(19) IPOS INTELLECTUAL PROPERTY OFFICE OF SINGAPORE

(11) Publication number: **SG 187757 A1**
(43) Publication date: **28.03.2013**
(51) Int. Cl: **C07F 5/02, A61K 31/69, A61P 31/04;**

(12) Patent Application

(21) Application number: **2013009378**
(22) Date of filing: **08.08.2011**
(30) Priority: **US 61/372,296 10.08.2010**
US 61/488,655 20.05.2011

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(54) **Title:**
CYCLIC BORONIC ACID ESTER DERIVATIVES AND THERAPEUTIC USES THEREOF

(57) **Abstract:**
Disclosed herein are antimicrobial compound compositions, pharmaceutical compositions, the use and preparation thereof. The invention relates to cyclic boronic acid ester derivatives of formula I and their use as therapeutic agents particularly in the treatment of bacterial infections.

This PDF First Page has been artificially created from the Singaporian Abstracts

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 February 2012 (16.02.2012)

PCT

(10) International Publication Number
WO 2012/021455 A1

(51) International Patent Classification:
C07F 5/02 (2006.01) *A61P 31/04* (2006.01)
A61K 31/69 (2006.01)

(21) International Application Number:
PCT/US2011/046957

(22) International Filing Date:
8 August 2011 (08.08.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/372,296 10 August 2010 (10.08.2010) US
61/488,655 20 May 2011 (20.05.2011) US

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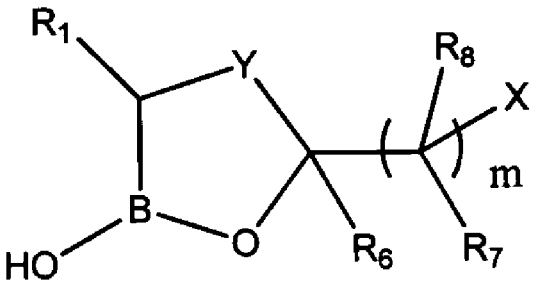
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: CYCLIC BORONIC ACID ESTER DERIVATIVES AND THERAPEUTIC USES THEREOF



Formula (I)

(57) **Abstract**: Disclosed herein are antimicrobial compound compositions, pharmaceutical compositions, the use and preparation thereof. The invention relates to cyclic boronic acid ester derivatives of formula I and their use as therapeutic agents particularly in the treatment of bacterial infections.

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CYCLIC BORONIC ACID ESTER DERIVATIVES AND THERAPEUTIC USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Nos. 61/372,296, filed August 10, 2010, and 61/488,655, filed May 20, 2011, both of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0001] The present invention relates to antimicrobial compounds, compositions, their use and preparation as therapeutic agents. In particular, the present invention relates to cyclic boronic acid ester compounds.

BACKGROUND OF THE INVENTION

[0002] Antibiotics have been effective tools in the treatment of infectious diseases during the last half-century. From the development of antibiotic therapy to the late 1980s there was almost complete control over bacterial infections in developed countries. However, in response to the pressure of antibiotic usage, multiple resistance mechanisms have become widespread and are threatening the clinical utility of anti-bacterial therapy. The increase in antibiotic resistant strains has been particularly common in major hospitals and care centers. The consequences of the increase in resistant strains include higher morbidity and mortality, longer patient hospitalization, and an increase in treatment costs

[0003] Various bacteria have evolved β-lactam deactivating enzymes, namely, β-lactamases, that counter the efficacy of the various β-lactams. β-lactamases can be grouped into 4 classes based on their amino acid sequences, namely, Ambler classes A, B, C, and D. Enzymes in classes A, C, and D include active-site serine β-lactamases, and class B enzymes, which are encountered less frequently, are Zn-dependent. These enzymes catalyze the chemical degradation of β-lactam antibiotics, rendering them inactive. Some β-lactamases can be transferred within and between various bacterial

strains and species. The rapid spread of bacterial resistance and the evolution of multi-resistant strains severely limits β-lactam treatment options available.

[0004] The increase of class D β-lactamase-expressing bacterium strains such as *Acinetobacter baumannii* has become an emerging multidrug-resistant threat. *A. baumannii* strains express A, C, and D class β-lactamases. The class D β-lactamases such as the OXA families are particularly effective at destroying carbapenem type β-lactam antibiotics, e.g., imipenem, the active carbapenems component of Merck's Primaxin® (Montefour, K.; *et al.* Crit. Care Nurse 2008, 28, 15; Perez, F. *et al.* Expert Rev. Anti Infect. Ther. 2008, 6, 269; Bou, G.; Martinez-Beltran, J. Antimicrob. Agents Chemother. 2000, 40, 428. 2006, 50, 2280; Bou, G. *et al*, J. Antimicrob. Agents Chemother. 2000, 44, 1556). This has imposed a pressing threat to the effective use of drugs in that category to treat and prevent bacterial infections. Indeed the number of catalogued serine-based β-lactamases has exploded from less than ten in the 1970s to over 300 variants. These issues fostered the development of five "generations" of cephalosporins. When initially released into clinical practice, extended-spectrum cephalosporins resisted hydrolysis by the prevalent class A β-lactamases, TEM-1 and SHV-1. However, the development of resistant strains by the evolution of single amino acid substitutions in TEM-1 and SHV-1 resulted in the emergence of the extended-spectrum β-lactamase (ESBL) phenotype.

[0005] New β-lactamases have recently evolved that hydrolyze the carbapenem class of antimicrobials, including imipenem, biapenem, doripenem, meropenem, and ertapenem, as well as other β-lactam antibiotics. These carbapenemases belong to molecular classes A, B, and D. Class A carbapenemases of the KPC-type predominantly in *Klebsiella pneumoniae* but now also reported in other *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The KPC carbapenemase was first described in 1996 in North Carolina, but since then has disseminated widely in the US. It has been particularly problematic in the New York City area, where several reports of spread within major hospitals and patient morbidity have been reported. These enzymes have also been recently reported in France, Greece, Sweden, United Kingdom, and an outbreak in Germany has recently been reported. Treatment of resistant strains with carbapenems can be associated with poor outcomes.

[0006] Another mechanism of β-lactamase mediated resistance to carbapenems involves combination of permeability or efflux mechanisms combined with hyper production of beta-lactamases. One example is the loss of a porin combined in hyperproduction of ampC beta-lactamase results in resistance to imipenem in

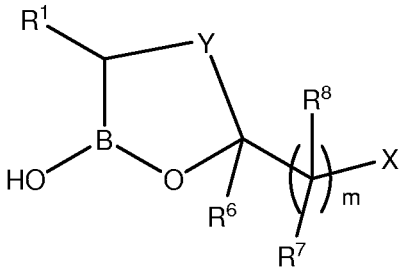
Pseudomonas aeruginosa. Efflux pump over expression combined with hyperproduction of the ampC β-lactamase can also result in resistance to a carbapenem such as meropenem.

[0007] Because there are three major molecular classes of serine-based β-lactamases, and each of these classes contains significant numbers of β-lactamase variants, inhibition of one or a small number of β-lactamases is unlikely to be of therapeutic value. Legacy β-lactamase inhibitors are largely ineffective against at least Class A carbapenemases, against the chromosomal and plasmid-mediated Class C cephalosporinases and against many of the Class D oxacillinases. Therefore, there is a need for improved β-lactamase inhibitors.

SUMMARY OF THE INVENTION

[0008] The present invention relates to antimicrobial agents and potentiators thereof. Some embodiments include compounds, compositions, pharmaceutical compositions, use and preparation thereof. In particular, some embodiments, relate to cyclic boronic acid ester derivatives.

