), -C(O)N(R⁺)-OR⁺, -C(O)N(R⁺)C(=NR⁺)-N(R⁺)₂, -N(R⁺)C(=NR⁺)-N(R⁺)₂, -N(R⁺)C(=NR⁺)-NR⁺-OR⁺, -NR⁺=N-OR⁺, -P(O)-(R⁺)₂, -P(O)(OR⁺)₂, and -N(OR⁺)-N(R⁺)₂, wherein R⁺ is an optionally substituted aliphatic, aryl, or heteroaryl group, and R⁺ and R⁺ are as defined above, or two adjacent substituents, taken together with their intervening atoms, form a 5-6 membered unsaturated or partially unsaturated ring having 0-3 ring atoms selected from the group consisting of N, O, and S.

An aliphatic group or a non-aromatic heterocyclic ring may be substituted with one or more substituents. Examples of suitable substituents on the saturated carbon of an aliphatic group or on a non-aromatic heterocyclic ring include, without limitation, those listed above for the unsaturated carbon of an aryl or heteroaryl group and the following: =O, =S, =N=N(R⁺)₂, =N-OR⁺, =N-NHC(O)R⁺, =N-NHCO₃R⁺, -N-NH₂SO₃R⁺, or =N-R⁺, where each R⁺ and R⁺ is as defined above.

Suitable substituents on a substitutable nitrogen atom of a heteroaryl or non-aromatic heterocyclic ring include -R⁺, -N(R⁺)₂, -C(O)R⁺, -CO₂R⁺, -C(O)-C(O)R⁺, -C(O)-CH₂C(O)R⁺, -SO₂R⁺, -SO₂N(R⁺)₂, -C(=S)N(R⁺)₂, -C(=NH)N(R⁺)₂, and -NR⁺SO₂R⁺, wherein each R⁺ is as defined above. A ring nitrogen atom of a heteroaryl or non-aromatic heterocyclic ring also may be oxidized to form the corresponding N-hydroxy or N-oxide.
compound. A nonlimiting example of such a heteroaryl having an oxidized ring nitrogen atom is N-oxidopyridyl.

[040] The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 10%.

[041] As used herein, the term "comprises" means "includes, but is not limited to."

[042] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention. Unless otherwise stated, structures depicted herein are also meant to include all geometric (or conformational) isomers, i.e., (Z) and (E) double bond isomers and (Z) and (E) conformational isomers, as well as all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. When a mixture is enriched in one stereoisomer relative to another stereoisomer, the mixture may contain, for example, an enantiomeric excess of at least 50%, 75%, 90%, 99%, or 99.5%.

[043] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of a hydrogen atom by a deuterium or tritium, or the replacement of a carbon atom by a $^{13}$C- or $^{14}$C-enriched carbon are within the scope of the invention.

[044] In the compounds of formula (I), R is a C$_{14}$ aliphatic or C$_{14}$ fluoroaliphatic group that is substituted with 0-1 R$^a$, and R$^b$ is C$_{14}$ aliphatic or C$_{14}$ fluoroaliphatic group; or R$^a$ and R$^b$, taken together with the carbon atom to which they are attached, form a substituted or unsubstituted 3- to 6-membered cycloaliphatic group. R$^A$ is a substituted or unsubstituted aromatic or cycloaliphatic ring. In some embodiments, R$^A$ is a substituted or unsubstituted aryl. In certain embodiments, R$^A$ is a substituted or unsubstituted phenyl group. In certain particular embodiments, R$^A$ is phenyl substituted with 0-3 substituents.
independently selected from the group consisting of halo, C\textsubscript{1-4} aliphatic, or C\textsubscript{1-4} fluoroaliphatic.

[045] In some embodiments, R\textsuperscript{a} is -(CH\textsubscript{2})\textsubscript{n}R\textsuperscript{A}, where n is 1 or 2, and R\textsuperscript{A} is phenyl substituted with 0-3 substituents independently selected from the group consisting of halo, C\textsubscript{1-4} aliphatic, or C\textsubscript{1-4} fluoroaliphatic.

[046] In some other embodiments, R\textsuperscript{a} and R\textsuperscript{b} are each independently a C\textsubscript{1-4} aliphatic or C\textsubscript{1-4} fluoroaliphatic group. In certain embodiments, R\textsuperscript{a} and R\textsuperscript{b} are each -CH\textsubscript{3}.

[047] In some other embodiments, R\textsuperscript{a} and R\textsuperscript{b}, taken together with the carbon atom to which they are attached, form a 3- to 6-membered cycloaliphatic group. In some such embodiments, R\textsuperscript{a} and R\textsuperscript{b}, taken together with the carbon atom to which they are attached, form a cyclopropyl or cyclobutyl ring, either of which is substituted with 0-2 substituents -R\textsuperscript{b}. Each R\textsuperscript{b} independently is a C\textsubscript{1-4} aliphatic, C\textsubscript{1-4} fluoroaliphatic, -R\textsuperscript{b}, or -T\textsuperscript{2}-R\textsuperscript{b}, where T\textsuperscript{2} is C\textsubscript{1-4} alkylen and R\textsuperscript{b} is a substituted or unsubstituted aromatic or cycloaliphatic group.

[048] In some embodiments, R\textsuperscript{b} is a substituted or unsubstituted phenyl group. In some such embodiments, R\textsuperscript{b} is phenyl substituted with 0-3 substituents independently selected from the group consisting of halo, C\textsubscript{1-4} aliphatic, or C\textsubscript{1-4} fluoroaliphatic.

[049] In the compounds of formula (J), R\textsuperscript{c} is a C\textsubscript{1-4} aliphatic or C\textsubscript{1-4} fluoroaliphatic group that is substituted with 0-1 R\textsuperscript{c}, where R\textsuperscript{c} is a substituted or unsubstituted aromatic or cycloaliphatic ring. In some embodiments, R\textsuperscript{c} has the formula -(CH\textsubscript{2})\textsubscript{m}-R\textsuperscript{c}, where m is 1 or 2, and R\textsuperscript{c} is substituted or unsubstituted phenyl. In certain embodiments, R\textsuperscript{c} is phenyl substituted with 0-3 substituents independently selected from the group consisting of halo, C\textsubscript{1-4} aliphatic, or C\textsubscript{1-4} fluoroaliphatic.

[050] In some other embodiments, R\textsuperscript{c} is C\textsubscript{1-4} aliphatic. In certain embodiments, R\textsuperscript{c} is isobutyl.

[051] In the compounds of formula (I), the variable P is an amino-group-blocking moiety. Non-limiting examples of amino-group-blocking moieties can be found in P.G.M. Wuts and T.W. Greene, Greene's Protective Groups in Organic Synthesis (4\textsuperscript{th} ed.), John Wiley & Sons, NJ (2007), and include, e.g., acyl, sulfonyl, oxyacyl, and aminoacyl groups.
In some embodiments, P is R\textsuperscript{d} C(O)-, R\textsuperscript{d} O-C(O)-, R\textsuperscript{d} N(R\textsuperscript{x}) C(O)-, R\textsuperscript{d} S(O)\textsubscript{2}, or R\textsuperscript{d} N(R\textsuperscript{x}) S(O)\textsubscript{2}, where the variable R\textsuperscript{d} is selected from the group consisting of C\textsubscript{1-6} aliphatic, C\textsubscript{1-6} fluoroaliphatic, -R\textsuperscript{D}, -T\textsuperscript{1}-R\textsuperscript{D}, and -T\textsuperscript{1}-R\textsuperscript{2d}, and the variables T\textsuperscript{1}, R\textsuperscript{D}, R\textsuperscript{3d}, and R\textsuperscript{8} have the values described below.

The variable R\textsuperscript{8} is hydrogen, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} fluoroalkyl, or C\textsubscript{6,10} ar(C\textsubscript{1-6} alkyl), the aryl portion of which is substituted or unsubstituted. In some embodiments, R\textsuperscript{4} is hydrogen or C\textsubscript{1-6} alkyl. In certain particular embodiments, R\textsuperscript{4} is hydrogen.

The variable T\textsuperscript{1} is a C\textsubscript{1-6} alkyene chain substituted with 0-2 independently selected R\textsuperscript{1a} or R\textsuperscript{3b}, wherein the alkyene chain optionally is interrupted by -Q R\textsuperscript{5}=Q R\textsuperscript{5}-, -C=C-, or -O. Each R\textsuperscript{3b} independently is selected from the group consisting of -F, -OH, -0(C\textsubscript{1-6} alkyl), -CN, -N(R\textsuperscript{5})\textsubscript{2}-C(O)(C\textsubscript{1-6} alkyl), -CO\textsubscript{2}H, -CO\textsubscript{2}(C\textsubscript{1-6} alkyl), -C(O)NH\textsubscript{2}, and -C(O)-NH(C\textsubscript{1-6} alkyl). Each R\textsuperscript{3b} independently is a C\textsubscript{1-6} aliphatic optionally substituted with R\textsuperscript{3b} or R\textsuperscript{3}. Each R\textsuperscript{3} is a substituted or unsubstituted aromatic group. In some embodiments, T\textsuperscript{1} is a C\textsubscript{1-6} alkyene chain.

The variable R\textsuperscript{2d} is halo, -OR\textsuperscript{5}, -SR\textsuperscript{5}, -S(O)R\textsuperscript{5}, -SO\textsubscript{2}R\textsuperscript{5}, -SO\textsubscript{2}N(R\textsuperscript{4}), ... -N(R\textsuperscript{4}), -NR\textsuperscript{4}C(O)R\textsuperscript{5}, -NR\textsuperscript{4}C(O)N(R\textsuperscript{4}), -NR\textsuperscript{4}CO\textsubscript{2}R\textsuperscript{5}, -N(R\textsuperscript{4})SO\textsubscript{2}R\textsuperscript{5}, -N(R\textsuperscript{4})SO\textsubscript{2}N(R\textsuperscript{4}), -O-C(O)R\textsuperscript{5}, -OC(O)-N(R\textsuperscript{4})\textsubscript{2}-C(O)R\textsuperscript{5}, -CO\textsubscript{2}R\textsuperscript{5}, or -C(O)N(R\textsuperscript{4})\textsubscript{2}, where:

- each R\textsuperscript{4} independently is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, or heterocyclyl group; or two R\textsuperscript{4} on the same nitrogen atom, taken together with the nitrogen atom, form an optionally substituted 4- to 8-membered heterocyclyl ring having, in addition to the nitrogen atom, 0-2 ring heteroatoms independently selected from N, O, and S;

- each R\textsuperscript{5} independently is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, or heterocyclyl group; and

- each R\textsuperscript{5} independently is an optionally substituted aliphatic, aryl, or heteroaryl group.

The variable R\textsuperscript{9} is a substituted or unsubstituted aromatic, heterocyclyl, or cycloaliphatic ring, any of which is optionally fused to a substituted or unsubstituted aromatic, heterocyclyl or cycloaliphatic ring. In some embodiments, R\textsuperscript{9} is a substituted or
unsubstituted mono- or bicyclic ring system selected from the group consisting of furanyl, thienyl, pyrrol, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzofuranyl, benzothiophenyl, indolyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, indazolyl, purinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and tetrahydroquinoxalinyl.

[057] In some embodiments, P has the formula $R^d$-$C(O)$-, where $R^d$ is $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, or $C_{6-10}$ ar(C$_{1-4}$) alkyl, the aryl portion of which is substituted or unsubstituted. In some other embodiments, P has the formula $R^D$-$C(O)$-, where $R^D$ is a substituted or unsubstituted phenyl, pyridinyl, pyrazinyl, pyrimidinyl, quinolinyl, or quinoxalinyl. In certain particular embodiments, P has the formula $R^D$-$C(O)$-, where $R^D$ is a phenyl, pyridinyl, pyrazinyl, pyrimidinyl, quinolinyl, or quinoxalinyl substituted with 0-3 substituents independently selected from the group consisting of halo, $C_{1-4}$ aliphatic, and $C_{1-4}$ fluoroaliphatic.

[058] Representative examples of compounds of formula (I), wherein $Z^1$ and $Z^2$ are each -OH are shown in Table 1.

Table 1: Proteasome Inhibitors

<p>| | |</p>
<table>
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<tr>
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<tbody>
<tr>
<td><img src="image1.png" alt="Image 1" /></td>
<td><img src="image2.png" alt="Image 2" /></td>
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<tr>
<td><img src="image3.png" alt="Image 3" /></td>
<td><img src="image4.png" alt="Image 4" /></td>
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The compounds in Table 1 above may also be identified by the following chemical names:

<table>
<thead>
<tr>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [(1R)-2-(4-chlorophenyl)-1-[(2-methyl-2-[(pyrazin-2-ylcarbonyl)amino]propanoyl)amino]ethyl]boronic acid</td>
</tr>
<tr>
<td>2 [(1R)-1-[[1-[(4-chlorobenzoyl)amino]cyclopropyl]carbonyl]amino]-2-(3-methylphenyl)ethyl]boronic acid</td>
</tr>
<tr>
<td>3 {(1R)-3-methyl-1-[[((1S,2S)-2-phenyl-1-[(pyrazin-2-ylcarbonyl)amino]cyclopropyl]carbonyl]amino]butyl]boronic acid</td>
</tr>
<tr>
<td>4 {(1R)-2-(4-chlorophenyl)-1-[(2-methyl-2-[(trifluoromethyl)benzoyl]amino]propanoyl)amino]ethyl]boronic acid</td>
</tr>
<tr>
<td>5 [(1R)-1-[[2-[(4-chlorobenzoyl)amino]-2-methylpropanoyl]amino]-2-(4-methylphenyl)ethyl]boronic acid</td>
</tr>
<tr>
<td>6 {(1R)-1-[[1-[(tert-butoxycarbonyl)amino]cyclobutyl]carbonyl]amino]-3-methylbutyl]boronic acid</td>
</tr>
<tr>
<td>7 [(1R)-1-[[2-[(4-chlorobenzoyl)amino]-2-methylpropanoyl]amino]-2-(4-chlorophenyl)ethyl]boronic acid</td>
</tr>
<tr>
<td>8 {(1R)-3-methyl-1-[[2-methyl-2-[(phenylacetyl)amino]propanoyl]amino]butyl]boronic acid</td>
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As used herein, the term "boronic acid" refers to a chemical compound containing a -B(OH)₂ moiety. In some embodiments, boronic acid compounds can form oligomeric anhydrides by dehydration of the boronic acid moiety. For example, Snyder et al., J. Am. Chem. Soc. 80:3611 (1958), reports oligomeric arylboronic acids.
As used herein, the term "boronic acid anhydride" refers to a chemical compound formed by combination of two or more molecules of a boronic acid compound, with loss of one or more water molecules. When mixed with water, the boronic acid anhydride compound is hydrated to release the free boronic acid compound. In various embodiments, the boronic acid anhydride can comprise two, three, four, or more boronic acid units, and can have a cyclic or linear configuration. Non-limiting examples of oligomeric boronic acid anhydrides of peptide boronic acids compound of the invention are illustrated below:

\[
\text{HO-B-O(B-OH)_\gamma}
\]

(1)

\[
\text{HO-B-O(B-OH)_{p+1}}
\]

(2)

In formulae (1) and (2), the variable \( \gamma \) is an integer from 0 to about 10, preferably 0, 1, 2, 3, or 4. In some embodiments, the boronic acid anhydride compound comprises a cyclic trimer ("boroxine") of formula (2), wherein \( p \) is 1. The variable \( W \) has the formula (3):

\[
\text{P-R^a-R^b-N-R^c}
\]

(3)

wherein the variables \( P, R^a, R^b, \) and \( R^c \) have the values described above for formula (1).