[0009] Some embodiments include compounds having the structure of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

Y is a 1-4 atom alkylene or 2-4 atom alkenylene linker, optionally substituted by one or more substituents selected from the group consisting of Cl, F, CN, CF_3, $-R^9$, $-OR^9$, $-C(=O)NR^9R^{10}$, and $-C(=O)OR^9$, wherein said alkylene or alkenylene linker is optionally fused to an optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^1 is selected from a group consisting of -C_{1-9}alkyl, -C_{2-9}alkenyl, -C_{2-9}alkynyl, –NR^9R^{10}, -C_{1-9}alkylR^{11}, -C_{2-9}alkenylR^{11}, -C_{2-9}alkynylR^{11}, -carbocyclyl-R^{11}, -CH(OH)C_{1-9}alkylR^9, -CH(OH)C_{2-9}alkenylR^9, -CH(OH)C_{2-9}alkynylR^9, -CH(OH)carbocyclyl-R^9, -C(=O)R^9, -C(=O)C_{1-9}alkylR^9, -C(=O)C_{2-9}alkenylR^9, -C(=O)C_{2-9}alkynylR^9, -C(=O)C_{2-9}carbocyclyl-R^9, -C(=O)NR^9R^{10}, -N(R^9)C(=O)R^9, –N(R^9)C(=O)NR^9R^{10}, –N(R^9)C(=O)OR^9, -N(R^9)C(=O)C(=NR^{10})R^9, -N(R^9)C(=O)C(=CR^9R^{10})R^9, -N(R^9)C(=O)C_{1-4}alkylN(R^9)C(=O)R^9, –N(R^9)C(=NR^{10})R^9, -C(=NR^{10})NR^9R^{10}, -N=C(R^9)NR^9R^{10}, -N(R^9)SO_2R^9, –N(R^9)$SO_2NR^9R^{10}$, -N=CHR^9, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

R^6 is selected from a group consisting of H, -C_{1-9}alkyl, C_{2-9}alkenyl, -C_{2-9}alkynyl, carbocyclyl, -C_{1-9}alkylR^{11}, -C_{2-9}alkenylR^{11}, -C_{2-9}alkynylR^{11}, carbocyclyl-R^{11}, -C(=O)OR^9, -C_{1-9}alkylCO_2R^9, -C_{2-9}alkenylCO_2R^9, –C_{2-9}alkynylCO_2R^9, and -carbocyclyl-CO_2R^9, or alternatively:

(i) R^6 and an R^7 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl,

(ii) R^6 and a carbon atom in Y are taken together with intervening atoms to form a substituted or unsubstituted carbocyclyl or substituted or unsubstitued heterocyclyl, or

(iii) R^6 is absent when the carbon to which it is attached is a ring atom in an aryl or heteroaryl ring;

each R^7 is independently selected from a group consisting of H, halo , -C_{1-9}alkyl, -C_{2-9}alkenyl, -C_{2-9}alkynyl, –NR^9R^{10}, -OR^9, -C_{1-9}alkylCO_2R^9, -C_{2-9}alkenylCO_2R^9, –C_{2-9}alkynylCO_2R^9, and -carbocyclyl-CO_2R^9, or independently:

(i) R^6 and an R^7 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl,

(ii) R^7 and an R^8 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl,

(iii) an R^7 and a carbon atom in Y are taken together with intervening atoms to form a substituted or unsubstituted carbocyclyl or substituted or unsubstitued heterocyclyl,

(iv) each of the following conditions are met:

(a) Y is a 3-4 atom alkylene or 3-4 atom alkenylene linker,

(b) R^6 is absent,

(c) R^7 and a carbon atom in Y are taken together with intervening atoms to form a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl, and

(d) each R^8 attached to a ring atom forming part of the substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl formed by R^7 and Y is absent;

each R^8 is independently selected from a group consisting of H, halo , -C_{1-9}alkyl, -C_{2-9}alkenyl, -C_{2-9}alkynyl, –NR^9R^{10}, -OR^9, -C_{1-9}alkylCO_2R^9, -C_{2-9}alkenylCO_2R^9,–C_{2-9}alkynylCO_2R^9, -carbocyclyl-CO_2R^9, or independently:

(i) an R^7 and an R^8 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl,

(ii) a geminal R^7 and R^8 together form–C_{2-9} alkenylenylCO_2R^9, or

(iii) each R^8 attached to a ring atom forming part of a substituted or unsubstituted aryl is absent;

each R^9 is independently selected from a group consisting of H, -C_{1-9}alkyl, C_{2-9}alkenyl, -C_{2-9}alkynyl, carbocyclyl, -C_{1-9}alkylR^{11}, -C_{2-9}alkenylR^{11}, -C_{2-9}alkynylR^{11}, -carbocyclyl-R^{11}, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

each R^{10} is independently selected from a group consisting of H, -C_{1-9}alkyl, -OR^9, -CH(=NH), -C(=O)OR^9, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

each R^{11} is independently selected from a group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

X is selected from a group consisting of H, $-CO_2R^{12}$, and carboxylic acid isosteres;

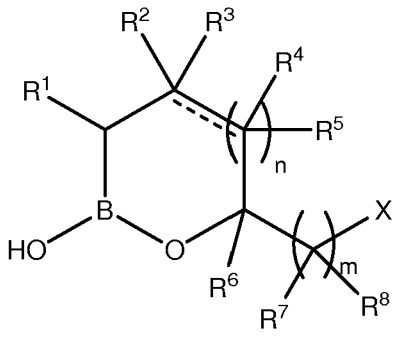
R^{12} is selected from a group consisting of H, C_{1-9}alkyl, $-(CH_2)_{0-3}-R_{11}$, $-C(R^{13})_2OC(O)C_{1-9}$alkyl, $-C(R^{13})_2OC(O)R^{11}$, $-C(R^{13})_2OC(O)OC_{1-9}$alkyl and $-C(R^{13})_2OC(O)OR^{11}$;

each R^{13} is independently selected from a group consisting of H and C_{1-4}alkyl; and

m is independently zero or an integer from 1 to 2,

wherein each C_{1-9}alkyl, C_{2-9}alkenyl, and C_{2-9}alkynyl is independently optionally substituted.

[0010] In some embodiments, the compound of formula I has the structure of formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

the bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond with the proviso that the dashed and solid line can only be a double bond when n is 1;

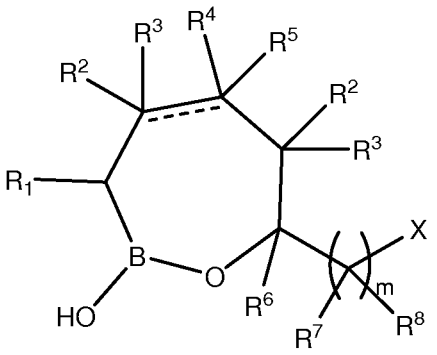
R^2 and R^4 are independently selected from a group consisting of Cl, F, CN, CF_3, $-R^9$, $-OR^9$, $-C(=O)NR^9R^{10}$, and $-C(=O)OR^9$; or alternatively, R^2 and R^4 are taken together with the atoms to which they are attached to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

R^3 and R^5 are independently selected from a group consisting of Cl, F, CN, CF_3, $-R^9$, $-OR^9$, $-C(=O)NR^9R^{10}$, and $-C(=O)OR^9$, with the proviso that if the bond

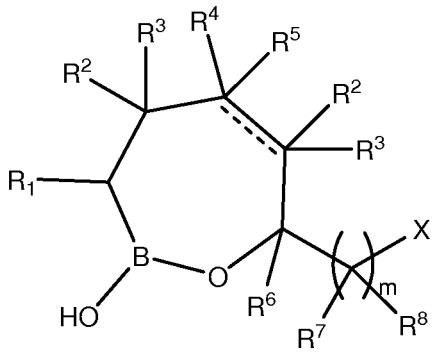
represented by a dashed and solid line is a double bond then R^3 and R^5 are absent; and

n is independently zero or an integer from 1 to 2.

[0011] In some embodiments, the compound of formula I the structure of formula IIIa or IIIb:



IIIa



IIIb

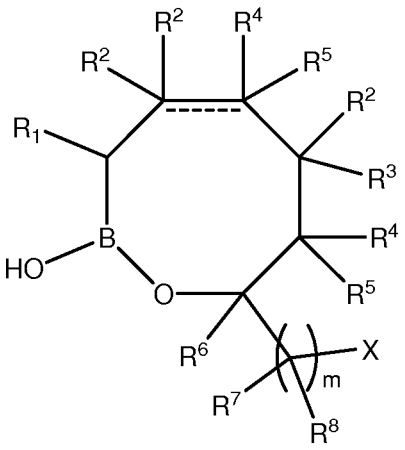
or a pharmaceutically acceptable salt thereof, wherein:

the bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond;

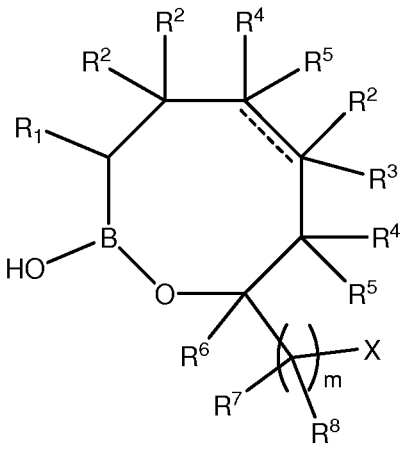
each R^2 and R^4 are independently selected from a group consisting of Cl, F, CN, CF_3, $-R^9$, $-OR^9$, $-C(=O)NR^9R^{10}$, and $-C(=O)OR^9$; or alternatively, an R^2 and R^4 are taken together with the atoms to which they are attached to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

each R^3 and R^5 are independently selected from a group consisting of Cl, F, CN, CF_3, $-R^9$, $-OR^9$, $-C(=O)NR^9R^{10}$, and $-C(=O)OR^9$, with the proviso that if the bond represented by a dashed and solid line is a double bond then R^3 and R^5 are absent.

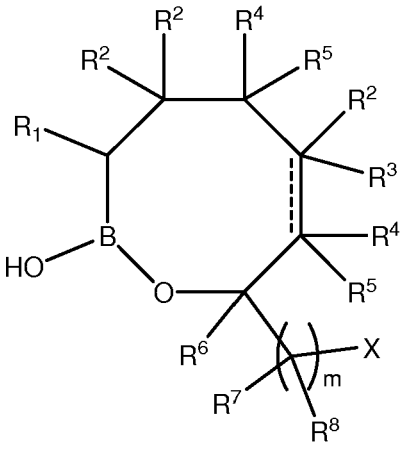
[0012] In some embodiments, the compound of formula I has the structure of formula IVa, IVb, or IVc:



IVa



IVb



IVc

or a pharmaceutically acceptable salt thereof, wherein:

the bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond;

each R^2 and each R^4 are independently selected from a group consisting of Cl, F, CN, CF_3, $-R^9$, $-OR^9$, $-C(=O)NR^9R^{10}$, and $-C(=O)OR^9$; or alternatively, an R^2 and an R^4 are taken together with the atoms to which they are attached to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

each R^3 and each R^5 are independently selected from a group consisting of Cl, F, CN, CF_3, $-R^9$, $-OR^9$, $-C(=O)NR^9R^{10}$, and $-C(=O)OR^9$, with the proviso that if the bond represented by a dashed and solid line is a double bond then the R^3 and R^5 attached to the carbon atoms bonded that bond are absent.

[0013] Some embodiments include a pharmaceutical composition comprising a therapeutically effective amount of any one of the foregoing compounds and a pharmaceutically acceptable excipient.

[0014] Some embodiments include any one of the foregoing compounds or compositions for use in the treatment or prevention of a bacterial infection.

[0015] Some embodiments include methods for treating or preventing a bacterial infection comprising administering to a subject in need thereof, an effective amount of any one of the foregoing compounds or compositions.

[0016] Some embodiments include the use of any one of the foregoing compounds or compositions in the preparation of a medicament for the treatment or prevention of a bacterial infection.

[0017] Some embodiments further comprise administering an additional medicament, either is a separate composition or in the same composition.

[0018] In some embodiments, the additional medicament includes an antibacterial agent, antifungal agent, an antiviral agent, an anti-inflammatory agent or an anti-allergic agent.

[0019] In some embodiments, the additional medicament comprises an antibacterial agent such as a β-lactam.

[0020] In some embodiments, the β-lactam includes Amoxicillin, Ampicillin (Pivampicillin, Hetacillin, Bacampicillin, Metampicillin, Talampicillin), Epicillin, Carbenicillin (Carindacillin), Ticarcillin, Temocillin, Azlocillin, Piperacillin, Mezlocillin, Mecillinam (Pivmecillinam), Sulbenicillin, Benzylpenicillin (G), Clometocillin, Benzathine benzylpenicillin, Procaine benzylpenicillin, Azidocillin, Penamecillin, Phenoxymethylpenicillin (V), Propicillin, Benzathine phenoxymethylpenicillin, Pheneticillin, Cloxacillin (Dicloxacillin, Flucloxacillin), Oxacillin, Meticillin, Nafcillin, Faropenem, Biapenem, Doripenem, Ertapenem, Imipenem, Meropenem, Panipenem, Tomopenem, Razupenem, Cefazolin, Cefacetrile, Cefadroxil, Cefalexin, Cefaloglycin, Cefalonium, Cefaloridine, Cefalotin, Cefapirin, Cefatrizine, Cefazedone, Cefazaflur, Cefradine, Cefroxadine, Ceftezole, Cefaclor, Cefamandole, Cefminox, Cefonicid, Ceforanide, Cefotiam, Cefprozil, Cefbuperazone, Cefuroxime, Cefuzonam, Cefoxitin, Cefotetan, Cefmetazole, Loracarbef, Cefixime, Ceftazidime, Ceftriaxone, Cefcapene, Cefdaloxime, Cefdinir, Cefditoren, Cefetamet, Cefmenoxime, Cefodizime, Cefoperazone, Cefotaxime, Cefpimizole, Cefpiramide, Cefpodoxime, Cefsulodin, Cefteram, Ceftibuten, Ceftiolene, Ceftizoxime, Flomoxef, Latamoxef, Cefepime, Cefozopran, Cefpirome, Cefquinome, Ceftobiprole, Ceftaroline, CXA-101, RWJ-54428, MC-04,546, ME1036, BAL30072, SYN 2416, Ceftiofur, Cefquinome, Cefovecin, Aztreonam, Tigemonam, Carumonam, RWJ-442831, RWJ-333441, or RWJ-333442.

[0021] In some embodiments, the β-lactam includes Ceftazidime, Biapenem, Doripenem, Ertapenem, Imipenem, Meropenem, or Panipenem.

[0022] In some embodiments, the β-lactam is selected from Aztreonam, Tigemonam, BAL30072, SYN 2416, or Carumonam.