In some embodiments, at least 80% of the boronic acid present in the boronic acid anhydride compound exists in a single oligomeric anhydride form. In some embodiments, at least 85%, 90%, 95%, or 99% of the boronic acid present in the boronic acid anhydride compound exists in a single oligomeric anhydride form. In certain preferred embodiments, the boronic acid anhydride compound consists of, or consists essentially of, a boroxine having formula (3).

The boronic acid anhydride compound preferably can be prepared from the corresponding boronic acid by exposure to dehydrating conditions, including, but not
limited to, recrystallization, lyophilization, exposure to heat, and/or exposure to a drying agent. Nonlimiting examples of suitable recrystallization solvents include ethyl acetate, dichloromethane, hexanes, ether, acetonitrile, ethanol, and mixtures thereof.

In some embodiments, \( Z^1 \) and \( Z^2 \) together form a moiety derived from a boronic acid complexing agent. For purposes of the invention, the term "boronic acid complexing agent" refers to any compound having at least two functional groups, each of which can form a covalent bond with boron. Nonlimiting examples of suitable functional groups include amino and hydroxyl. In some embodiments, at least one of the functional groups is a hydroxyl group. The term "moiety derived from a boronic acid complexing agent" refers to a moiety formed by removing the hydrogen atoms from two functional groups of a boronic acid complexing agent.

As used herein, the terms "boronate ester" and "boronic ester" are used interchangeably and refer to a chemical compound containing a \(-B(Z^1)(Z^2)\) moiety, wherein at least one of \( Z^1 \) or \( Z^2 \) is alkoxy, aralkoxy, or aryloxy; or \( Z^1 \) and \( Z^2 \) together form a moiety derived from a boronic acid complexing agent having at least one hydroxyl group.

In some embodiments, \( Z^1 \) and \( Z^2 \) together form a moiety derived from a compound having at least two hydroxyl groups separated by at least two connecting atoms in a chain or ring, said chain or ring comprising carbon atoms and, optionally, a heteroatom or heteroatoms which can be N, S, or O, wherein the atom attached to boron in each case is an oxygen atom.

As employed herein, the term "compound having at least two hydroxyl groups" refers to any compound having two or more hydroxyl groups. For purposes of the invention, the two hydroxyl groups preferably are separated by at least two connecting atoms, preferably from about 2 to about 5 connecting atoms, more preferably 2 or 3 connecting atoms. For convenience, the term "dihydroxy compound" may be used to refer to a compound having at least two hydroxyl groups, as defined above. Thus, as employed herein, the term "dihydroxy compound" is not intended to be limited to compounds having only two hydroxyl groups. The moiety derived from a compound having at least two hydroxyl groups may be attached to boron by the oxygen atoms of any two of its hydroxyl groups. Preferably, the boron atom, the oxygen atoms attached to boron, and the atoms connecting the two oxygen atoms together form a 5- or 6-membered ring.
[069] For purposes of the present invention, the boronic acid complexing agent preferably is pharmaceutically acceptable, i.e., suitable for administration to humans. In some preferred embodiments, the boronic acid complexing agent is a sugar. The term "sugar" includes any polyhydroxy carbohydrate moiety, including monosaccharides, disaccharides, polysaccharides, sugar alcohols and amino sugars. In some embodiments, the sugar is a monosaccharide, disaccharide, sugar alcohol, or amino sugar. Non-limiting examples of suitable sugars include glucose, sucrose, fructose, trehalose, mannitol, sorbitol, glucosamine, and N-methylglucosamine. In certain embodiments, the sugar is mannitol or sorbitol. Thus, in the embodiments wherein the sugar is mannitol or sorbitol, $Z^1$ and $Z^2$ together form a moiety of formula $C_6H_{12}O_6$ wherein the oxygen atoms of the two deprotonated hydroxyl groups form covalent attachments with boron to form a boronate ester compound. In certain particular embodiments, $Z^1$ and $Z^2$ together form a moiety derived from D-mannitol.

[070] In some embodiments, the compound of formula (T) is formulated as a lyophilized powder, as described in Plamondon et al., WO 02/059131, hereby incorporated by reference in its entirety. In some embodiments, the lyophilized powder also comprises free dihydroxy compound. Preferably, the free dihydroxy compound and the compound of formula (T) are present in the mixture in a molar ratio ranging from about 0.5:1 to about 100:1, more preferably from about 5:1 to about 100:1. In various embodiments wherein the dihydroxy compound is mannitol, the lyophilized powder comprises free mannitol and mannitol boronate ester in a molar ratio ranging from about 10:1 to about 100:1, from about 20:1 to about 100:1, or from about 40:1 to about 100:1.

[071] In some embodiments, the lyophilized powder comprises mannitol and a compound of formula (T), substantially free of other components. However, the composition can further comprise one or more other pharmaceutically acceptable excipients, carriers, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations containing these materials is described in, e.g., Remington: The Science and Practice of Pharmacy, 20th Ed., ed. A. Gennaro, Lippincott Williams & Wilkins, 2000, or latest edition.

[072] The lyophilized powder comprising the compound of formula (T) preferably is prepared according to the procedures described in Plamondon et al., WO 02/059131. Thus, in some embodiments, the method for preparing the lyophilized powder comprises:
(a) preparing an aqueous mixture comprising a peptide boronic acid and a dihydroxy compound; and (b) lyophilizing the mixture.

**General Synthetic Methodology**

[073] The compounds of formula (I) can be prepared by methods known to one of ordinary skill in the art. See, e.g., Adams et al., U.S. Patent No. 5,780,454; Pickersgill et al., International Patent Publication WO 2005/097809. An exemplary synthetic route is set forth in Scheme 1 below.

**Scheme 1:**

![Scheme 1](image)

[074] Coupling of compound i with an N-protected amino acid (ii), followed by N-terminal deprotection, provides compound iii. Examples of suitable protecting groups (PG) include, without limitation, acyl protecting groups, e.g., formyl, acetyl (Ac), succinyl (Sue), and methoxysuccinyl; and urethane protecting groups, e.g., tert-butoxycarbonyl (Boc), benzoxycarbonyl (Cbz), and fluorenlymethoxycarbonyl (Fmoc). The peptide coupling reaction can be conducted by prior conversion of the carboxylic acid moiety of compound ii to an activated ester, e.g., an O-(N-hydroxysuccinimide) ester, followed by treatment with compound i. Alternatively, the activated ester can be generated *in situ* by contacting the carboxylic acid with a peptide coupling reagent. Examples of suitable peptide coupling reagents include, without limitation, carbodiimide reagents, *e.g.*, dicyclohexylcarbodiimide (DCC) or l-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC); phosphonium reagents, *e.g.*, benzotriazol-l-yl oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP); and uranium reagents, *e.g.*, O-(1H-benzotriazol-l-yl)-N,N,N',N'-tetramethyluronium tetrafluorborate (TBTU).
Compound iii is then coupled with an amino-group-blocking moiety, e.g., R^4-C(O)-, to afford compound iv. The peptide coupling conditions described above for the coupling of compounds i and ii are also suitable for coupling compound iii with R^4-CO_2H. Deprotection of the bororuc acid moiety then affords compound v. The deprotection step preferably is accomplished by transesterification in a biphasic mixture comprising the bororuc ester compound iv, an organic bororuc acid acceptor, a lower alkanol, a C_8-hydrocarbon solvent, and aqueous mineral acid.

Scheme 2:

Alternatively, the order of coupling reactions can be reversed, as shown in Scheme 2. Thus, an O-protected amino acid (vi) is first coupled with an amino-group-blocking moiety, e.g., R^4-C(O)-, followed by ester hydrolysis, to form compound vii. Coupling with compound i and bororuc acid deprotection are then accomplished as described above for Scheme 1 to afford compound v.

Uses, Formulation, and Administration

The present invention provides compounds that are potent inhibitors of one or more peptidase activities of the proteasome. The compounds can be assayed in vitro or in vivo for their ability to inhibit proteasome-mediated peptide hydrolysis or protein degradation.
In another aspect, therefore, the invention provides a method for inhibiting one or more peptidase activities of a proteasome in a cell, comprising contacting a cell in which proteasome inhibition is desired with a compound described herein, or a pharmaceutically acceptable salt, boronic ester, or boronic acid anhydride thereof. In some embodiments, one or more peptidase activities of immunoproteasome is inhibited at a concentration of the compound that is lower than the concentration of the compound required to inhibit one or more peptidase activities of constitutive proteasome. In some embodiments, the concentration of compound required to inhibit at least one peptidase activity of the immunoproteasome is at least 2-fold, at least 5-fold, or at least 10-fold lower than the concentration required to inhibit at least one peptidase activity of constitutive proteasome.

The invention also provides a method for inhibiting cell proliferation, comprising contacting a cell in which such inhibition is desired with a compound described herein. The phrase "inhibiting cell proliferation" is used to denote the ability of a compound of the invention to inhibit cell number or cell growth in contacted cells as compared to cells not contacted with the inhibitor. An assessment of cell proliferation can be made by counting cells using a cell counter or by an assay of cell viability, e.g., an MTT or WST assay. Where the cells are in a solid growth (e.g., a solid tumor or organ), such an assessment of cell proliferation can be made by measuring the growth, e.g., with calipers, and comparing the size of the growth of contacted cells with non-contacted cells.

Preferably, the growth of cells contacted with the inhibitor is retarded by at least about 50% as compared to growth of non-contacted cells. In various embodiments, cell proliferation of contacted cells is inhibited by at least about 75%, at least about 90%, or at least about 95% as compared to non-contacted cells. In some embodiments, the phrase "inhibiting cell proliferation" includes a reduction in the number of contacted cells, as compared to non-contacted cells. Thus, a proteasome inhibitor that inhibits cell proliferation in a contacted cell may induce the contacted cell to undergo growth retardation, to undergo growth arrest, to undergo programmed cell death (i.e., apoptosis), or to undergo necrotic cell death.

In another aspect, the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or boronic acid anhydride thereof, and a pharmaceutically acceptable carrier.

If a pharmaceutically acceptable salt of the compound of the invention is utilized in these compositions, the salt preferably is derived from an inorganic or organic acid or

[083] Nonlimiting examples of suitable acid addition salts include the following: acetate, adipate, alginate, aspartate, benzoate, benzene sulfonate, bisulfate, butyrate, citrate, camphorate, camphor sulfonate, cydopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, lucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate.

[084] Suitable base addition salts include, without limitation, ammonium salts, alkali metal salts, such as lithium, sodium and potassium salts; alkaline earth metal salts, such as calcium and magnesium salts; other multivalent metal salts, such as zinc salts; salts with organic bases, such as dicyclohexylamine, N-methyl-D-glucamine, f-butylamine, ethylene diamine, ethanolamine, and choline; and salts with amino acids such as argirine, lysine, and so forth. In some embodiments, the pharmaceutically acceptable salt is a base addition salt of a boronic acid compound of formula (1), wherein $Z_1$ and $Z_2$ are both hydroxy.

[085] The term "pharmaceutically acceptable carrier" is used herein to refer to a material that is compatible with a recipient subject, preferably a mammal, more preferably a human, and is suitable for delivering an active agent to the target site without terminating the activity of the agent. The toxicity or adverse effects, if any, associated with the carrier preferably are commensurate with a reasonable risk/benefit ratio for the intended use of the active agent.

[086] The terms "carrier", "adjuvant", or "vehicle" are used interchangeably herein, and include any and all solvents, diluents, and other liquid vehicles, dispersion or suspension aids, surface active agents, pH modifiers, isotonic agents, thickeners or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington: The Science and Practice of Pharmacy, 20th Ed., ed. A. Gennaro, Lippincott Williams & Wilkins, 2000 discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or
otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, carbonates, magnesium hydroxide and aluminum hydroxide, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, pyrogen-free water, salts or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, and zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose, sucrose, and mannitol, starches such as corn starch and potato starch, cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate, powdered tragacanth; malt, gelatin, t alc, excipients such as cocoa butter and suppository waxes, oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil, glycols such as propylene glycol and polyethylene glycol, esters such as ethyl oleate and ethyl laurate, agar, alginic acid, isotonic saline, Ringer's solution, alcohols such as ethanol, isopropyl alcohol, hexadecyl alcohol, and glycerol, cyclodextrins such as hydroxypropyl β-cyclodextrin and sulfobutylether β-cyclodextrin, lubricants such as sodium laurel sulfate and magnesium stearate, petroleum hydrocarbons such as mineral oil and petrolatum. Coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[087] The pharmaceutical compositions of the invention can be manufactured by methods well known in the art such as conventional granulating, mixing, dissolving, encapsulating, lyophilizing, or emulsifying processes, among others. Compositions may be produced in various forms, including granules, precipitates, or particulates, powders, including freeze dried, rotary dried or spray dried powders, amorphous powders, tablets, capsules, syrup, suppositories, injections, emulsions, elixirs, suspensions or solutions.

[088] According to a preferred embodiment, the compositions of this invention are formulated for pharmaceutical administration to a mammal, preferably a human being. Such pharmaceutical compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous,
intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intravenously, or subcutaneously. The formulations of the invention may be designed to be short-acting, fast-releasing, or long-acting. Still further, compounds can be administered in a local rather than systemic means, such as administration (e.g., by injection) at a tumor site.

[089] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, cyclodextrins, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[090] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 13-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use. Compositions formulated for parenteral administration may be injected by bolus injection or by timed push, or may be administered by continuous infusion.

[091] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at
least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or
dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose,
mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates,
gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar, guar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents such as phosphates or carbonates.

[092] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[093] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally,
in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[094] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[095] In some embodiments, the compound of formula (I) is administered intravenously. In such embodiments, the compound of formula (T) wherein Z¹ and Z² together form a moiety derived from a boronic acid complexing agent can be prepared in the form of a lyophilized powder, as described above. The lyophilized powder preferably is reconstituted by adding an aqueous solvent suitable for pharmaceutical administrations. Examples of suitable reconstitution solvents include, without limitation, water, saline, and phosphate buffered saline (PBS). Preferably, the lyophilized powder is reconstituted with normal (0.9%) saline. Upon reconstitution, an equilibrium is established between a boronate ester compound and the corresponding free boronic acid compound. In some embodiments, equilibrium is reached quickly, e.g., within 10-15 minutes, after the addition of aqueous medium. The relative concentrations of boronate ester and boronic acid present at equilibrium is dependent upon parameters such as, e.g., the pH of the solution, temperature, the nature of the boronic acid complexing agent, and the ratio of boronic acid complexing agent to boronate ester compound present in the lyophilized powder.

[096] The pharmaceutical compositions of the invention preferably are formulated for administration to a patient having, or at risk of developing or experiencing a recurrence of, a proteasome-mediated disorder. The term "patient", as used herein, means an animal, preferably a mammal, more preferably a human. Preferred pharmaceutical compositions of the invention are those formulated for oral, intravenous, or subcutaneous administration. However, any of the above dosage forms containing a therapeutically effective amount of a compound of the invention are well within the bounds of routine experimentation and
therefore, well within the scope of the instant invention. In some embodiments, the pharmaceutical composition of the invention may further comprise another therapeutic agent. In some embodiments, such other therapeutic agent is one that is normally administered to patients with the disease or condition being treated.

[097] By "therapeutically effective amount" is meant an amount sufficient to cause a detectable decrease in proteasome activity or the severity of a proteasome-mediated disorder. The amount of proteasome inhibitor needed will depend on the effectiveness of the inhibitor for the given cell type and the length of time required to treat the disorder. It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, and diet of the patient, time of administration, rate of excretion, drug combinations, the judgment of the treating physician, and the severity of the particular disease being treated. The amount of additional therapeutic agent present in a composition of this invention typically will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably, the amount of additional therapeutic agent will range from about 50% to about 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[098] In another aspect, the invention provides a method for treating a patient having, or at risk of developing or experiencing a recurrence of, a proteasome-mediated disorder. As used herein, the term "proteasome-mediated disorder" includes any disorder, disease or condition which is caused or characterized by an increase in proteasome expression or activity, or which requires proteasome activity. The term "proteasome-mediated disorder" also includes any disorder, disease or condition in which inhibition of proteasome activity is beneficial.

[099] For example, compounds and pharmaceutical compositions of the invention are useful in treatment of disorders mediated via proteins (e.g., NFKB, p27^[kip], p21^[WAF1/CIP1], p53) which are regulated by proteasome activity. Relevant disorders include inflammatory disorders (e.g., rheumatoid arthritis, inflammatory bowel disease, asthma, chronic obstructive pulmonary disease (COPD), osteoarthritis, dermatosis (e.g., atopic dermatitis, psoriasis)), vascular proliferative disorders (e.g., atherosclerosis, restenosis), proliferative ocular disorders (e.g., diabetic retinopathy), benign proliferative disorders (e.g., hemangiomas), autoimmune diseases (e.g., multiple sclerosis, tissue and organ rejection), as well as inflammation associated with infection (e.g., immune responses), neurodegenerative
disorders (e.g., Alzheimer's disease, Parkinson's disease, motor neurone disease, neuropathic pain, triplet repeat disorders, astrocytoma, and neurodegeneration as result of alcoholic liver disease), ischemic injury (e.g., stroke), and cachexia (e.g., accelerated muscle protein breakdown that accompanies various physiological and pathological states, (e.g., nerve injury, fasting, fever, acidosis, HTV infection, cancer affliction, and certain endocrinopathies))

[0100] The compounds and pharmaceutical compositions of the invention are particularly useful for the treatment of cancer. As used herein, the term "cancer" refers to a cellular disorder characterized by uncontrolled or disregulated cell proliferation, decreased cellular differentiation, inappropriate ability to invade surrounding tissue, and/or ability to establish new growth at ectopic sites. The term "cancer" includes, but is not limited to, solid tumors and bloodborne tumors. The term "cancer" encompasses diseases of skin, tissues, organs, bone, cartilage, blood, and vessels. The term "cancer" further encompasses primary and metastatic cancers.

[0101] Non-limiting examples of solid tumors that can be treated with the disclosed proteasome inhibitors include pancreatic cancer; bladder cancer; colorectal cancer; breast cancer, including metastatic breast cancer; prostate cancer, including androgen-dependent and androgen-independent prostate cancer; renal cancer, including, e.g., metastatic renal cell carcinoma; hepatocellular cancer; lung cancer, including, e.g., non-small cell lung cancer (NSCLC), bronchioloalveolar carcinoma (BAC), and adenocarcinoma of the lung; ovarian cancer, including, e.g., progressive epithelial or primary peritoneal cancer; cervical cancer; gastric cancer; esophageal cancer; head and neck cancer, including, e.g., squamous cell carcinoma of the head and neck; melanoma; neuroendocrine cancer, including metastatic neuroendocrine tumors; brain tumors, including, e.g., glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma; bone cancer; and soft tissue sarcoma.

[0102] Non-limiting examples of hematologic malignancies that can be treated with the disclosed proteasome inhibitors include acute myeloid leukemia (AML); chronic myelogenous leukemia (CML), including accelerated CML and CML blast phase (CML-BP); acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); Hodgkin's disease (HD); non-Hodgkin's lymphoma (NHL), including follicular lymphoma and mantle cell lymphoma; B-cell lymphoma; T-cell lymphoma; multiple myeloma (MM); Waldenstrom's macroglobulinemia; myelodysplastic syndromes (MDS), including refractory anemia (RA), refractory anemia with ringed siderblasts (RARS), (refractory anemia with
excess blasts (RAEB), and RAEB in transformation (RAEB-T); and myeloproliferative syndromes.

In some embodiments, the compound or composition of the invention is used to treat a patient having or at risk of developing or experiencing a recurrence in a cancer selected from the group consisting of multiple myeloma and non-Hodgkins lymphoma (NHL).

In some embodiments, the proteasome inhibitor of the invention is administered in conjunction with another therapeutic agent. The other therapeutic agent may also inhibit the proteasome, or may operate by a different mechanism. In some embodiments, the other therapeutic agent is one that is normally administered to patients with the disease or condition being treated. The proteasome inhibitor of the invention may be administered with the other therapeutic agent in a single dosage form or as a separate dosage form. When administered as a separate dosage form, the other therapeutic agent may be administered prior to, at the same time as, or following administration of the proteasome inhibitor of the invention.

In some embodiments, a proteasome inhibitor of formula (I) is administered in conjunction with an anticancer agent. As used herein, the term "anticancer agent" refers to any agent that is administered to a subject with cancer for purposes of treating the cancer.

Non-limiting examples of DNA damaging chemotherapeutic agents include topoisomerase I inhibitors (e.g., irinotecan, topotecan, camptothecin and analogs or metabolites thereof, and doxorubicin); topoisomerase II inhibitors (e.g., etoposide, teniposide, and daunorubicin); alkylating agents (e.g., melphalan, chlorambucil, busulfan, thiotepa, ifosfamide, carmustine, lomustine, semustine, streptozocin, decarbazine, methotrexate, mitomycin C, and cyclophosphamide); DNA intercalators (e.g., cisplatin, oxaliplatin, and carboplatin); DNA intercalators and free radical generators such as bleomycin; and nucleoside mimetics (e.g., 5-fluorouracil, capecitabine, gemcitabine, fludarabine, cytarabine, mercaptopurine, thioguanine, pentostatin, and hydroxyurea).

Chemotherapeutic agents that disrupt cell replication include: paclitaxel, docetaxel, and related analogs; vincristine, vinblastin, and related analogs; thalidomide, lenalidomide, and related analogs (e.g., CC-5013 and CC-4047); protein tyrosine kinase inhibitors (e.g., imatinib mesylate and gefitinib); proteasome inhibitors (e.g., bortezomib); NF-κB inhibitors, including inhibitors of IκB kinase; antibodies which bind to proteins overexpressed in cancers and thereby downregulate cell replication (e.g., trastuzumab,
rituximab, cetuximab, and bevacizumab); and other inhibitors of proteins or enzymes known to be upregulated, over-expressed or activated in cancers, the inhibition of which downregulates cell replication.

[0108] In order that this invention be more fully understood, the following preparative and testing examples are set forth. These examples illustrate how to make or test specific compounds, and are not to be construed as limiting the scope of the invention in any way.
EXAMPLES

Abbreviations
ACN acetonitrile
AIB aminoisobutyric acid
BOC ferf-butoxycarbonyl
DCM methylene chloride
DIEA diisopropylethyl amine
DMF dimethylformamide
EDCI N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
EtOAc ethyl acetate
h hours
HPLC high performance liquid chromatography
HATU O-(7-azabor^otriazol-l-yl)-N,N,N^N'-tetramethyluronium hexafluorophosphate
HOBt 1-hydroxybenztriazole hydrate
LC/MS liquid chromatography mass spectrum
MeOH methanol
min minutes
NMM 4-methylmorpholine
R retention time from diode array spectra
TBTU o-benzotriazol-l-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate

Analytical LC-MS Methods

LC-MS analyses of boronic acids were run on a Hewlett-Packard HPII00 Waters Symmetry C18 3.5 μm 4.6 x 100 mm ID column using the following gradient (Formic Acid Purity method):
Solvent A: 1% acetonitrile, 99% water, 0.1% Formic Acid
Solvent B: 95% acetonitrile, 5% water, 0.1% Formic Acid

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<th>B [%]</th>
<th>Flow [mL/min]</th>
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<tr>
<td>9.8</td>
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</table>
LC-MS analysis of intermediates were run on a Hewlett-Packard HPII00 with a Waters Symmetry C18 3.5 µm 4.6 x 100 mm ID column using the following conditions:

Formic Acid method: 2.5 mL/min gradient of ACN containing 0 to 100 percent 0.1% Formic Acid in H₂O for 3 min

Ammonium Acetate method: 2.5 mL/min gradient of ACN containing 0 to 100 percent 10 mM Ammonium Acetate in H₂O for 3 min.

General Procedures

Example 1: \( \text{f(} \text{IR')-2-(2-fluorophenyl')-l-(lα,5,5-trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-yl)ethynamino-l,l-dimethyl-2-oxoethy} \)propanoyllaminotetllboronic acid (37)

Step IA: tert-Butyl \( \text{(2-\{[(lR)-2-(2-fluorophenyl)-l-(3f} \)t,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)ethylamino}\)l,l-dimethyl-2-oxoethy carbamate

DIPEA (0.3 mL, 1.60 mmol) was added to a solution of BOC-AIB-OH (0.094 g, 0.46 mmol), (IR)-2-(2-fluorophenyl)-l-(3f ,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)ethanamine (0.200 g, 0.46 mmol) and TBTU (0.164 g, 0.51 mmol) in DMF (2.5 mL). The reaction was stirred at 22 °C then diluted with H₂O and extracted using EtOAc. The organic layer was washed with H₂O (2x), dried (MgSO₄), filtered, and concentrated to give the title compound (0.235, 101%). LC/MS: \( \text R_1 = 2.55 \text{ min, ES}^+ 504 \) (Formic Acid method).

Step IB: 2-amino-N-\{[(lR)-2-(2-fluorophenyl)-l-(3f,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)ethyn-2-methylpropanamide *HCl

[0114] tert-Butyl \( \text{(2-} \{[(lR)-2-(2-fluorophenyl)-l-(3 α,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)ethylamino\)l,l-dimethyl-2-oxoethyl)carbamate (0.231 g, 0.46 mmol) was stirred in 4N HCl in dioxane (2.0 mL) for 2 h then concentrated to give the title compound as a yellow solid (0.228 g, 112%). LC/MS: \( \text R_1 = 1.29 \text{ min, ES}^+ 403 \) (Formic Acid method).
Step 1C: N-(2-l f(IRV2-(2-fluorophenyl)-l-(3f,5,5-trimethylhexahydro-4,6-methano-1,3,2-
benzodioxaborol-2-yl)emylaminol-l,1-dimethyl-2-oxoethyl)quinoxaline-2-
carboxamide

[0115] The title compound was prepared following the procedure described in Example 1, step A using 2-quinoxalinecarboxylic acid (0.080 g, 0.46 mmol). The peach-colored solid was purified by flash chromatography (75% EtOAc in hexanes) to give a yellow solid (0.129 g, 50%). LC/MS: Rm = 2.51 min, ES+ 560 (Formic Acid method). 1H NMR (CD3OD, 400 MHz, δ): 9.49 (s, 1H); 8.97 (s, 1H); 8.92 (s, 1H); 8.29-8.18 (m, 2H); 8.06-7.97 (m, 2H); 7.32-7.24 (m, 1H); 7.18-7.09 (m, 1H); 7.07-6.99 (m, 1H); 6.95-6.89 (m, 1H); 4.13 (d, J= 8.5Hz, 1H); 2.88-2.67 (m, 3H); 2.28-2.08 (m, 1H); 1.99 (s, 3H); 1.94-1.77 (m, 2H); 1.75-1.69 (m, 1H); 1.66-1.62 (m, 1H); 1.61 (s, 3H); 1.58 (s, 3H); 1.25 (s, 3H); 1.20 (s, 3H); 1.12-1.06 (m, 1H).

Step ID: r(IRV2-(2-fluoropheny l)-l-(2-methyl-2-[quinoxalin-2-ylcarbonyl]amino)propanoyllaminoethylboronic acid

[0116] N-(2-[(IR)-2-(2-fluorophenyl)-l-(3f,5,5-trimethylhexahydro-4,6-methano-
1,3,2-benzodioxaborol-2-yl)emyl]airrino]-l,1-dimethyl-2-oxoethyl)quinoxaline-2-
carboxamide (0.129 g, 0.23 mmol) was stirred in MeOH (0.8 mL) and hexanes (0.8 mL). 2-
methylpropylboronic acid (0.053 g, 0.52 mmol) was added followed by IN HCl (0.4 mL). The reaction was stirred at 22 °C overnight. The solution was diluted with hexanes and the aqueous layer was extracted with hexanes (2x). The aqueous layer was concentrated to give the title compound as a yellow solid that was purified using reverse phase chromatography (0.050 g, 51%). LC/MS: Rm = 1.34 min, ES+ 447 (Na+) (Formic Acid method).

Step IE: r(IR)-2-(2-fluorophenyl)-l-(2-methyl-2-[quinoxalin-2-ylcarbonyl]amino)
propanoyllaminoethylboronic acid. 20 D-mannitol (37)

[0117] To a solution of [(IR)-2-(2-fluorophenyl)-l-(2-methyl-2-[quinoxalin-2-
ycarbonyl]amino) propanoyl]aminoethylboronic acid (0.050 g, 0.11 mmol) in i-butyl alcohol (4 mL) and water (15 mL) was added D-mannitol (0.431 g, 0.23 mmol). The solution was stirred for 2 hrs then frozen and the solvent removed by lyophilization to give [(IR)-2-
(2-fluorophenyl)-l-(2-methyl-2-[quinoxalin-2-ylcarbonyl]amino]
propanoyl]aminoethylboronic acid·20 D-mannitol (37) (0.430 g, 89%).

[0118] AU subsequently reported boronic acids were converted to 20 D-mannitol esters according to the procedure in step IE.
**Example 2:** [3-methyl-l-(12-methyl-2-f(quinoxalin-2-ylcarbonyl)aminolpropanoyl|amino)-butyliboronic acid (21)]

**Step 2A:** tert-butylic (1,1-dimethyl-2-U3-methyl-l-(3fl,5,5-trimethylhexahydrcH4,6-methano-1,3,2-benzodioxaborol-2-yl)butyl|amino]-2-oxoethyl|carbamate

The title compound was prepared following the procedure described in Example 1, step A using 3-methyl-l-(3fl,5,5-trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-yl)butan-l-amine (0.250 g, 0.659 mmol). The reaction was diluted with H₂O and filtered to give a white solid (0.266 g, 90%).

**Step 2B:** 2-amino-2-methyl-N-f3-methyl-l-(3g,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)butylpropanamide • HCl

The title compound was prepared following the procedure described in Example 1, step B using tert-butyl (1,1-dimethyl-2-{[3-methyl-l-(3fl,5,5-trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-yl)butyl|amino]-2-oxoethyl|carbamate (0.266 g, 0.591 mmol) to give a white solid (0.207 g, 100%). LC/MS: R₁ = 1.53 min, ES⁺ 352 (Formic Acid method).

**Step 2C:** N-(I,l-dimethyl-2-lf3-methyl-l-(3g,5,5-trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-yl)butyllaminol-2-oxoethyl)quinoxaline-2-carboxamide

The title compound was prepared following the procedure described in Example 1, step C using 2-quinoxalinecarboxylic acid (0.103 g, 0.590 mmol) and collected as a precipitate (0.334 g, 112%). ¹H NMR (CD₃OD, 400 MHz, δ): 9.45 (s, IH); 8.99 (s, IH); 8.79 (s, IH); 8.25-8.17 (m, 2H); 8.05-7.98 (m, 2H); 4.13 (d, J= 7.4Hz, IH); 2.67-2.59 (m, IH); 2.28-2.16 (m, 0.5H); 2.10-1.97 (m, 0.5H); 1.86 (t, J= 5.8Hz, IH); 1.83-1.75 (m, IH); 1.74-1.65 (m, 2H); 1.62 (s, 3H); 1.61 (s, 3H); 1.38-1.28 (m, 4H); 1.27 (s, 3H); 1.22 (s, 3H); 0.84 (s, 3H); 0.82 (s, 3H); 0.81 (s, 3H). LC/MS: R₁ = 2.22 min, ES⁺ 507 (Formic Acid method).