[0023] In some embodiments, the β-lactam Tigemonam, the composition is suitable for oral administration, X is $-CO_2R^{12}$, and R^{12} is selected from a group consisting of $C_{1\text{-}9}$alkyl, $-(CH_2)_{0\text{-}3}\text{-}R_{11}$, $-C(R^{13})_2OC(O)C_{1\text{-}9}$alkyl, $-C(R^{13})_2OC(O)R^{11}$, $-C(R^{13})_2OC(O)OC_{1\text{-}9}$alkyl and $-C(R^{13})_2OC(O)OR^{11}$.

[0024] In some embodiments, the infection that is treated or prevented comprises a bacteria that includes *Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas acidovorans, Pseudomonas alcaligenes, Pseudomonas putida, Stenotrophomonas maltophilia, Burkholderia cepacia, Aeromonas hydrophilia, Escherichia coli, Citrobacter freundii, Salmonella typhimurium, Salmonella typhi, Salmonella paratyphi, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Francisella tularensis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia alcalifaciens, Providencia rettgeri, Providencia stuartii, Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Yersinia intermedia, Bordetella pertussis, Bordetella parapertussis, Bordetella bronchiseptica, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus ducreyi, Pasteurella multocida, Pasteurella haemolytica, Branhamella catarrhalis, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Borrelia burgdorferi, Vibrio cholerae, Vibrio parahaemolyticus, Legionella pneumophila, Listeria monocytogenes, Neisseria gonorrhoeae, Neisseria meningitidis, Kingella, Moraxella, Gardnerella vaginalis, Bacteroides fragilis, Bacteroides distasonis, Bacteroides 3452A homology group, Bacteroides vulgatus, Bacteroides ovalus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides eggerthii, Bacteroides splanchnicus, Clostridium difficile, Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium leprae, Corynebacterium diphtheriae, Corynebacterium ulcerans, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus*

intermedius, *Staphylococcus hyicus subsp. hyicus*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, or *Staphylococcus saccharolyticus*.

[0025] In some embodiments, the infection that is treated or prevented comprises a bacteria that includes *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Stenotrophomonas maltophilia*, *Escherichia coli*, *Citrobacter freundii*, *Salmonella typhimurium*, *Salmonella typhi*, *Salmonella paratyphi*, *Salmonella enteritidis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Serratia marcescens*, *Acinetobacter calcoaceticus*, *Acinetobacter haemolyticus*, *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Yersinia intermedia*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Haemophilus haemolyticus*, *Haemophilus parahaemolyticus*, *Helicobacter pylori*, *Campylobacter fetus*, *Campylobacter jejuni*, *Campylobacter coli*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Legionella pneumophila*, *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Moraxella*, *Bacteroides fragilis*, *Bacteroides vulgatus*, *Bacteroides ovalus*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides eggerthii*, or *Bacteroides splanchnicus*.

[0026] Some embodiments include a sterile container, comprising any one of the foregoing compounds in solid form and an antibacterial agent in solid form. In some embodiments, the antimicrobial agent is one of the additional medicaments described above. Some embodiments include a method of preparing a pharmaceutical composition for administration, comprising reconstituting the contents of the sterile container using a pharmaceutically acceptable diluent. In some embodiments, the reconstituted solution is administered intravenously to a patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] FIGURE 1 is a graph depicting the plasma concentration profile of a cyclic boronic acid ester derivative as a function of time after administration to Sprague Dawley rats.

[0028] FIGURE 2 is a graph depicting the plasma concentration profile of a prodrug of the cyclic boronic acid ester derivative of Figure 1 as a function of time after administration to Sprague Dawley rats.

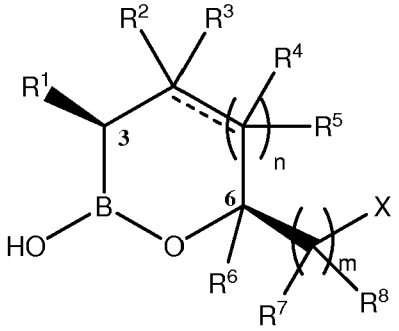
[0029] FIGURE 3 is an X-ray powder diffraction of a crystalline form of a cyclic boronic acid ester derivative.

[0030] FIGURE 4 is a graph depicting an overlay of differential scanning calorimetry and thermogravimetric results for the crystalline form of Figure 3.

DETAILED DESCRIPTION

[0031] The present invention relates to antimicrobial agents and potentiators thereof. Some embodiments include compounds, compositions, pharmaceutical compositions, uses thereof, including methods of preparation, and methods of treatment. In particular, the present invention relates to cyclic boronic acid ester derivatives. In some embodiments, the cyclic boronic acid ester derivatives have the structure of formula I, II, IIIa, IIIb, IVa, IVb, or IVc as described above.

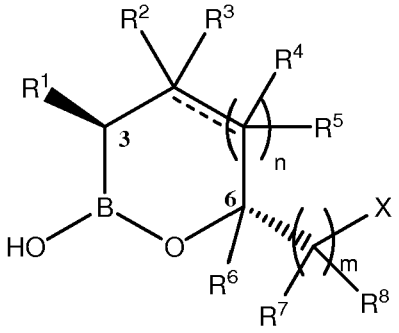
[0032] Some embodiments of the compound of formula II have the defined 3,6-cis-stereochemistry shown in formula IIa:



IIa

or a pharmaceutically acceptable salt thereof.

[0033] Some embodiments of the compound of formula II have the defined 3,6-trans-stereochemistry shown in formula IIb:



IIb

or a pharmaceutically acceptable salt thereof.

[0034] In one embodiment of the compound of formula II:

R^1 is selected from a group consisting of -C_{1-9}alkyl, -C_{2-9}alkenyl, -C_{2-9}alkynyl, –NR^9R^{10}, -C_{1-9}alkylR^{11}, -C_{2-9}alkenylR^{11}, -C_{2-9}alkynylR^{11}, -CH(OH)C_{1-}

$_{9}$alkylR^9, -CH(OH)C_{2-9}alkenylR^9, -CH(OH)C_{2-9}alkynylR^9, -C(=O)R^9, -C(=O)C_{1-9}alkylR^9, -C(=O)C_{2-9}alkenylR^9, -C(=O)C_{2-9}alkynylR^9, -C(=O)NR^9R^{10}, -N(R^9)C(=O)R^9, –N(R^9)C(=O)NR^9R^{10}, –N(R^9)C(=O)OR^9, -N(R^9)C(=O)C(=NR^{10})R^9, -N(R^9)C(=O)C_{1-4}alkylN(R^9)C(=O)R^9, –N(R^9)C(=NR^{10})R^9, -C(=NR^{10})NR^9R^{10}, -N=C(R^9)NR^9R^{10}, -N(R^9)SO_2R^9, –N(R^9)$SO_2NR^9R^{10}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

R^6 is selected from a group consisting of H, -C_{1-9}alkyl, C_{2-9}alkenyl, -C_{2-9}alkynyl, -C_{1-9}alkylR^{11}, -C_{2-9}alkenylR^{11}, -C_{2-9}alkynylR^{11}, -C(=O)OR^9, and -C_{1-9}alkylCO_2R^9, -C_{2-9}alkenylCO_2R^9, and –C_{2-9}alkynylCO_2R^9, or alternatively R^6 and an R^7 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

each R^7 is independently selected from a group consisting of H, –NR^9R^{10}, -OR^9, and -C_{1-9}alkylCO_2R^9, -C_{2-9}alkenylCO_2R^9, and –C_{2-9}alkynylCO_2R^9, or independently, R^6 and an R^7 or independently an R^7 and an R^8 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

each R^8 is independently selected from a group consisting of H, –NR^9R^{10}, -OR^9, and -C_{1-9}alkylCO_2R^9, -C_{2-9}alkenylCO_2R^9, and –C_{2-9}alkynylCO_2R^9, or independently, an R^7 and an R^8 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

each R^9 is independently selected from a group consisting of H, -C_{1-9}alkyl, C_{2-9}alkenyl, -C_{2-9}alkynyl, -C_{1-9}alkylR^{11}, -C_{2-9}alkenylR^{11}, -C_{2-9}alkynylR^{11}, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -$(CH_2)_{0-3}$carbocyclyl, and substituted or unsubstituted heterocyclyl;

each R^{10} is independently selected from a group consisting of H, -C_{1-9}alkyl, -OR^9, -CH(=NH), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl; and

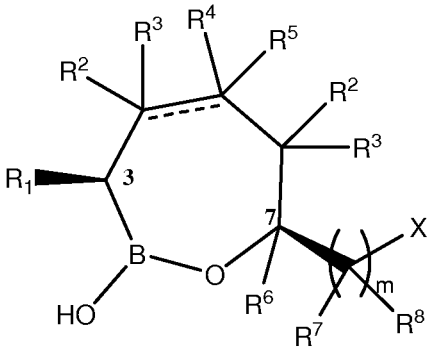
X is selected from a group consisting of H, -CO_2H and carboxylic acid isosteres.