**Step 2D:** r3-methyl-l-(2-methyl-2-f(quinoxalin-2-ylcarbonyl)amino)propanoyl|amino)-butyliboronic acid (21)

The title compound was prepared following the procedure described Example 1, step D using N-(1,l-dimethyl-2-{[3-methyl-l-(3fl,5,5-trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-yl)butyl|amino]-2-oxoethyl)quinoxaline-2-carboxamide (0.299 g, 0.590 mmol) to obtain a brown solid (0.184 g, 84%). LC/MS: R₁ = 1.27 min, ES⁺ 395 (Na⁺) (Formic Acid method).
Example 3: [(IR)-3,3-dimethyl-l-[(2-methyl-2-[(pyrazin-2-ylcarbonyl)amino]propanoyl]-amino]butynboronic acid

Step 3F: Methyl 2-methyl-2-[(pyrazin-2-ylcarbonyl)amino]propanoate

[0122] To a suspension of 2-pyrazinecarboxylic acid (1.22 g, 9.8 mmol), methyl 2-amino-2-methylpropanoate HCl (1.50 g, 9.8 mmol) and collidine (3.9 mL, 29.4 mmol) in CH₂Cl₂ (25 mL) was added HATU (4.47 g, 11.8 mmol) in one portion. After 2 h, DMF (5 mL) and CH₂Cl₂ (25 mL) was added in order to solubilize the reaction. After stirring an addition 3 h, the reaction was diluted with EtOAc and the washed with 1 N HCl, IN NaOH, saturated NaHCO₃ and brine. The organic layer was dried (Na₂SO₄), filtered and concentrated. The material was used without further purification. ¹H NMR (300 MHz, CDCl₃) δ 9.16 (d, J = 1.4 Hz, IH); 8.75 (d, J = 2.4 Hz, IH); 8.53 (dd, J = 1.5, 2.5 Hz, IH); 8.33 (s, IH); 3.79 (s, 3H); 1.70 (s, 6H). LC/MS: Rₜ = 1.45 min, ES⁺ 224 (Formic Acid method).

Step 3G: 2-methyl-2-l[(pyrazin-2-ylcarbonyl)amino]propanoic acid

[0123] A solution of methyl 2-methyl-2-[(pyrazin-2-ylcarbonyl)amino]propanoate (9.8 mmol) and 1 M NaOH in water (19.6 mL) was stirred in methanol for 6 hours. The reaction was diluted with brine and EtOAc and the layers were separated. The aqueous layer was acidified with 1 M HCl in water (28 mL) to an approximate pH ~2. The aqueous was extracted with EtOAc (3x). These three combined extracts were dried (Na₂SO₄), filtered and concentrated to obtain 1.96 g (96% over two steps) of the title compound. ¹H NMR (300 MHz, CD₂OD) δ 9.16 (d, J = 1.3 Hz, IH); 8.75 (d, J = 2.4 Hz, IH); 8.65 (dd, J = 1.5, 2.4 Hz, IH); 1.63 (s, 6H). LC/MS: Rₜ = 1.27 min, ES⁺ 210 (Formic Acid Method).

Step 3A: N-2-p-i[(IRV3,3-dimethyl-l-[(3aS,4S,6S,7aRV3a,5.5-trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-ynburyliaminoVl,l-dimethyl-2__oxoethynpyrazine-2-carboxamide

[0124] To a solution of 2-methyl-2-[(pyrazin-2-ylcarbonyl)amino]propanoic acid (53 mg, 0.25 mmol), (IR)-3,3-dimethyl-l-[(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-yl]butan-l-amine .TFA (Pickersgill et al., WO 2005097809) (100 mg, 0.25 mmol), and TBTU (88 mg, 0.28 mmol) in DMF (2.5 mL) at 0°C was added diisopropylethylamine (131 µL, 0.75 mmol) dropwise over 20 minutes. The mixture was stirred for two hours, diluted with EtOAc, washed with saturated aqueous NaHCO₃ and brine, dried (Na₂SO₄), filtered and concentrated to obtain 150 mg of unpurified material. ¹H
NMR (300 MHz, CDCl₃) δ 9.33 (d, / = 1.6 Hz, IH); 8.73 (d, / = 2.4 Hz, IH); 8.51 (dd, / = 1.5, 2.4 Hz, IH); 8.35 (s, IH); 7.08 (s, IH); 4.24 (dd, / = 2.1, 9.1 Hz, IH); 3.17-3.11 (m, IH); 2.32-2.24 (m, IH); 2.13-2.04 (m, IH); 1.96-1.92 (m, IH); 1.86-1.82 (m, 2H); 1.68 (s, 6H); 1.63 (d, / = 3.7 Hz, IH); 1.43-1.32 (m, 4H); 1.28-1.23 (m, 4H); 0.90 (s, 9H); 0.80 (s, 3H). LC/MS: R₁ = 2.39 min, ES⁺ 472 (Formic Acid method).

Step 3D: r(lRV3,3-dimethyl-l-\pi 2-methyl-2-f(pyrazin-2-yl)carbonyl)aminolpropanoyllamino)butylboronic acid (38)

[0125] To a solution of unpurified N-[2-{[((IR)-3,3-dimethyl-l-[3aS,4S,6S,7aR]-3a,5,5-trimethylhexahydro-4,6-methano-13,2-benzodioxaborol-2-yl]butyl}amino]-l,1-dimethyl-2-oxoethyl]pyrazine-2-carboxamide (150 mg, 0.25 mmol estimate based on crude purity) and isobutylboronic acid (45 mg, 0.44 mmol) in hexanes/methanol (1:1, 1.7 mL) was added 560 µL 1 M HCl. The mixture was stirred for 24 h, washed twice with hexanes, and concentrated to obtain a residue. This was purified by HPLC purification to obtain 16 mg of the title compound.

1H NMR (300 MHz, CD₃OD) δ 9.21 (d, / = 1.6 Hz, IH); 8.81 (d, / = 2.7 Hz, IH); 8.71 (dd, / = 1.5, 2.5 Hz, IH); 2.74 (dd, / = 5.1, 7.5 Hz, IH); 1.76-1.69 (m, IH); 1.70 (s, 6 H); 1.28 (dd, / = 5.1, 13.8 Hz, IH); 0.90 (s, 9 H). LC/MS: R₁ = 1.47 min, ES⁺ (M - H₂O) 319 (Formic Acid method).

Example 4: Synthesis of l(lRV1,3-methyl-l-f[l-f(phenylacetyl)aminolcyclopropyl]-carbonyDaminolbutylboronic acid (22)

Step 4A: tert-butyl ll-r(lIK)-3-methyl-l-r(3aS,4S,6S,7aRV3a,5,5-trimethylhexahydro-4,6-methano-1.3.2-benzodioxaborol-2-yl]butyl)amino)carbonylll-cyclopropyl)- carbamate

[0126] l-((tert-butoxycarbonylamino)cyclopropanecarboxylic acid (0.531g, 2.64 mmol) was dissolved in 6 mL of DMF. (l?)-3-methyl-l-[(3aS,4S,6S,7a?)-3a,5,5-trimethylhexahydro-4,6-methano-13,2-benzodioxaborol-2-yl]butan-l-amine (Ig, 2.64 mmol, trifluoroacetate salt) was added followed by TBTU (0.931g, 2.9 mmol.) The solution was cooled to 0°C and DIEA (1.4 mL, 7.1 mmol) added dropwise over a period of 45 minutes at 0°C. Stirring at 0°C was then continued for 30 minutes. Water (20 mL) was added and the resulting precipitate collected by filtration to give a white solid (1.44g, 122%). LC/MS: R₁ = 2.18 min, ES⁺ 449 (Formic Acid method).
Step 4B: l-amino-N-KlR)-3-memyl-H(3aS,4S,6S7aR)-3a33-rrimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yllbutyl leyclopropanecarboxamide hydrochloride

[0127] The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a white solid.

LC/MS: R, = 1.50 min, ES+ 351 (Formic Acid method).

Step 4C: N-UlR)-3-methyl-l-(3aS,4S,6S,7aRV3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynbutyll-l(f(phenylacetyl)aminolcyclopropane-carboxamide

[0128] The title compound was prepared following the procedure described in Example 1, step C using the appropriate reagents to give the product as a white solid (0.134 g, 77%). LC/MS: R, = 2.17 min, ES+ 467 (Formic Acid method).

Step 4D: KIRVS-methyl-l-fdl-KphenylacetyDaminoicyclopropyllcarbonyboronic acid (22)

[0129] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.0195 g, 20%). LC/MS: R, = 5.13 min, ES+ 315 (M-H2O) (Formic Acid Purity method).

Example 5: Synthesis of f(li?)'-3-methyl-l-(l2-methyl-2-[(phenylacetyl )aminolpropanoyl]-amino)butylboronic acid (8)

Step 5A: tert-butyl ri,l-dimethyl-2-(l(lRV3-methyl-l-[(3aS,4S,6S,7aR)]-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yllbutyllamino)-2-oxoethylcarbamate

[0130] 2-(tert-butoxycarbonylamino)-2-methylpropanoic acid (0.536 g, 2.64 mmol) was dissolved in 6 mL of DMF. (1R)-3-methyl-l-[(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]butan-l-amine (Ig, 2.64 mmol, trifluoroacetate salt) was added followed by TBTU (0.931g, 2.9 mmol.) The solution was cooled to 0 °C and DIEA (1.4 mL, 7.1 mmol) added dropwise over a period of 45 minutes at 0 °C. Stirring at 0 °C was then continued for 30 minutes. Water (20 mL) was added and the resulting precipitate collected by filtration to give a white solid (1.1g, 93%). LC/MS: R, = 2.23 min, ES+ 451 (Formic Acid method).
Step 5B: 2-amino-2-methyl-AH(lR)-3-methyl-l-r(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynbutyl)propanamide hydrochloride

The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a white solid. LC/MS: R₁ = 1.50 min, ES⁺ 351 (Formic Acid method).

Step 5C: 2-methyl-N-i-L-3-methyl-1-r(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynbutyl)-2-f(phenylacetyl)amino1propanamide

The title compound was prepared following the procedure described in Example 1, step C using the appropriate reagents to give the product as a white solid (0.126 g, 73%). LC/MS: R₁ = 2.20 min, ES⁺ 469 (Formic Acid method).

Step 5D: l(LR3-methyl-l-I2-methyl-2-f(phenylacetyl)amino1propanoyllamino)butyn-boronic acid (8)

The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.05 g, 56%). LC/MS: R₁ = 5.28 min, ES⁺ 317 (M-H₂O) (Formic Acid Purity method).

Example 6: IQVR3-methyl-l-r(2-memyl-2-U2-(trifluoromemynbei\zoyllamino)propanoyDaminolbutyllboronic acid (11)

Step 6A: tert-butyl W,l-dimethyl-2-d (IR3-methyl-l-r(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yllburyl]amino)-2-oxoethylcarbamate

2-(tert-butoxycarbonylamino)-2-methylpropanoic acid (0.536 g, 2.64 mmol) was dissolved in 6 mL of DMF. (IR)-3-methyl-l-[(3aS,4S,6S,7a?)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]butan-l-amine (1g, 2.64 mmol, trifluoroacetate salt) was added followed by TBTU (0.931g, 2.9 mmol.) The solution was cooled to 0 °C and DIEA (1.4 mL, 7.1 mmol) added dropwise over a period of 45 minutes at 0 °C. Stirring at 0 °C was then continued for 30 minutes. Water (20 mL) was added and the resulting precipitate collected by filtration to give a white solid (1.lg, 93%). LC/MS: R₁ = 2.23 min, ES⁺ 451 (Formic Acid method).
Step β: 2-amino-2-methyl-N-[(RS)-3-methyl-l-(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]butyl]propanamide hydrochloride

The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a white solid.

LC/MS: R₁ = 1.50 min, ES⁺ 351 (Formic Acid method).

Step β C: N-[(RS)-3-methyl-l-(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]butyl]amino)-2-oxoethyl]-2-(trifluoromethyl)benzamide

The title compound was prepared following the procedure described in Example 1, step C using the appropriate reagents to give the product as a yellow oil (0.154 g, 79%).

LC/MS: R₁ = 2.28 min, ES⁺ 523 (Formic Acid method).

Step 6D: KlR)-3-methyl-l-r(2-methyl-2-(trifluoromethyl)benzoyl)aminol propanoylaminobutyllboronic acid (11)

The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.063 g, 55%).

LC/MS: R₁ = 5.64 min, ES⁺ 371 (M-H₂O) (Formic Acid Purity method).

Example 7: ((IR)-3-methyl-l-[(l-lf2-(trifluoromethyl)benzoyllamino)cyclopropyl)carbonyl}aminobutyloboronic acid (30)

Step 7A: tert-butyl U-[(IR)-3-methyl-l-{(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]butyl]amine (1g, 2.64 mmol, trifluoroacetate salt) was added followed by TBTU (0.931g, 2.9 mmol.). The solution was cooled to 0°C and DIEA (1.4 mL, 7.1 mmol) added dropwise over a period of 45 minutes at 0°C. Stirring at 0°C was then continued for 30 minutes. Water (20 mL) was added and the resulting precipitate collected by filtration to give a white solid (1.44g, 122%).

LC/MS: R₁ = 2.18 min, ES⁺ 449 (Formic Acid method).
Step 7B: \textit{l-amino-N-l(lRV3-methyl-l-l(3aS,4S,6S,7aR')-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ylbutyl)cyclopropanecarboxamide hydrochloride}

[0138] The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a white solid.

LC/MS: R$_1$ = 1.50 min, ES$^+$ 351 (Formic Acid method).

Step 7C: \textit{N-l-l(lIR)-3-methyl-l-l(3aS,4S,6S,7aR')-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ylbutyl)amino)cyclopropyl)carbonylbromide (27)

[0139] The title compound was prepared following the procedure described in Example 1, step C using the appropriate reagents to give the product as a white solid (0.167 g, 88%). LC/MS: R$_1$ = 2.28 min, ES$^+$ 521 (Formic Acid method).

Step 7D: \textit{(lR)-3-methyl-l-l(2S)-2-methyl-3-phenyl-2-(pyrazin-2-ylcarbonylamino)-3-pypropanoylbutylboronic acid (30)}

[0140] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.075 g, 60%). LC/MS: R$_1$ = 5.51 min, ES$^+$ 369 (M-H$_2$O) (Formic Acid Purity method).

Example 8: \textit{(lR)-3-methyl-l-l(l (2S)-2-methyl-3-phenyl-2-(pyrazin-2-ylcarbonylamino)-propanoylamino)butylboronic acid (33)}

Step 8A: \textit{fert-butyl r(lS)-l-benzyl-l-methyl-2-(((lR)-3-methyl-l-l(3aS,4S,6S,7aR')-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ylbutyl)amino)carbonylbromide (30) oxoethylcarbamate}

[0141] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as a white solid (0.664 g, 96%). LC/MS: R$_1$ = 2.65 min, ES$^+$ 527 (Formic Acid method).