[0035] In some embodiments of compounds of formulas II, IIa, or IIb, n is 1.

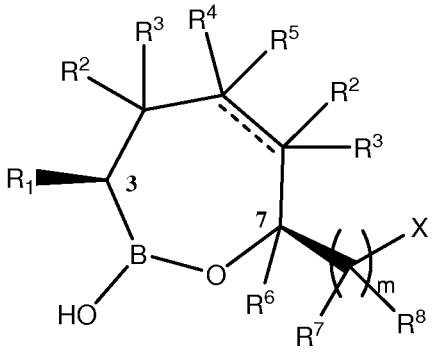
[0036] In some embodiments of compounds of formulas II, IIa, or IIb, n is zero.

[0037] In some embodiments of compounds of formulas II, IIa, or IIb, n is 2.

[0038] Some embodiments of the compounds of formula IIIa or IIIb have the 3,7-cis-stereochemistry shown in formula IIIc and IIId:



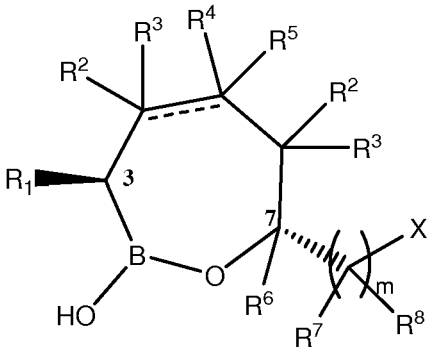
IIIc



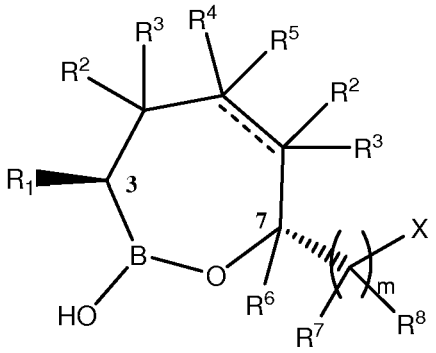
IIId

or a pharmaceutically acceptable salt thereof.

[0039] Some embodiments of the compounds of formula IIIa or IIIb have the 3,7-trans-stereochemistry shown in formula IIIe and IIIf:



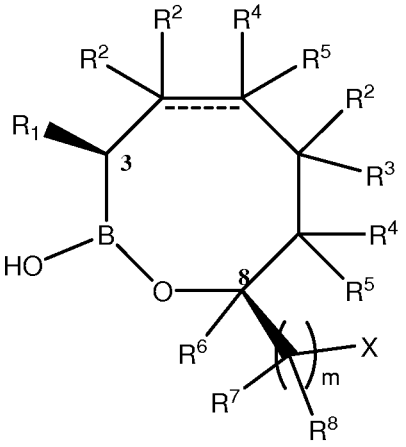
IIIe



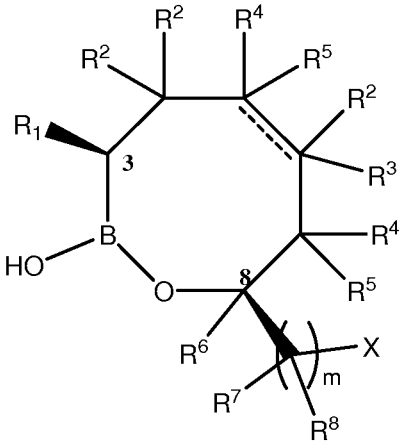
IIIf

or a pharmaceutically acceptable salt thereof.

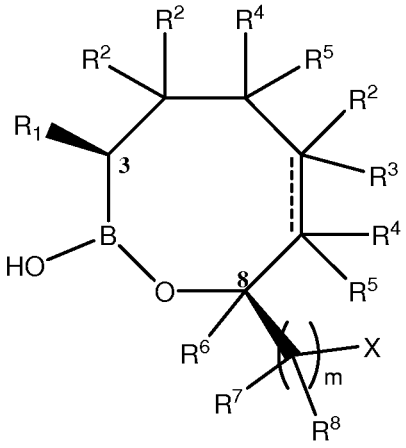
[0040] Some embodiments of the compounds of formulas IVa, IVb, or IVc have the 3,8-cis-stereochemistry shown in formula IVd, IVe, and IVf:



IVd



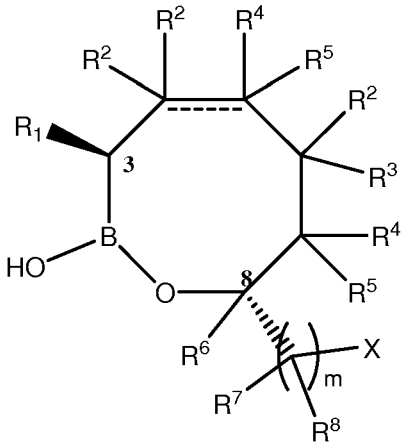
IVe



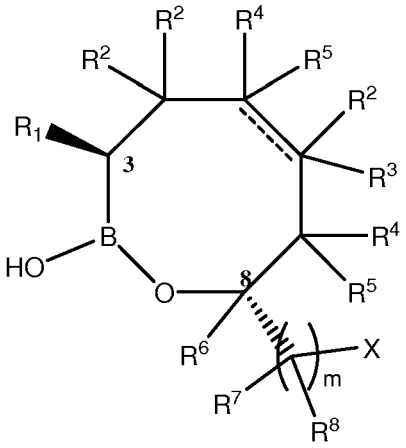
IVf

or a pharmaceutically acceptable salt thereof.

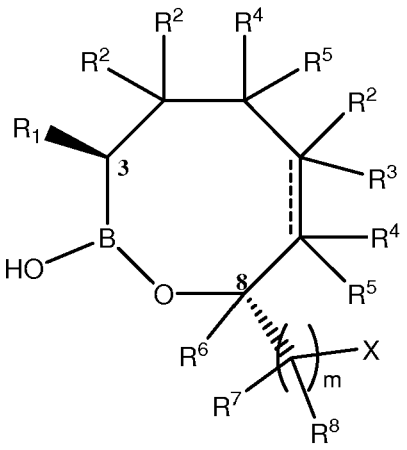
[0041] Some embodiments of the compounds of formulas IVa, IVb, or IVc have the 3,8-trans-stereochemistry shown in formula IVg, IVh, and IVi:



IVg



IVh



IVi

or a pharmaceutically acceptable salt thereof.

[0042] In some embodiments of the compounds of formulas II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, each R^2, R^3, R^4, and R^5 are hydrogen.