Step 8B: \textit{(2SV2-amino-2-methyl-N-((lRV3-methyl-l-l(3aS,4S,6S,7aR')-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ylbutyl)amino)propanamide hydrochloride}

[0142] The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a white solid.

LC/MS: R$_1$ = 1.42 min, ES$^+$ 427 (Formic Acid method).
Step 8C: N-\((lS)-l\)-benzyl-\(l\)-methyl-2-\(l(lR)-3\)-methyl-\(l\)-\((3aS,4S,6S,7aR)-3a,5,5-\)
tris\(\text{hexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ylbutyllamino}\)-2-oxoethylpyrazine-2-carboxamide

[0143] The title compound was prepared following the procedure described in Example 1, step C using the appropriate reagents to give the product as an oil (0.123 g, 99%).

LC/MS: \(R_t = 2.33\) min, ES+ 533 (Formic Acid method).

Step 8D: \((lRI-3\)-methyl-\(l\)-\((2S)-2\)-methyl-3-phenyl-2-\((\text{pyrazin-2-ylcarbonyl)amino})\)butyl\]boronic acid (33)

[0144] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.088 g, 96%). LC/MS: \(R_t = 5.93\) min, ES+ 381 (M-H\(2\)O) (Formic Acid Purity method).

Example 9: \((lRI)-3\)-methyl-\(l\)-(\(2R\)-2-methyl-3-phenyl-2-\((\text{pyrazin-2-ylcarbonyl)amino})\)butynboronic acid (10)

Step 9A: tert-butyl \((lR)-l\)-benzyl-l-methyl-2-l(lR)-3-methyl-l-r\((3aS,4S,6S,7aRV3a,5,5-\)
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynbutyllamino)-2-oxoethylcarbamate

[0145] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as a white solid (0.55g, 80%). LC/MS: \(R_t = 2.51\) min, ES+ 527 (Formic Acid method).

Step 9B: \((2R)-2\)-amino-2-methyl-N-l\((lR)-3\)-methyl-l-f \((3aS,4S,6S,7aR)-3a,5,5-\)
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynbutyll-3-phenylpropanamide hydrochloride

[0146] The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a white solid.

LC/MS: \(R_t = 1.41\) min, ES+ 427 (Formic Acid method).

Step 9C: N-\((lRV1)-benzyl-\(l\)-methyl-2-\((l(lRV3)-methyl-l-l(3aS,4S,6S,7aRV3a,5,5-\)
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)butyl]amino)-2-oxoethylpyrazine-2-carboxamide

[0147] The title compound was prepared following the procedure described in Example 1, step C using the appropriate reagents to give the product as an oil (0.115 g, 99%).

LC/MS: \(R_t = 2.31\) min, ES+ 533 (Formic Acid method).
Step 9D: \( r(lRV^3\text{-methyl-l-}(U^2R')-2\text{-methyl-3-phenyl-2-f(pyrazin-2-ylcarbonyl)aminolpropanoyl}amino)butyl\]boronic acid (10)

The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.023 g, 27%). LC/MS: \( R_1 = 5.97 \text{ min, } \text{ES}^+ 381 \text{ (M-H}_2\text{O) (Formic Acid Purity method).} \)

Example 10: \( \{(lR)-3\text{-methyl-l-[(KlS,2S)-2-phenyl-l-[(pyrazin-2-ylcarbonyl)aminol-cyclopropyllcarbonyDaminolbutyllboronic acid (3) \}

Step IQA: tert-butyl KIS,2S)-l-r(l(lR)-3-methyl-l-r(3aS,4S,6S,7aR)-3a,5,5-trimethyl-hexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ylbutyl)amino)carbonyl1-2-phenylcyclopropylcarbamate

[0148] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as a white solid (0.216 g, 99%). LC/MS: \( R_1 = 2.49 \text{ min, } \text{ES}^+ 525 \text{ (Formic Acid method).} \)

Step IQB: \( (lS,2S)-l-amino-N-l(lR)-3\text{-methyl-l-r(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ylbutyl)-2-phenylcyclopropanecarboxamide \)

[0149] The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a yellow solid. LC/MS: \( R_1 = 2.41 \text{ min, } \text{ES}^+ 425 \text{ (Ammonium Acetate method).} \)

Step IQC: N-l(lS,2S)-l-r(KIR)-3-methyl-l-r(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ylbutyllamino)carbonyll-2-phenylcyclopropylpyrazine-2-carboxamide

The title compound was prepared following the procedure described in Example 1, step C using the appropriate reagents to give the product as an oil (0.195 g, 99%). LC/MS: \( R_1 = 2.49 \text{ min, } \text{ES}^+ 531 \text{ (Ammonium Acetate method).} \)

Step IQD: l(lRV3-methyl-l-m(IS,2S)-2-phenyl-H(pyrazin-2-ylcarbonylnaminol- cycloproDcarbonyDaminolbutylDboronic acid (3) \)

[0150] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.010 g, 15%). LC/MS: \( R_1 = 5.37 \text{ min, } \text{ES}^+ 379 \text{ (M-H}_2\text{O) (Formic Acid Purity method).} \) \(^1\)H NMR (CD\(_3\)OD, 300 MHz, \( \delta \)): 9.14-9.05 (m, IH); 8.88-8.79 (m, IH); 8.72-8.64 (m, IH); 7.45-7.20 (m, IH).
Example 11: (1R)-3-methyl-l-r([pyrazin-2-ylcarbonyl]amino)cyclopropylcarbonyl)-aminolbutylboronic acid (12)

Step HA: tert-butyl U-r(3aS,4S,6S,7aR)-3a5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ylbutyl)cyclopropylcarbamate

The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as a white solid (1.22 g, 99%). LC/MS: R₁ = 2.26 min, ES⁺ 449 (Formic Acid method).

Step HB: 1-amino-N-l(3aS,4S,6S,7aR)-3a5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ylbutylcyclopropanecarboxamide hydrochloride

The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a white solid (0.10 g, 95%).

Step HC: N-l(3aS,4S,6S,7aR)-3a5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ylbutylpyrazine-2-carboxamide

The title compound was prepared following the procedure described in Example 1, step C using the appropriate reagents to give the product as an oil (0.60 g, 99%).

Step HD: (1R)-3-methyl-l-f([pyrazin-2-ylcarbonyl]amino)cyclopropylcarbonylV aminolbutylboronic acid (12)

The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.472 g, 99%). LC/MS: R₁ = 3.91 min, ES⁺ 303 (M-H₂O) (Formic Acid Purity method).

Example 12: [(1R)-l-([l-(acetylamino)cyclopropylcarbonyl]amino)-3-methylbutyl]boronic acid (23)
Step 12A: tert-butyl 1-f(KIRV3-methyl-1-r(3aS,4S,6S,7aRV3a,5,5-trimethylhexahydro-4,6-
memancyI^P-benzodioxaborol^y-ylbutylaminokarbonyl)cyclopropyl-
carbamate

[0155] The title compound was prepared following the procedure described in
Example 1, step A using the appropriate reagents to give the product as a white solid (1.22 g,
99%). LC/MS: R, = 2.26 min, ES+ 449 (Formic Acid method).

Step 12B: l-amino-N-l(lR)-3-methyl-l-(3aS,4S,6S,7aR')-3a,5,5-trimethylhexahydro-4,6-
methano-I,3,2-benzodioxaborol-2-y1butylcyclopropanecarboxamide hydrochloride

[0156] The title compound was prepared following the procedure described in
Example 1, step B using the appropriate reagents to give the product as a white solid.

Step 12C: l-(acetylamino)-N-l(lR)-3-methyl-l-(3aS,4S,6S,7aR')-3a,5,5-trimethylhexahydro-
4,6-methano-I,3,2-benzodioxaborol-2-ylbutyl)cyclopropanecarboxamide

[0157] To a solution of l-amino-N-{(lR)-3-methyl-l-(3aS,4S,6S,7aR')-3a,5,5-
trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-ylbutyl)cyclopropane-
carboxamide hydrochloride (0.50 g, 1.30 mmol) in DMF (5.0 mL) was added acetic
anhydride (0.15 g, 1.43 mmol). The reaction mixture was cooled to 0°C, and DIEA (0.34 g,
2.6 mmol) was added slowly over 1 h. The reaction was allowed to stir at 0°C. After 1.5 h,
the reaction mixture was diluted with H2O (20 mL) and washed with EtOAc (2 x 30 mL).
The organic layers were combined and washed with H2O (2 x 20 mL), dried over MgSO4,
filtered, and concentrated to give the title compound (0.473 g, 93%). LC/MS: R, = 1.78 min,
ES+ 391 (Formic Acid method).

Step 12D: f(IRV1-(ir-(acetylamino)cyclopropylcarboxyllumino)-3-methylbutyl]boronic
acid (23)

[0158] The title compound was prepared following the procedure described in
Example 1, step D using the appropriate reagents to give the product as a white solid (0.336
g, 99%). LC/MS: R, = 3.26 min, ES+ 239 (M-H2O) (Formic Acid Purity method). 1H NMR
(CD3OD, 300 MHz, δ): 2.72-2.59 (m, 3H); 1.96 (s, 3H); 1.73-1.57 (m, 3H); 1.41-1.17 (m, 4H);
0.90 (dJ = 6.6Hz, 6H).

Example 13: KIR]-l-[2-f(benzyloxy)carboxylluminol-2-methylpropanoyl]amino1-3-
methylbutyl]boronic acid (32)
Step 13A: benzyl _ri,l-dimethyl-2-(l(lR)-3-methyl-l-r(3aS,4S,6S,7aRV3a,5,5-
trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-yllbutyl)amino)-2-
oxoethyl|carbamate

[0159] The title compound was prepared following the procedure described in
Example 1, step A using the appropriate reagents to give the product as a white solid (0.84 g,
82%). LC/MS: R, = 2.31 min, ES+ 485 (Formic Acid method).

Step 13D: KIR)-l-(2-[((benzoyloxy)carbonylamino)-2-methylpropanoyl)amino1-3-
methylbuty|boronic acid (32)

[0160] The title compound was prepared following the procedure described in
Example 1, step D using the appropriate reagents to give the product as a white solid (0.675
g, 99%). LC/MS: R, = 3.33 min, ES+ 591 (M-H2O) (Formic Acid Purity method).

Example 14: l(lR)-l-[((tert-butoxycarbonylamino)-2-methylpropanoyl)amino|2-
phenylethyllboronic acid (17)

Step 14A: benzyl _ri,l-dimethyl-2-oxo-2-(l(l _RV2-phenyl-14(3aS,4S,6S,7aRV3a,5,5-
trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-
ynethyl)amino)ethyl|carbamate

[0161] The title compound was prepared following the procedure described in
Example 1, step A using the appropriate reagents to give the product as a white solid (1.15 g,
99%). LC/MS: R, = 2.31 min, ES+ 519 (Formic Acid method).

Step 14D: l(lJ?-l-[((benzoyloxy)carbonylamino)-2-methylpropanoyl)aminol-2-
phenylethyllboronic acid (17)

[0162] The title compound was prepared following the procedure described in
Example 1, step D using the appropriate reagents to give the product as a white solid (0.97 g,
99%). LC/MS: R, = 6.21 min, ES+ 367 (M-H2O) (Formic Acid Purity method).

Example 15: l(lR)-l-f(U-f(tert-butoxycarbonyl)aminolcyclobutyllcarbonyDaminol-2-
phenylethvDb oronic acid (15)
Step 15A: tert-buty1 H-f(KiKV2-phenyl-l-[(3aS,4S,6S,7aR3a,5,5-trimethylhexahydro-4,6-memano-13,2-benzodioxaborol-2-yllethyllamino)carbonyl]kydobyllcarbamate

[0163] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as an oil (0.59 g, 99%).

LC/MS: R<sub>t</sub> = 2.39 min, ES<sup>+</sup> 497 (Formic Acid method).

Step 15D: ((lRVl-fdl-fitterNbutoxycarbonyDaminolcyclobutyllcarbonylDaminol^-phenylethyllboronic acid (15)

[0164] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.387 g, 93%). LC/MS: R<sub>t</sub> = 6.03 min, ES<sup>+</sup> 345 (M-H<sub>2</sub>O) (Formic Acid Purity method).

Example 16: KLIR)-l-f((fert-butoxycarbonyl)amino]cyclobutyl)carbonyl)aminol-3-methylbutyl]boronic acid (6)

Step 16A: tert-butyl H-f(KiRV3-methyl-l-r(3aS,4S,6S,7aR3a,5,5-trimethylhexahydro-4,6-methano-13,2-benzodioxaborol-2-yllethyllamino)carbonyl]kydobyllcarbamate

[0165] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as an oil (0.53 g, 99%).

LC/MS: R<sub>t</sub> = 2.39 min, ES<sup>+</sup> 463 (Formic Acid method).


[0166] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.332 g, 99%).

Example 17: [(lRVl-(II-(acetylamino)cyclopropyl]carbonyl)amino]-2-phenylethyl]boronic acid (9)

Step 17A: tert-butyl II-[(lQRV2-phenyl-l-[(3aS,4S,6S7aR3a,5,5-trimethylhexahydro-4,6-memano-13,2-benzo[d]ioxaborol-2-yllethyllamino)carbonyl]cyclopropyllcarbamate

[0167] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as a white solid (0.84 g, 70%). LC/MS: R<sub>t</sub> = 2.26 min, ES<sup>+</sup> 483 (Formic Acid method).
Step 17B: 1-amino-N-l-(lR)-2-phenyl-l-[(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynethyl]cyclopropanecarboxamide hydrochloride

The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a brown solid (0.68 g, 73%).

Step 17C: 1-(acetylamino)-N-l-(lR)-2-phenyl-l-[(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynethyl]cyclopropanecarboxamide

The title compound was prepared following the procedure described in Example 12, step C using the appropriate reagents to give the product as an oil (0.217 g, 32%). LC/MS: R, = 1.83 min, ES+ 425 (Formic Acid method).

Step 17D: [(1K)-l-I-(lri-(acetylamino)cyclopropyl]carbonyl|airrino)-2-phenylethyllboronic acid (9)

The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.173 g, 99%). LC/MS: R, = 3.64 min, ES+ 273 (M-H2O) (Formic Acid Purity method). 1H NMR (CD3OD, 300 MHz, δ): 7.38-7.04 (m, 5H); 2.93-2.72 (m, 2H); 2.72-2.53 (m, 1H); 1.94 (s, 3H); 1.77-1.66 (m, 1H); 1.66-1.54 (m, 1H); 1.35-1.15 (m, 2H).

Example 18: ((1R)-l-I-[l-I[(1-bei)zyloxy]carbonyll]arruno)cyclobutyl)carbonyllaminol-3-methylbutyliboronic acid (26)

Step 18A: benzyl H-r(lIRV3-methyl-l-[3a5,4S,6S,7aR]-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynbutyl]aminokarboallcylobutyl]carbamate

The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as a white solid (0.554 g, 99%). LC/MS: R, = 2.39 min, ES+ 497 (Formic Acid method).


The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.181 g, 45%). LC/MS: R, = 6.04 min, ES+ 345 (M-H2O) (Formic Acid Purity method).

Example 19: f(lR)-l-[(2-[(4-chlorobenzoyl)amino]-2-methylpropanoyllamino]-2-(3-methylphenyl]ethyliboronic acid (31)
Step 19A: tert-butyl rU-dimemyl-2-(IQRV2-(3-memylphenyl)-H(3aS,4S,6S,7aR)-3a,5,5-
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yethyllamino
)-2-
oxoethylcarbamate

[0173] The title compound was prepared following the procedure described in
Example 1, step A using the appropriate reagents to give the product as a white solid.
LC/MS: R₁ = 2.34 min, ES⁺ 499 (Formic Acid method).