[0043] In some embodiments of the compounds of formulas II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, at least one R^2 is substituted or unsubstituted aryl.

[0044] In some embodiments of the compounds of formulas II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, at least one R^4 is substituted or unsubstituted aryl.

[0045] In some embodiments of the compounds of formulas II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, at least one R^2 and R^4 are taken together with the atoms to which they are attached to form a substituted or unsubstituted aryl.

[0046] In some embodiments of the compounds of formulas II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, the bond represented by a dashed and solid line is a single bond. In other embodiments, the bond represented by a dashed and solid line is a double bond.

[0047] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^6 and each R^7 and R^8 is hydrogen.

[0048] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-NHC(=O)C_{1\text{-}9}alkylR^{11}$.

In some such embodiments, R^{11} is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In some such embodiments, R^{11} is thien-2-yl.

[0049] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-NHC(=O)C(=NOR^9)R^{9'}$, wherein $R^{9'}$ is selected from the group consisting of C_{1-9}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl and substituted or unsubstituted heterocyclyl.

[0050] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-NHC(=O)C_{1-9}alkylR^{11}$. In some such embodiments, R^{11} is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl.

[0051] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-NHC(=O)R^{9'}$, wherein $R^{9'}$ is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl.

[0052] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-NR^9R^{10}$.

[0053] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-C_{1-9}alkylR^{11}$.

[0054] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-CH(OH)C_{1-9}alkylR^9$.

[0055] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-C(=O)C_{1-9}alkyl\ R^9$.

[0056] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-C(=O)NR^9R^{10}$.

[0057] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-N(R^8)C(=O)N\ R^9R^{10}$.

[0058] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-N(R^9)C(=O)O\ R^9$.

[0059] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-N(R^9)C(=O)C_{1-4}alkylN(R^9)C(=O)\ R^9$.

[0060] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-N(R^9)C(=NR^{10})\ R^9$.

[0061] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-C(=NR^{10})N\ R^9R^{10}$.

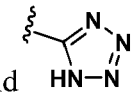
[0062] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-N=C(R^9)N\ R^9R^{10}$.

[0063] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-C(=O)C(=NR^{10})\ R^9$.

[0064] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-N(R^9)SO_2\ R^9$.

[0065] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^1 is $-N(R^9)SO_2N\ R^9R^{10}$.

[0066] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, X is $-CO_2H$.

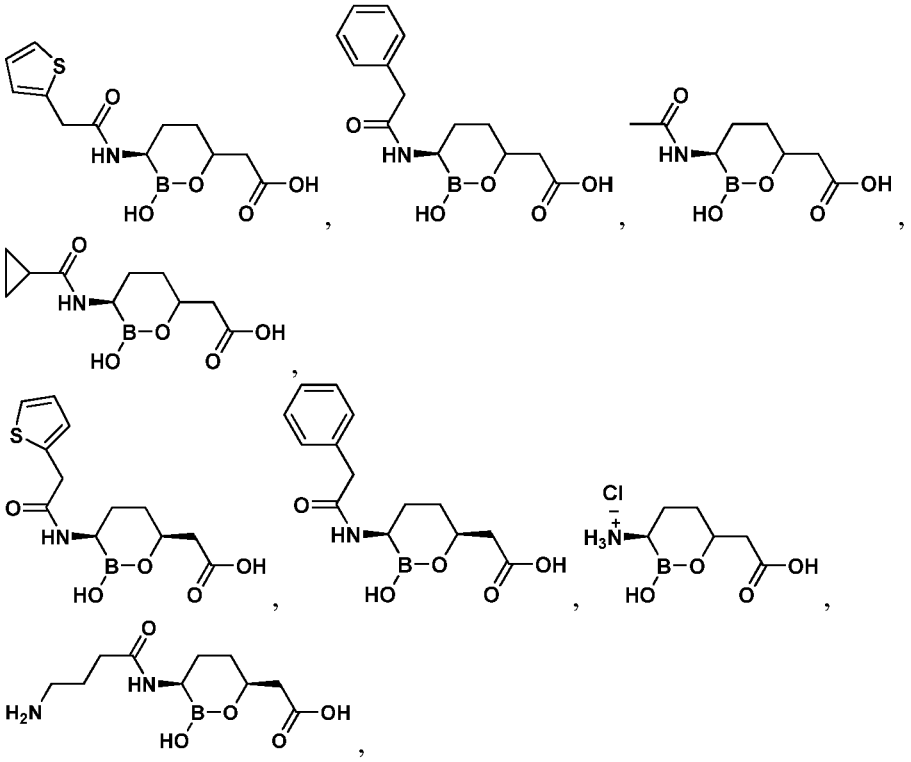
[0067] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, X is a carboxylic acid isostere. In some such embodiments, the carboxylic acid isostere is selected from the group consisting of $-P(O)(OR^9)_2$, $-P(O)(R^9)(OR^9)$,$-P(O)(OR^{12'})_2$, $-P(O)(R^9)(OR^{12'})$, $-CON(R^9)OH$, $-SO_3H$, $-SO_2N(R^9)OH$, and , wherein $R^{12'}$ is selected from the group consisting of H, R_{11}, $-C(R^{13})_2OC(O)C_{1\text{-}9}$alkyl, $-C(R^{13})_2OC(O)R^{11}$, $-C(R^{13})_2OC(O)OC_{1\text{-}9}$alkyl and $-C(R^{13})_2OC(O)OR^{11}$.

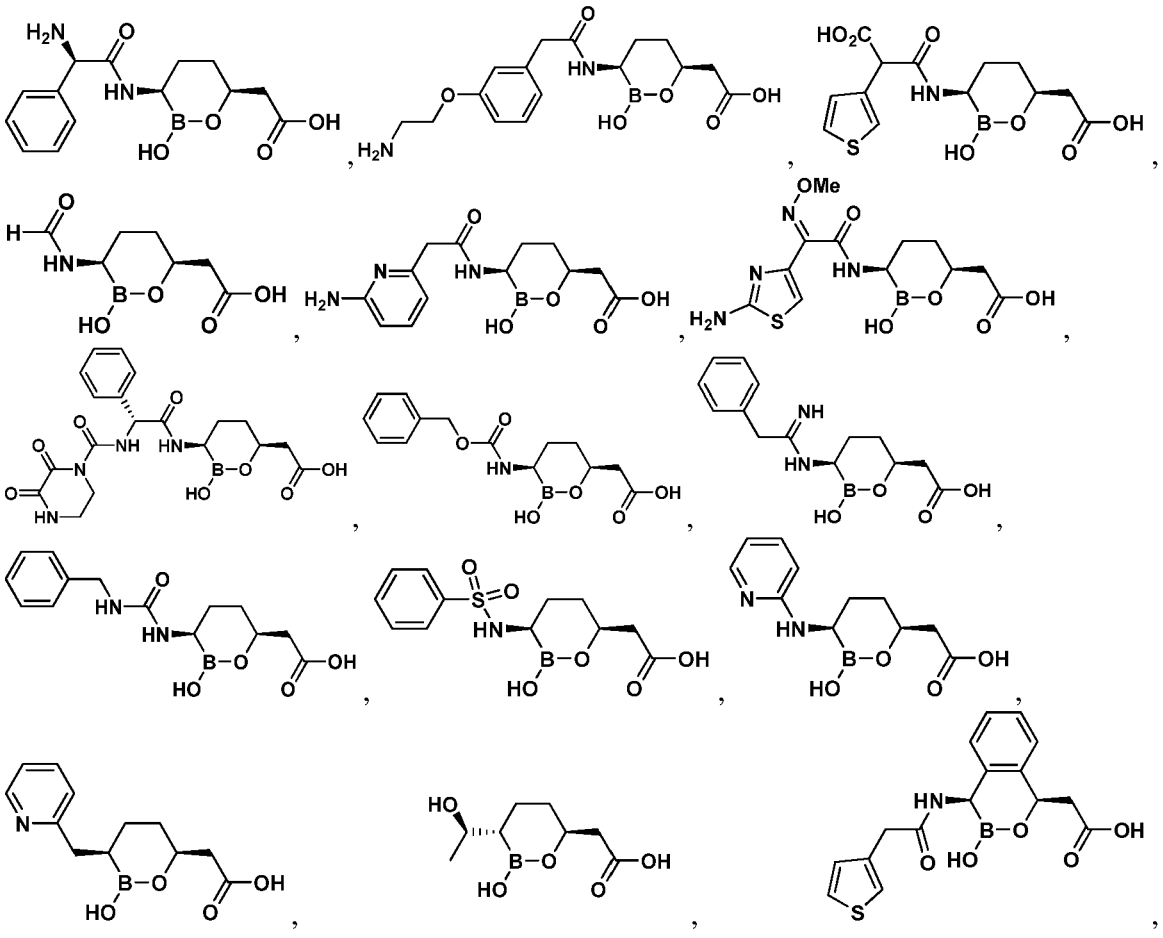
[0068] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, m is 1.

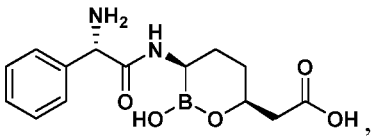
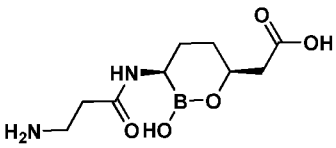
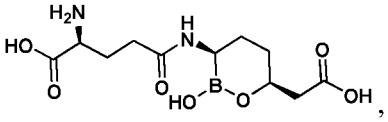
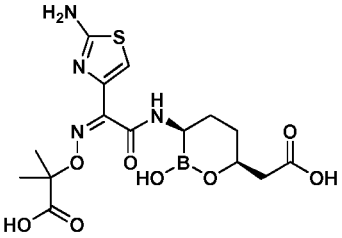
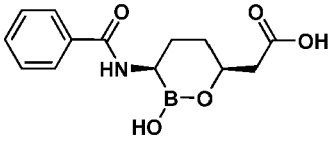
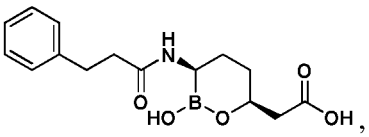
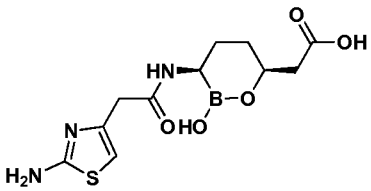
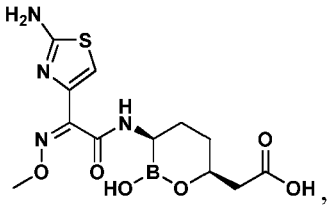
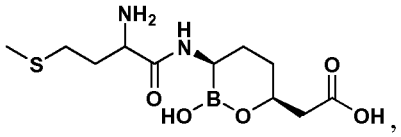
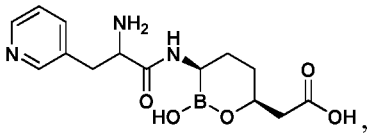
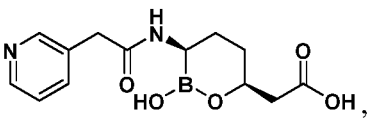
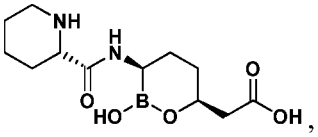
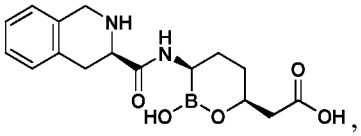
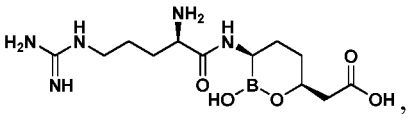
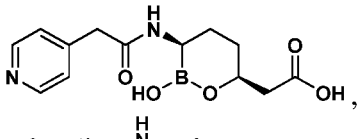
[0069] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^6, R^7 and R^8 are H.

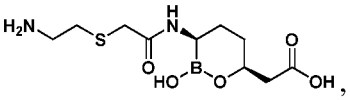
[0070] In some embodiments of the compounds of formulas I, II, IIa, IIIa, IIIb, IIIc, IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, and IVi, R^7 is H; R^8 is $-C_{1\text{-}9}$alkylCO_2R^9; and R^9 is H.

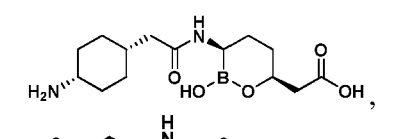
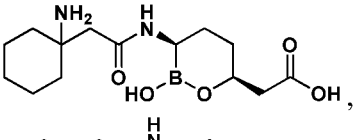
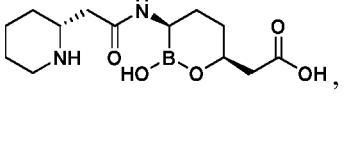
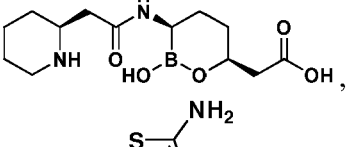
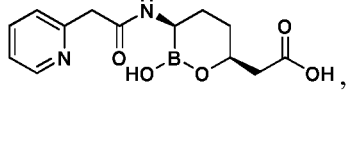
[0071] Some embodiments include a compound selected from the group consisting of:

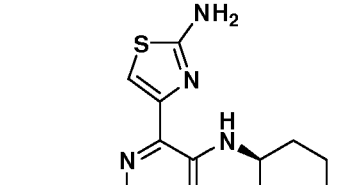


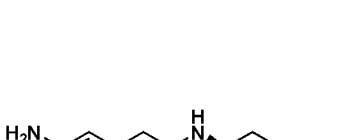
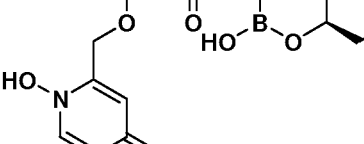