Step 19B: 2-amino-2-memyl-N-IQRV2-(3-methylphenyl)-l-r(3aS,4S,6S,7aRV3a,5,5-
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynethylpropanamide
hydrochloride

[0174] The title compound was prepared following the procedure described in
Example 1, step B using the appropriate reagents to give the product as a white solid.

Step 19C: 4-chloro-N-n.l-dimethyl-2-«(lRV2-(3-methylphenyl)-l-f(3aS,4S,6S,7aK)-3a,5,5-
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynethyl)amino)-2-
oxoethylbenzamide

[0175] To a solution of 4-chlorobenzoic acid (0.087 g, 0.553 mmol) in CH₂Cl₂ were
added 2-amino-2-methyl-N-{(IR)-2-(3-methylphenyl)-l-[{3aS,4S,6S,7aK}-3a,5,5-
trimethylhexahydro-4,6-methano-13 2-benzodioxaborol-2-y[ethyl]propanamide
hydrochloride (0.20 g, 0.503 mmol), HOBt (0.075 g, 0.553 mmol), 4-methylmorpholine (0.204 g, 2.42 mmol) and EDCI (0.106 g, 0.553 mmol). The reaction mixture was allowed to stir at 22
₀C. After 12 h, the reaction mixture was quenched with a saturated solution of sodium bicarbonate and the product partitioned into DCM. The organic layer was dried over
MgSO₄, filtered and concentrated to give the title compound (0.210 g, 77%). LC/MS: R₁=
2.29 min, ES⁺ 537 (Formic Acid method).

Step 19D: r(lR)-l-((2-r(4-chlorobenzoyl)amino1-2-methylpropanoyl|amino)-2-(3-
methylphenylethyllboronic acid (311)

[0176] The title compound was prepared following the procedure described in
Example 1, step D using the appropriate reagents to give the product as a white solid (0.080 g, 51%). LC/MS: R₁ = 6.77 min, ES⁺ 385 (M-H₂O) (Formic Acid Purity method).

Example 20: ((lRV2-(3-methylphenyl)-l-r(2-methyl-2-lf2-(trifluoromethyl)benzoynamino)-
propanoDaminolethyllboronic acid (20)
Step 2OA: tert-butyl 1,1-dimethyl-2-((l|lRV2-(3-methylphenyl)-l-(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)ethyl)amino)-2-oxoethylcarbamate

[0177] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as a white solid. LC/MS: R, = 2.34 min, ES+ 499 (Formic Acid method).

Step 2OB: 2-amino-2-methyl-N-l(lRV2-(3-methylphenyl)-l-(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)ethyl)propanamide hydrochloride

[0178] The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a white solid.

Step 2OC: N-ri,1-dimethyl-2-((l|lRV2-(3-methylphenyl)-l-(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)ethyl)amino)-2-oxoethyl-2-(trifluoromethyl)benzamide

[0179] The title compound was prepared following the procedure described in Example 19, step C using the appropriate reagents to give the title compound (0.160 g, 99%). LC/MS: R, = 2.25 min, ES+ 571 (Formic Acid method).

Step 2OD: KlRV2-(3-methylphenyl)-l-l(2-methyl-2-(trifluoromethyl)benzoyl)amino)ethyllboronic acid (20)

[0180] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.100 g, 82%). LC/MS: R, = 6.39 min, ES+ 419 (M-H2O) (Formic Acid Purity method). 1H NMR (CD3OD, 300 MHz, δ): 7.97-7.87 (m, 1H); 7.87-7.74 (m, 2H); 7.71-7.58 (m, 1H); 7.34-7.14 (m, 4H); 3.09-2.92 (m, 2H); 2.86-2.71 (m, 1H); 2.44 (s, 3H); 1.74 (s, 3H); 1.69 (s, 3H).

Example 21: f(lR)-2-(3-methylphenyl)-l-l(2-methyl-2-f(pyrazin-2-ylcarbonyl)amino)propioy Daminoethylboronic acid (34)

Step 21A: tert-butyl H,1-dimethyl-2-((KlRV2-(3-methylphenyl)-l-(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)ethyl)amino)-2-oxoethylcarbamate

[0181] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as a white solid. LC/MS: R, = 2.34 min, ES+ 499 (Formic Acid method).
Step 21B: 2-amino-2-methyl-N-N-[4R2-(3-methylphenyl-1-[3aS,4S,6S,7aR]-3a,5,5-
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynethyllpropanamide
hydrochloride

[0182] The title compound was prepared following the procedure described in
Example 1, step B using the appropriate reagents to give the product as a white solid.

Step 21C: N-N,N,N-diethyl-2-(4R2-(3-methylphenyl-1-[3aS,4S,6S,7aR]-3a,5,5-
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynethyllamino)-2-
oxoethynpyrazine-2-carboxamide

[0183] The title compound was prepared following the procedure described in
Example 19, step C using the appropriate reagents to give the title compound (0.37 g, 99%).

Step 21D: αR)-2-(3-methylphenyl-1-[(2-methyl-2-f(pyrazin-2-ylcarbonyl)minol-
propanoylliminotethyllboronic acid

[0184] The title compound was prepared following the procedure described in
Example 1, step D using the appropriate reagents to give the product as a white solid (0.300
g, 99%). 1H NMR (CD3OD, 300 MHz, δ): 9.41 (s, 1H); 8.94 (s, 1H); 8.82 (s, 1H); 7.20-7.06 (m,
3H); 7.06-6.95 (m, 1H); 3.04-2.87 (m, 2H); 2.82-2.65 (m, 1H); 2.28 (s, 3H); 1.82 (s, 3H); 1.77 (s,
3H).

Example 22: α(R)-2-(4-chlorophenyl)-1-[(2-methyl-2-f(pyrazin-2-ylcarbonyl)minol-
propanoylliminotethyllboronic acid (34)

Step 22A: tert-butyl f2-π(4R2-(4-chlorophenyl-1-[3aS,4S,6S,7aR]-3a,5,5-
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-ynethyllamino)-1,l-
dimethyl-2-oxoethyl1carbamate

[0185] The title compound was prepared following the procedure described in
Example 1, step A using the appropriate reagents to give the product as a white solid (0.65 g,
81%).

Step 22B: 2-amino-N-1 QRV2-(4-chlorophenyl-14(3aS,4S,6S,7aR')-3a,5,5-trimethyl-
hexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]ethyll-2-methylpropanamide
hydrochloride

[0186] The title compound was prepared following the procedure described in
Example 1, step B using the appropriate reagents to give the product as a white solid (0.54 g,
99%). LC/MS: R1 = 1.35 min, ES+ 419 (Formic Acid method).
Step 22C: N-r2-(l(lRV2-(4-chlorophenyn-l-r(3aS,4S,6S,7aRV3a,5,5-trimethylhexahydro-4,6-
methano-l,3,2-benzodioxaborol-2-yllethyUamino)-l,l-dimethyl-2-
oxothlpyrazine-2-carboxamide

[0187] The title compound was prepared following the procedure described in
Example 19, step C using the appropriate reagents to give the title compound (0.47 g, 57%).
LC/MS: R, = 2.07 min, ES+ 525 (Formic Acid method).

Step22D: r(lR)-2-(4-chlorophenyl)-l-(|2-methyl-2-f(pyrazin-2-ylcarbonyDamino1-
propanoyllamino)ethylboronic acid (1)

[0188] The title compound was prepared following the procedure described in
Example 1, step D using the appropriate reagents to give the product as a white solid (0.35 g,
99%). 1H NMR (CD,OD, 300 MHz, δ): 9.39 (s, 1H); 9.01-8.91 (m, 1H); 8.85-8.79 (m, 1H); 7.38-
7.18 (m, 4H); 3.03-2.89 (m, 2H); 2.84-2.70 (m, 1H); 1.82 (s, 3H); 1.78 (m, 3H).

Example 23: f(lR)-l-(|2-[(4-chlorobenzoyl)aminol-2-methylpropanoyllamino)-2-(4-
chlorophenyl)ethyUboronic acid (7)

Step 23A: fert-buryl f2-(l(lRV2-(4-chlorophenyn-l-r(3aS,4S,6S,7aRV3a,5,5-
trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-yllethyUamino)-l,l-
dimethyl-2-oxothlcarbamate

[0189] The title compound was prepared following the procedure described in
Example 1, step A using the appropriate reagents to give the product as a white solid (0.65 g,
81%).

Step 23B: ^2-amino-N-l(l(lR)-2-(4-chlorophenyn-l-[3aS,4S,6S,7aRV3a,5,5-
trimethylhexahydro-4.6-methano-l,3,2-benzodioxaborol-2-yUlethyllamino)-l,l-
dimethyl-2-oxothlcarbamate hydrochloride

[0190] The title compound was prepared following the procedure described in
Example 1, step B using the appropriate reagents to give the product as a white solid (0.54 g,
99%). LC/MS: R, = 1.35 min, ES+ 419 (Formic Acid method).

Step 23C: 4-chloro-N-r2-(l(lR)-2-(4-chlorophenyn-l-f(3aS,4S,6S,7aRV3a,5,5-
trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-yUlethyllamino)-l,l-
dimethyl-2-oxothlbenzamide

[0191] The title compound was prepared following the procedure described in
Example 19, step C using the appropriate reagents to give the title compound (0.18 g, 74%).
LC/MS: R, = 2.58 min, ES+ 557 (Formic Acid method).
The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid.

LC/MS: R, = 6.50 min, ES+ 405 (M-H2O) (Formic Acid Purity method).

\[ \text{\[^{1}H\] NMR (CD3OD, 300 MHz, } \delta \text{): 7.98 (d, } J = 8.9 \text{ Hz, 2H); 7.64 (d, } J = 8.9 \text{ Hz, 2H); 7.36-7.20 (m, 4H); 3.02-2.88 (m, 2H); 2.85-2.69 (m, 1H); 1.77 (s, 3H); 1.72 (s, 3H).} \]

Example 24: l(lR)-2-(4-chlorophenyl)-l-[(2-methyl-2-](2-(trifluoromethyl)benzoyl)amino)-propanoyl]aminolethyllboronic acid (4)

The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as a white solid (0.65 g, 81%).

LC/MS: R, = 1.35 min, ES+ 419 (Formic Acid method).

Example 25: l(lR)-2-(4-methylphenyl)-l-(l2-methyl-2-f(pyrazin-2-ylcarbonyl)aminol-propanoyl]aminolethyllboronic acid (27)
Step 25A: **fert-butyl n,1-dimethyl-2-[(lRV2-(4-methylphenyn-l-\(r\)(3aS,4S,6S,7aJ?V3a,5,5-
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-y methyl) amino)-2-
oxoethyl]carbamate**

[0197] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as a white solid (0.41 g, 67%).

Step 25B: **2-amino-2-methyl-N-\(\alpha\)RV2-(4-methylphenyD-1-r(3aS,4S,6S,7aRV3a,5,5-
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yllethyllpropanamide hydrochloride**

[0198] The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a white solid (0.34 g, 99%).

Step 25C: **N-ri,l-dimethyl-2-\(\pi\)(lRV2-(4-methylphenylVl-[\(3aS,4S,6S,7aR\)-3a,5,5-
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-y methyl) amino)-2-
oxoethyIpyrazine-2-carboxamide**

[0199] The title compound was prepared following the procedure described in Example 19, step C using the appropriate reagents to give the title compound (0.20 g, 51%).

**LC/MS:** R\(_1\) = 2.06 min, ES\(^+\) 505 (Formic Acid method).

Step 25D: **r(lR)-2-(4-methylphenyl)-l-\((2-methyl-2-r(pyrazin-2-yIcarbonyl)amino1-
propanoyl)amino\)ethyl]boronic acid (27)**

[0200] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.15 g, 90%). **LC/MS:** R\(_1\) = 5.03 min, ES\(^+\) 353 (M-\(\text{H}_{2}\text{O}\)) (Formic Acid Purity method). **\(^1\)HNMR**

(CD\(_3\)OD, 300 MHz, \(\delta\)): 9.39 (s, IH); 8.95 (s, IH); 8.82 (s, IH); 7.26-7.13 (m, 2H); 7.12-6.97 (m, 2H); 3.03-2.85 (m, 2H); 2.80-2.64 (m, IH); 2.33 (s, 3H); 1.82 (s, 3H); 1.77 (s, 3H).

**Example 26:** **[(lR)-l-\((2-\(\text{H}_{2}\text{O}\))amino2-methylpropanoyl)amino)-2-(4-
methylphenylPethyllboronic acid (5)**

Step 26A: **tert-buryl n,1-dimethyl-2-\[(lRV2-(4-methylphenyn-l-\(r\)(3aS,4S,6S,7aRV3a,5,5-
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-y methyl) amino)-2-
oxoethyl]carbamate**

[0201] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as a white solid (0.41 g, 67%).
Step 26B: 2-amino-2-methyl-N-(l(lR)-2-(4-methylphenyl)hexahydropyrido-4,6-methano-1,3,2-benzodioxaborol-2-yl)propanamide hydrochloride

[0202] The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a white solid (0.34 g, 99%).

Step 26C: 4-chloro-N-fl,l-dimethyl-2-(l(lR)-2-(4-methylphenyl)-3aS,4S,6S,7aR-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)amino)-2-oxoethylbenzamide

[0203] The title compound was prepared following the procedure described in Example 19, step C using the appropriate reagents to give the title compound (0.25 g, 93%).

Step 26D: [(lR)-l-l2-(l(4-chlorobenzoyl)amino)-2-(4-methylphenyl)ethynyl]boronic acid (5)

[0204] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.18 g, 96%). LC/MS: Rf = 6.56 min, ES+ 385 (M-H2O) (Formic Acid Purity method). 1H NMR (CD3OD, 300 MHz, δ): 7.98 (d, J = 8.7Hz, 2H); 7.62 (d, J = 8.8Hz, 2H); 7.22-6.99 (m, 4H); 3.01-2.86 (m, 2H); 2.81-2.64 (m, 1H); 2.27 (s, 3H); 1.77 (s, 3H); 1.71 (s, 3H).

Example 27: I(lRV2-(2-methyl-2-[l2-(trifluoromethyl)benzoyl]amino)-propanoyl)Daminioethylboronic acid (16)

Step 27A: tert-butyl ri.l-dimethyl-2-(iaR)-2-(4-methylphenyn-l-K3aS,4S,6S,7aRV3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)amino)-2-oxoethylcarbamate

[0205] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the product as a white solid (0.41 g, 67%).

Step 27B: 2-amino-2-methyl-N-l(lRV2-(4-methylphenyn-l-(3aS,4S,6S,7aKV3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl)ethyllpropanamide hydrochloride

[0206] The title compound was prepared following the procedure described in Example 1, step B using the appropriate reagents to give the product as a white solid (0.34 g, 99%).
Step 27C: 

N-[1,1-dimethyl-2-(l(1R)-2-(4-methylphenyl)-l-r(3aS,4S,6S,7aK)-3a,5,5-
trimethylhexahydro-4,6-methano-13,2-benzodioxaborol-2-yl1emlyl amino)-2-
oxoethyl]-2-(trifluoromethyl)benzamide

[0207] 
The title compound was prepared following the procedure described in
Example 19, step C using the appropriate reagents to give the title compound (0.15 g, 52%).

Step 27D: 

{(1R)-2-(4-methylphenyl)-l-rl(2-methyl-2-[(2-(trifluoromethyl)benzoyl)laminol-
propanoyDaminolethyllboronic__ acid (16)

[0208] 
The title compound was prepared following the procedure described in
Example 1, step D using the appropriate reagents to give the product as a white solid (0.14 g, 99%).
LC/MS: R, = 6.38 min, ES+ 419 (M-H2O) (Formic Acid Purity method). 1H NMR
(CD3OD, 300 MHz, δ): 7.93-7.88 (m, IH); 7.87-7.73 (m, 2H); 7.69-7.62 (m, IH); 7.35-7.09 (m,
4H); 3.12-2.91 (m, 2H); 2.84-2.71 (m, IH); 2.41 (s, 3H); 1.74 (s, 3H); 1.69 (s, 3H).

Example 28: 

f(lR)-3-methyl-1-[(2-methyl-2-[(pyrazin-2-ylcarbonyl)laminolpropanoyl]-
aminobutyllboronic acid (28)

Step 28F: 

methyl 2-methyl-2-[(pyrazin-2-ylcarbonyl)laminolpropanoate

[0209] 
To a solution of pyrazine-2-carboxylic acid (0.202 g, 1.6 mmol) in THF (6 mL)
at 0 °C were added methyl 2-amino-2-methylpropanoate trifluoroacetate (0.25 g, 1.6 mmol),
HOBt (0.22 g, 1.6 mmol), DIEA (0.21 g, 1.6 mmol) and EDCI (0.343 g, 1.8 mmol). The reaction
mixture was allowed to stir at 22 °C. After 12 h, the reaction mixture was quenched with a
saturated solution of sodium bicarbonate and the product partitioned into DCM. The
organic layer was dried over MgSO4, filtered and concentrated to give the title compound
(0.36 g, 99%). LC/MS: R, = 1.24 min, ES+ 224 (Formic Acid method).

Step 28G: 

2-methyl-2-[(pyrazin-2-ylcarbonyl)laminolpropanoic acid

[0210] 
A solution of methyl 2-methyl-2-[(pyrazin-2-ylcarbonyl)laminolpropanoate
(0.36, 1.6 mmol) in MeOH/Hp (2:1) (6.0 mL) was treated with LiOH (0.08 g, 3.2 mmol) and
stirred at 22 °C. After 12 h, the reaction was diluted with H2O and EtOAc and the layers
were separated. The aqueous layer was acidified with 1 M HCl in water (28 mL) to an
approximate pH ~2. The aqueous was extracted with EtOAc (3x). These three combined
extracts were dried (Na2SO4), filtered and concentrated to obtain the title compound (0.286 g, 88%).
Step 28A: N-ri,l-dimethyl-2-{(lIR3-methyl-1-[(3aS,4S,6S,7aJ?V3a,5,5-trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-yl)butyl]amino)-2-oxoethyl}pyrazine-2-carboxamide

[0211] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the title compound (0.638 g, 99%).

LC/MS: R, = 2.20 min, ES+ 457 (FA standard).

Step 28D: f(lJ?)-3-methyl-l-{[(pyrazin-2-ylcarbonyl)amino-2-carbonyl]amino}-butyllboronic acid (28)

[0212] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.066 g, 13%).
LC/MS: R, = 4.29 min, ES+ 305 (M-H₂O) (Formic Acid Purity method). ¹H NMR (CD₃OD, 300 MHz, δ): 9.21 (s, 1H); 8.80 (s, 1H); 8.71 (s, 1H); 2.76-2.65 (m, 1H); 1.69 (s, 7H); 1.44-1.27 (m, 2H); 0.90 (d, J = 6.6Hz, 6H).

Example 29: [(lR)-l-[(2R)-3-methyl-l-(4-chlorobenzoyl)aminol-2-methylpropanoyl]amino]-3-methylbutyllboronic acid (25)

Step 29F: methyl 2-f(4-chlorobenzoyl)aminol-2-methylpropanoate

[0213] The title compound was prepared following the procedure described in Example 28, step F using the appropriate reagents to give the title compound (0.45 g, 99%).
LC/MS: R, = 1.72 min, ES+ 256 (Formic Acid method).

Step 29G: 2-[(4-chlorobenzoyl)amino]l-2-methylpropanoic acid

[0214] The title compound was prepared following the procedure described in Example 28, step G using the appropriate reagents to give the title compound (0.39 g, 89%).

Step 29A: 4-chloro-N-rl,l-dimethyl-2-(l(lR)-3-methyl-1-[(3aS,4S,6S,7aJ?V3a,5,5-trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-yl)butyl]amino)-2-oxoethyl]benzamide

[0215] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the title compound (0.78 g, 99%).
LC/MS: R, = 2.35 min, ES+ 489 (FA standard).
Step 29D: [(lR)-l-(2-f(4-chlorobenzoyl)amino1-2-methylpropanoyl)amino)-3-
methylbutyllboronic acid (25)

[0216] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.085 g, 15%). LC/MS: R<sub>t</sub> = 5.84 min, ES<sup>+</sup> 337 (M-H<sub>2</sub>O) (Formic Acid Purity method). ¹H NMR (CD<sub>3</sub>OD, 300 MHz, δ): 7.82 (d, J = 8.5Hz, 2H); 7.47 (d, J = 8.7Hz, 2H); 2.74-2.64 (m, 1H); 1.62 (s, 7H); 1.43-1.22 (m, 2H); 0.90 (d, J = 6.6Hz, 6H).

Example 30: [(lK)-l-[l-(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-
methano-1,3,2-benzodioxaborol-2-ylbutyl]amino)bicyclopropyl] carbonylaminol-3-
methylbutyllboronic acid (14)

Step 30F: ethyl l-(4-chlorobenzoyl)aminolcyclopropyl]carboxylate

[0217] The title compound was prepared following the procedure described in Example 28, step F using the appropriate reagents to give the title compound (0.36 g, 99%). LC/MS: R<sub>t</sub> = 1.24 min, ES<sup>+</sup> 224 (Formic Acid method).

Step 30G: l-[4-chlorobenzoyl]aminolcyclopropyl]carboxylic acid

[0218] The title compound was prepared following the procedure described in Example 28, step G using the appropriate reagents to give the title compound (0.279 g, 92%).

Step 30A: 4-chloro-N-Il-(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-
methano-1,3,2-benzodioxaborol-2-ylbutyl)amino]carbonylcyclopropyl]-
benzamide

[0219] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the title compound (0.583 g, 99%). LC/MS: R<sub>t</sub> = 2.31 min, ES<sup>+</sup> 487 (FA standard).

Step 30D: KLR)-l-[l-(3f(4-chlorobenzoyl)aminolcyclopropyl])carbonyl]aminol-3-
methylbutyllboronic acid (14)

[0220] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.134 g, 32%). LC/MS: R<sub>t</sub> = 5.68 min, ES<sup>+</sup> 335 (M-H<sub>2</sub>O) (Formic Acid Purity method). ¹H NMR (CD<sub>3</sub>OD, 300 MHz, δ): 7.85 (d, J = 8.7Hz, 2H); 7.47 (d, J = 8.5Hz, 2H); 2.72-2.61 (m, 1H); 1.81-1.54 (m, 3H); 1.47-1.19 (m, 4H); 0.88 (d, J = 6.6Hz, 6H).

Example 31: [(lR)-l-[l-(4-chlorobenzoyl)aminolcyclopropyl]carbonyl]aminol-2-(4-
methylphenvDethyll]boronic acid (35)
Step 31F: ethyl L-[(4-chlorobenzoyl)aminocyclopropanecarboxylate

The title compound was prepared following the procedure described in Example 28, step F using the appropriate reagents to give the title compound (0.36 g, 99%).

LC/MS: $R_t = 1.24$ min, $ES^+ 224$ (Formic Acid method).

Step 31G: L-[(4-chlorobenzoyl)aminocyclopropanecarboxylic acid

The title compound was prepared following the procedure described in Example 28, step G using the appropriate reagents to give the title compound (0.279 g, 92%).

Step 31A: 4-chloro-N-[ll]-m\textsubscript{α}RV2-(4-methylphenyl)l-r(3aS,4S,6S,7aRV3a,5,5-
trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-
\textsubscript{yliethylaminokarbonyllcyclopropyllbenzamide

The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the title compound (0.34 g, 99%).

Step 31D: [IR]-L-[(II)-[(4-chlorobenzoyl)aminocyclopropyl]carbonyl]aminol-2-(4-
methylphenyPethyIboronic acid (35)

The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.19 g, 75%). LC/MS: $R_t = 6.65$ min, $ES^+ 383$ (M-H$_2$O) (Formic Acid Purity method).

Example 32: f(IR)-L-[(l)-[(4-chlorobenzoyl)cyclopropyl]carbonyl]aminol-2-(3-
methylphenyPethyIboronic acid (2)

Step 32F: ethyl L-[(4-chlorobenzoyl)cyclopropanecarboxylate

The title compound was prepared following the procedure described in Example 28, step F using the appropriate reagents to give the title compound (0.36 g, 99%).

LC/MS: $R_t = 1.24$ min, $ES^+ 224$ (Formic Acid method).

Step 32G: L-f(4-chlorobenzoyl)cyclopropanecarboxylic acid

The title compound was prepared following the procedure described in Example 28, step G using the appropriate reagents to give the title compound (0.279 g, 92%).
Step 32A: 4-chloro-N-ll-m(lK)-2-(3-methylphenyl)-l-r(3aS,4S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-ynethyl)amino)-carbonylicyclopropyllbenzamide

[0226] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the title compound (0.33 g, 99%).

Step 32D: l(lR)-l-f(ll-f(4-chlorobenzoyl)aminocyclopropyl)carbonylaminol-2-(3-methylphenyPethyllboronic acid (2)

[0227] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.24 g, 97%). LC/MS: R, = 6.65 min, ES+ 383 (M-H 2O) (Formic Acid Purity method).

Example 33: f(lR)-l-f(ll-[(4-chlorobenzoyl)aminocyclopropyllcarbonyl)aminol-2-(2-fluorophenyl)ethyllboronic acid (13)

Step 33F: ethyl l-f(4-chloroben2oyl)amino1cyclopropanecarboxylate

[0228] The title compound was prepared following the procedure described in Example 28, step F using the appropriate reagents to give the title compound (0.36 g, 99%). LC/MS: R, = 1.24 min, ES+ 224 (Formic Acid method).

Step 33G: l-r(4-chlorobenzoyl)amino1cyclopropanecarboxylic acid

[0229] The title compound was prepared following the procedure described in Example 28, step G using the appropriate reagents to give the title compound (0.279 g, 92%).

Step 33A: 4-chloro-N-ll-f(((lRV2-(2-fluorophenyl)-l-r(3aS,4S,7aR)-3a,5,5-trimethylhexahydro-4,6-methano-l,3,2-benzodioxaborol-2-yHethyl)amino)carbonylicyclopropyllbenzamide

[0230] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the title compound (0.25 g, 99%). LC/MS: R, = 2.14 min, ES+ 539 (Formic Acid method).

Step 33D: [(lR)-l-f(l-f(4-chlorobenzoyl)aminocyclopropyl)carbonyl)amino1-2-(2-fluorophenyDethyllboronic acid (13)

[0231] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.18 g, 99%). LC/MS: R, = 6.02 min, ES+ 387 (M-H 2O) (Formic Acid Purity method). 1H NMR (CD3OD, 300 MHz, δ): 7.85 (d, /= 8.7Hz, 2H); 7.49 (d, /= 8.8Hz, 2H); 7.30-7.20 (m, IH); 7.19-
7.08 (m, IH); 7.03-6.91 (m, 2H); 2.93-2.81 (m, 2H); 2.75-2.65 (m, IH); 1.90-1.77 (m, IH); 1.77-1.64 (m, IH); 1.50-1.33 (m, 2H).

**Example 34:** Ul^\(^\wedge\)O-methylphenyl-1-fdl-fpyrazin^\(^\wedge\)-ylcarbonyDaminolycyclopropyD-carbonyPaminoethylboronic acid (18)

Step 34F. Ethyl H(pyrazin-2-ylcarbonyl)aminolycyclopropanecarboxylate

The title compound was prepared following the procedure described in Example 28, step F using the appropriate reagents to give the title compound (0.26 g, 69%).

**Example 35:** l[(pyrazin-2-ylcarbonyl)amino]cyclopropanecarboxylic acid

The title compound was prepared following the procedure described in Example 3, step G using the appropriate reagents to give the title compound (0.24 g, 99%).

**Example 36:** N-(lR)-1(lRV2-(3-methylphenyl-1-r(lRV2-ylcarbonyl)aminolcyclopropyll-carbonyPaminoethylboronic acid (18)

Step 36A. Ethyl H(pyrazin-2-ylcarbonyl)aminolycyclopropanecarboxylate

The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the title compound (0.41 g, 74%).

**Example 37:** l[(pyrazin-2-ylcarbonyl)amino]cyclopropanecarboxylic acid

The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.31 g, 99%).

**Example 38:** Ethyl H(pyrazin-2-ylcarbonyl)aminolycyclopropanecarboxylate

The title compound was prepared following the procedure described in Example 28, step F using the appropriate reagents to give the title compound (0.26 g, 69%).
Step 35G: l-(pyrazin-2-ylcarbonyl)aminocyclopropanecarboxylic acid

The title compound was prepared following the procedure described in Example 3, step G using the appropriate reagents to give the title compound (0.24 g, 99%).

LC/MS: R1 = 4.97 min, ES+ 371 (M-H2O) (Formic Acid Purity method).

1H NMR (CD3OD, 300 MHz, δ): 9.38 (s, 1H); 8.92 (s, 1H); 8.81 (s, 1H); 7.43-7.23 (m, 4H); 3.04-2.86 (m, 2H); 2.84-2.67 (m, 1H); 2.02-1.81 (m, 2H); 1.67-1.51 (m, 2H).

Example 36: l(lR)-2-(4-methylphenyl)-l-(l-f(pyrazin-2-ylcarbonyl)aminocyclopropyl)carbonyDaminoethylboronic acid (19)

Step 36F: ethyl l-f(pyrazin-2-ylcarbonyl)aminocyclopropanecarboxylate

The title compound was prepared following the procedure described in Example 28, step F using the appropriate reagents to give the title compound (0.26 g, 69%).

LC/MS: R1 = 1.08 min, ES+ 236 (Formic Acid method).
Step 36D: 

(4-methylphenyl)-1-(1-((pyrazin-2-ylcarbonyl)aminocyclopropyl)-
carbonylaminolethyl)boronic acid (19)

[0242] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.33 g, 99%). LC/MS: R₁ = 4.65 min, ES⁺ 351 (M-H₂O) (Formic Acid Purity method). 

^1H NMR (CD₃OD, 300 MHz, δ): 9.20 (s, 1H); 8.79 (s, 1H); 8.70 (s, 1H); 2.76-2.65 (m, 1H); 1.68 (s, 6H); 1.44-1.25 (m, 2H); 1.92-1.80 (m, 1H); 1.68-1.50 (m, 2H).

Example 37: (QRV2-(4-methylphenyl)-1-l-

(((1-1r2-(trifluoromethyl)benzoynamino)cyclopropanecarboxylate

[0243] The title compound was prepared following the procedure described in Example 28, step F using the appropriate reagents to give the title compound.

Step 37G: 1-lf2-(trifluoromethyl)benzoylaminocyclopropanecarboxylic acid

[0244] The title compound was prepared following the procedure described in Example 3, step G using the appropriate reagents to give the title compound.

Step 37A: N-ll-r(l(lR)-2-(4-methylphenyl)-l-r(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-
4,6-methano-1,3,2-benzodioxaborol-2-ynyl)amino)carbonyl]cyclopropyl]-2-
(trifluoromethyl)benzamide

[0245] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the title compound (0.22 g, 83%).

Step 37D: ((lR)-2-(4-methylphenyl)-1-U(lr2-(trifluoromethyl)benzoylaminocyclopropyl)-
carbonylaminolethyriboronic acid (36)

[0246] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.16 g, 98%). LC/MS: R, = 6.12 min, ES⁺ 417 (M-H₂O) (Formic Acid Purity method).

Example 38: (1R)-2-(3-methylphenyl)l-

(((1-1r2-(trifluoromethyl)benzoylaminocyclopropyl)Dcarbonyllamino)ethyl)boronic acid (29)

Step 38F: ethyl 1-[2-(trifluoromethyl)benzoylaminocyclopropanecarboxylate

[0247] The title compound was prepared following the procedure described in Example 28, step F using the appropriate reagents to give the title compound.
Step 38G: 1-\{3(\text{trifluoromethyl)benzoyl}1\text{amino)cyclopropanecarboxylic acid}

[0248] The title compound was prepared following the procedure described in Example 3, step G using the appropriate reagents to give the title compound.

Step 38A: \text{N-\{3(3-methylphenyl)-1(3aS,4S,6S,7aR,3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yllethyl)amino)carbonyllcyclopropyl)-2-(trifluoromethyl)benzamide}

[0249] The title compound was prepared following the procedure described in Example 1, step A using the appropriate reagents to give the title compound (0.12 g, 46%).

Step 38D: \text{((3(3-methylphenyl)-1\text{-\{3(\text{trifluoromethyl)benzoyl}1\text{amino)cyclopropyl)carbonyliamino}lethylDboronic acid (29)}}

[0250] The title compound was prepared following the procedure described in Example 1, step D using the appropriate reagents to give the product as a white solid (0.10 g, 99%). LC/MS: \text{R}$_1$ = 6.17 min, ES$^+$ 417 (M-H$_2$O) (Formic Acid Purity method). \text{^1H NMR (CD$_3$OD, 300 MHz, (d): 7.94-7.86 (m, IH); 7.86-7.75 (m, 2H); 7.71-7.62 (m, IH); 7.34-7.25 (m, IH); 7.25-7.11 (m, 3H); 3.12-2.91 (m, 2H); 2.80-2.68 (m, IH); 2.39 (s, 3H); 2.01-1.90 (m, IH); 1.85-1.72 (m, IH); 1.57-1.43 (m, 2H).}

Example 39: 20S Proteasome Assay

Rat 20S (PA28 activation) β\text{li Proteasome Assay}

[0251] To 1 µL of test compound dissolved in DMSO in a 384-well black microtiter plate is added 25 µL of assay buffer at 37 °C containing human PA28 activator (Boston Biochem, 12 nM final) with Ac-PAL-AMC (ali selective substrate) (40 µM final), followed by 25 µL of assay buffer at 37 °C containing rat spleen 20S immunoproteasome (Boston Biochem, 0.25 nM final). Assay buffer is composed of 20 mM HEPES, 0.5 mM EDTA and 0.01% BSA, pH7.4. The reaction is followed on a BMG Galaxy plate reader (37 °C, excitation 380 nm, emission 460 nm, gain 20). Percent inhibition is calculated relative to 0% inhibition (DMSO) and 100% inhibition (10 µM bortezomib) controls.

Rat 20S (PA28 activation) β\text{si Proteasome Assay}

[0252] To 1 µL of test compound dissolved in DMSO in a 384-well black microtiter plate is added 25 µL of assay buffer at 37 °C containing human PA28 activator (Boston Biochem, 12 nM final) with with Ac-ANW-AMC »si selective substrate (30 µM final) followed by 25 µL of assay buffer at 37 °C containing rat spleen 20S immunoproteasome
(Boston Biochem, 0.25 nM final). Assay buffer is composed of 20 mM HEPES, 0.5 mM EDTA and 0.01% BSA, pH7.4. The reaction is followed on a BMG Galaxy plate reader (37 °C, excitation 380 nm, emission 460 nm, gain 20). Percent inhibition is calculated relative to 0% inhibition (DMSO) and 100% inhibition (10 µM bortezomib) controls.

**Human 20S (PA28 activation) βI Proteasome assay**

[0253] To 1 µL of test compound dissolved in DMSO in a 384-well black microtiter plate is added 25 µL of assay buffer at 37 °C containing human PA28 activator (Boston Biochem, 12 nM final) with Ac-LLE-AMC (α1 selective substrate) (15 µM final), followed by 25 µL of assay buffer at 37 °C containing human 20S proteasome (Boston Biochem, 0.25 nM final). Assay buffer is composed of 20 mM HEPES, 0.5 mM EDTA and 0.01% BSA, pH7.4. The reaction is followed on a BMG Galaxy plate reader (37 °C, excitation 380 nm, emission 460 nm, gain 20). Percent inhibition is calculated relative to 0% inhibition (DMSO) and 100% inhibition (10 µM bortezomib) controls.

**Human 20S (PA28 activation) βS Proteasome Assay**

[0254] To 1 µL of test compound dissolved in DMSO in a 384-well black microtiter plate is added 25 µL of assay buffer at 37 °C containing human PA28 activator (Boston Biochem, 12 nM final) with Ac-WLA-AMC (β5 selective substrate) (15 µM final), followed by 25 µL of assay buffer at 37 °C containing human 20S proteasome (Boston Biochem, 0.25 nM final). Assay buffer is composed of 20 mM HEPES, 0.5 mM EDTA and 0.01% BSA, pH7.4. The reaction is followed on a BMG Galaxy plate reader (37 °C, excitation 380 nm, emission 460 nm, gain 20). Percent inhibition is calculated relative to 0% inhibition (DMSO) and 100% inhibition (10 µM bortezomib) controls.

[0255] Compounds 1-8, 10-15, 17-25, and 27-38 exhibited an IC₅₀ value less than or equal to 50 µM in one or both of the βI or β5i assays described above. Compounds 2, 3, 6-8, 10-14, 18, 19, 21-23, 25, 27-37 exhibited an IC₅₀ value less than or equal to 10 µM in one or both of the βI or β5i assays described above. Compounds 3, 10-14, 18, 21, 22, 25, 28, 30, 32 exhibited an IC₅₀ value less than or equal to 1 µM in one or both of the βI or β5i assays described above. For most of the compounds in Table 1, the concentration of compound required to inhibit βI or β5i activity is lower than the concentration of compound required to inhibit βI or β5 activity.
Example 40: Antiproliferation Assay

HCT-116 (1000) or other tumor cells in 100 µL of appropriate cell culture medium (McCoy's 5A for HCT-116, Invitrogen) supplemented with 10% fetal bovine serum (Invitrogen) are seeded in wells of a 96-well cell culture plate and incubated overnight at 37 °C. Test compounds are added to the wells and the plates are incubated for 96 hours at 37 °C. MTT or WST reagent (10 µL, Roche) are added to each well and incubated for 4 hours at 37 °C as described by the manufacturer. For MTT the metabolized dye is solubilized overnight according to manufacturer's instructions (Roche). The optical density for each well is read at 595 nm (primary) and 690 nm (reference) for the MTT and 450 run for the WST using a spectrophotometer (Molecular Devices). For the MTT the reference optical density values are subtracted from the values of the primary wavelength. Percent inhibition is calculated using the values from a DMSO control set to 100%.

Example 41: In vivo Tumor Efficacy Model

Freshly dissociated HCT-116 (2.5 x 10^6) or other tumor cells in 100 µL of RPMI-1640 media (Sigma-Aldrich) are aseptically injected into the subcutaneous space in the right dorsal flank of female CD-1 nude mice (age 5-8 weeks, Charles River) using a 1 mL 26 3/8-ga needle (Becton Dickinson Ref#309625). Alternatively, some xenograft models require the serial passaging of tumor fragments. In these cases, small fragments of tumor tissue (approximately 1 mm³) are implanted subcutaneously in the right dorsal flank of anesthetized (3-5% isoflurane/ oxygen mixture) C.B-17/SCID mice (age 5-8 weeks, Charles River) via a 13-ga trocar (Popper & Sons 7927). Beginning at day 7 after inoculation tumors are measured twice weekly using a vernier caliper. Tumor volumes are calculated using standard procedures (0.5 x (length x width²)). When the tumors reach a volume of approximately 200 mm³ mice are randomized into treatment groups and begin receiving drug treatment. Dosing and schedules are determined for each experiment based on previous results obtained from pharmacokinetic/pharmacodynamic and maximum tolerated dose studies. The control group will receive vehicle without any drug. Typically, test compound (100-200 µL) is administered via intravenous (27-ga needle), oral (20-ga gavage needle) or subcutaneous (27-ga needle) routes at various doses and schedules. Tumor size and body weight are measured twice a week and the study is terminated when the control tumors reach approximately 2000 mm³.
While the foregoing invention has been described in some detail for purposes of clarity and understanding, these particular embodiments are to be considered as illustrative and not restrictive. It will be appreciated by one skilled in the art from a reading of this disclosure that various changes in form and detail can be made without departing from the true scope of the invention, which is to be defined by the appended claims rather than by the specific embodiments.

The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. 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. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure, including definitions, will control.
WHAT IS CLAIMED IS:

1. A compound of formula (I):

![Chemical Structure]

or a pharmaceutically acceptable salt or boronic acid anhydride thereof, wherein:

P is hydrogen or an amino-group-blocking moiety;

R^3 is a C_{1-4} aliphatic or C_{1-4} fluoroaliphatic group that is substituted with 0-1 R^A, or R^3 and R^B taken together with the carbon atom to which they are attached, form a substituted or unsubstituted 3- to 6-membered cycloaliphatic group;

R^A is a substituted or unsubstituted aromatic or cycloaliphatic ring;

R^B is a C_{1-4} aliphatic or C_{1-4} fluoroaliphatic group; or R^A and R^B, taken together with the carbon atom to which they are attached, form a substituted or unsubstituted 3- to 6-membered cycloaliphatic group;

R^C is a C_{1-4} aliphatic or C_{1-4} fluoroaliphatic group that is substituted with 0-1 R^C;

R^C is a substituted or unsubstituted aromatic or cycloaliphatic ring; and

Z^1 and Z^2 are each independently hydroxy, alkoxy, aryloxy, or aralkoxy; or Z^1 and Z^2 together form a moiety derived from a boronic acid complexing agent.

2. The compound of claim 1, wherein P is R^4-C(O)-, R^4-O-C(O)-,
R^4-N(R^A)-C(O)-, R^4-S(O)_2-, or R^4-N(R^A)-S(O)_2-:

R^A is selected from the group consisting of C_{1-6} aliphatic, C_{1-6} fluoroaliphatic, -R^D, -T^1-R^D, and -T'-R^D;

T^1 is a C_{1-6} alkylene chain substituted with 0-2 independently selected R^A or R^A, wherein the alkylene chain optionally is interrupted by -C(R^5)=C(R^5)-, -C≡C-, or -O-;
$R^P$ is a substituted or unsubstituted aromatic, heterocyclyl, or cycloaliphatic ring, any of which is optionally fused to a substituted or unsubstituted aromatic, heterocyclyl, or cycloaliphatic ring;

$R^{3a}$ is halo, -OR$^5$, -SR$^6$, -S(O)R$^5$, -SO$_2$NR$^6$, -SO$_2$N(R$^4$)$_2$, -N(R$^4$)$_2$, -NR$^4$C(O)R$^5$, -NR$^4$C(O)-N(R$^4$)$_2$, -N(R$^4$)SO$_2$N(R$^4$)$_2$, -O-C(O)R$^5$, -OC(O)N(R$^4$)$_2$, -C(O)R$^5$, -CO$_2$R$^5$, or -C(O)N(R$^4$)$_2$;

each $R^{3a}$ independently is selected from the group consisting of -F, -OH, -O(C$_{1-}a$ alkyl), -CN, -N(R$^4$)$_2$, -C(O)(C$_{1-}a$ alkyl), -CO$_2$H, -CO$_2$(C$_{1-}a$ alkyl), -C(O)NH$_2$, and -C(O)NH(C$_{1-}a$ alkyl);

each $R^{3a}$ independently is a C$_{1-3}$ aliphatic optionally substituted with $R^3b$ or $R^2$;

each $R^i$ independently is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, or heterocyclyl group; or two $R^i$ on the same nitrogen atom, taken together with the nitrogen atom, form an optionally substituted 4- to 8-membered heterocyclyl ring having, in addition to the nitrogen atom, 0-2 ring heteroatoms independently selected from N, O, and S;

each $R^g$ independently is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, or heterocyclyl group;

each $R^6$ independently is an optionally substituted aliphatic, aryl, or heteroaryl group;

each $R^7$ is a substituted or unsubstituted aromatic group; and

$R^{4a}$ is hydrogen, C$_{1-}a$ alkyl, C$_{1-}a$ fluoroalkyl, or C$_{6-10}$ ar(C$_{1-}a$)alkyl, the aryl portion of which is substituted or unsubstituted.

3. The compound of claim 2, wherein P is $R^4$-C(O)-.

4. The compound of claim 1, wherein $R^8$ is substituted or unsubstituted phenyl.

5. The compound of claim 1, wherein $R^4$ and $R^5$, taken together with the carbon atom to which they are attached, form a cyclopropyl or cyclobutyl ring, either of which is substituted with 0-2 substituents -R$^8$. 
each \( R^B \) independently is a \( C_{1-4} \) aliphatic, \( C_{1-4} \) fluoroaliphatic, \(-R^b, -T^2-R^\gamma\).

\( T^2 \) is \( C_{1-11} \) alkylene; and

\( R^b \) is a substituted or unsubstituted aromatic or cycoaliphatic group.

6. The compound of claim 4, wherein \( R^b \) is substituted or unsubstituted phenyl.

7. The compound of claim 1, wherein \( R^a \) and \( R^b \) are each \(-CH_3\).

8. The compound of claim 1, wherein \( R^c \) has the formula \(-(CH_2)_m-R^c\), \( m \) is 1 or 2, and \( R^c \) is substituted or unsubstituted phenyl.

9. The compound of claim 1, wherein \( R^c \) is \( C_{1-2} \) aliphatic.

10. The compound of claim 9, wherein \( R^c \) is isobutyl.

11. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

12. A method for treating cancer, comprising administering to a patient in need of such treatment a pharmaceutical composition according to claim 11.
**INTERNATIONAL SEARCH REPORT**

International application No
PCT/US2007/022079

A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07F  C07K  A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , BEILSTEIN Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of Box C.

**See patent family annex.**

- **A** document defining the general state of the art which is not considered to be of particular relevance.
- **E** earlier document but published on or after the international filing date.
- **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified).
- **O** document referring to an oral disclosure, use, exhibition or other means.
- **P** document published prior to the international filing date but later than the priority date claimed.
- **T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.
- **X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone.
- **Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- **A** document member of the same patent family.

Date of the actual completion of the international search
15 September 2008

Date of mailing of the international search report
29/09/2008

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
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Fax. (+31-70) 340-3016

Authorized officer
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<td>X</td>
<td>US 5 159 060 A (KINDER DAVID H [US] ET AL) 27 October 1992 (1992-10-27) figures 1,2,8; tables 1-3</td>
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</table>
### INTERNATIONAL SEARCH REPORT

#### Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.:
   - because they relate to subject matter not required to be searched by this Authority, namely:
   
   Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **☐** Claims Nos.:
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **☐** Claims Nos.:
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

#### Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- **☐** The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

- **☐** The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

- **☐** No protest accompanied the payment of additional search fees.
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