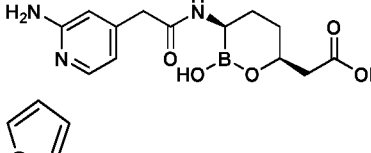

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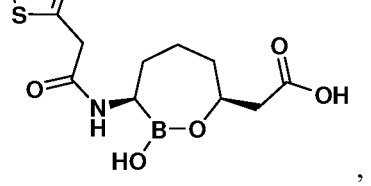
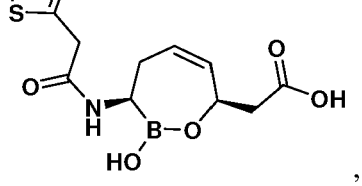
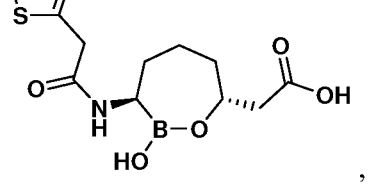
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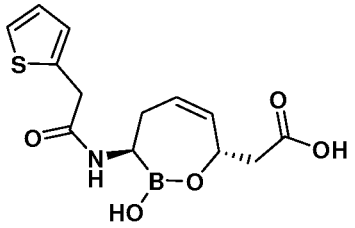
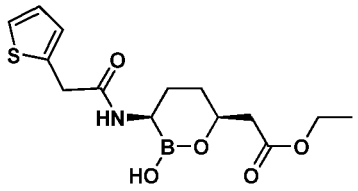
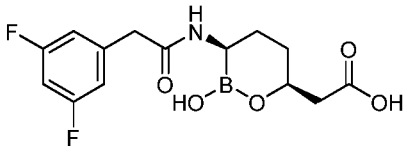
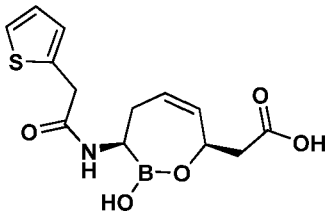
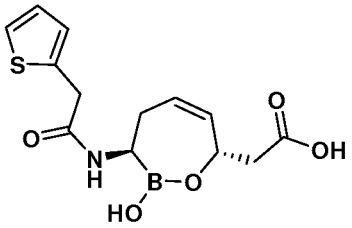
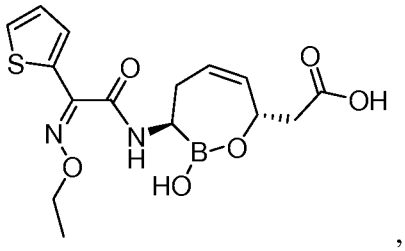
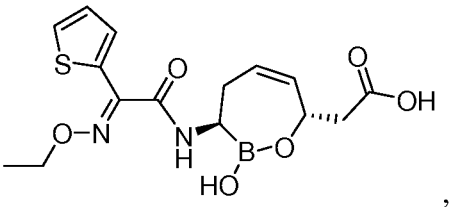
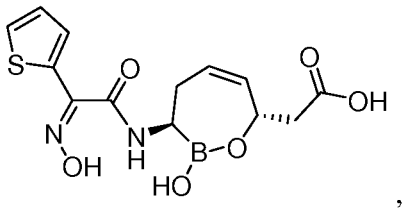
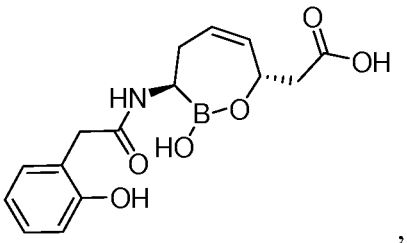
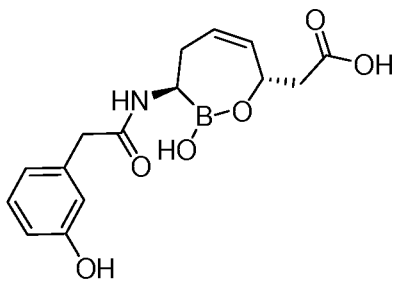
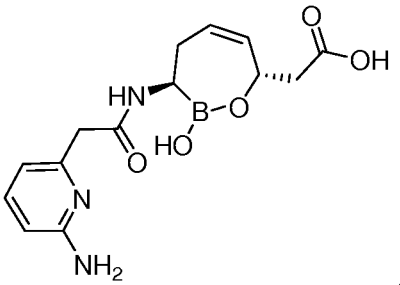
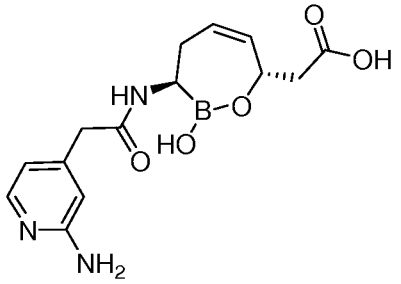
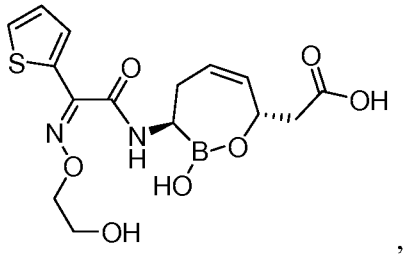
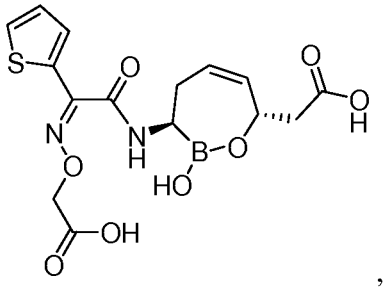
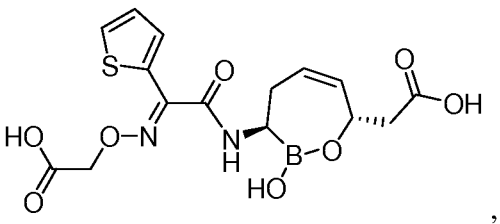
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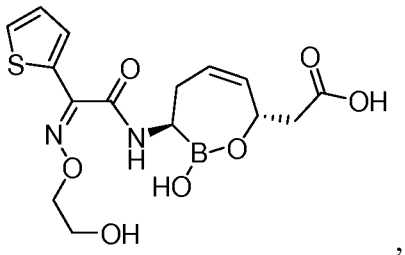
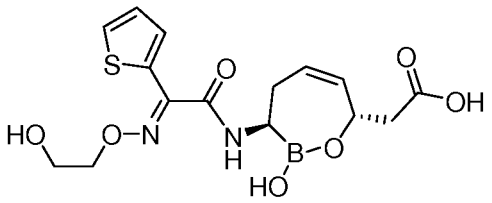
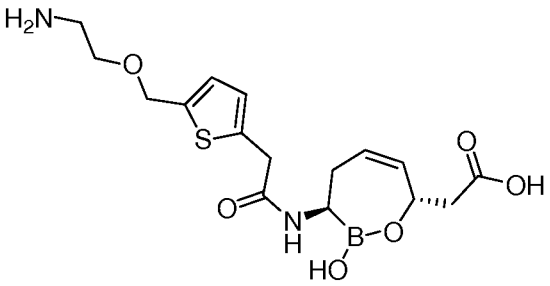
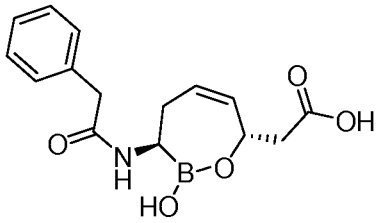
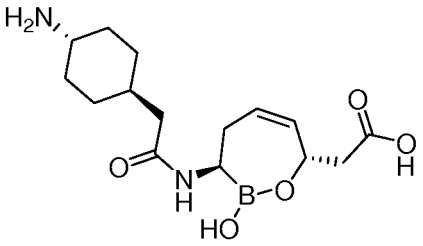
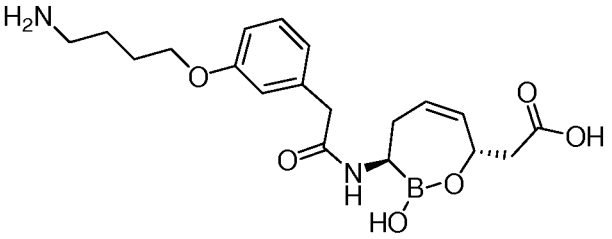
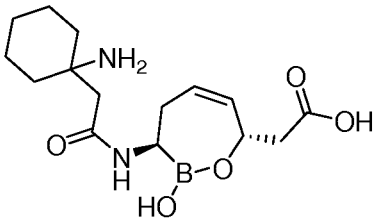
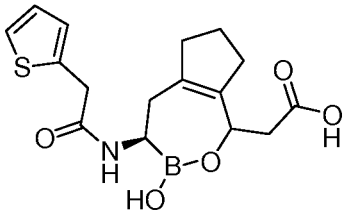
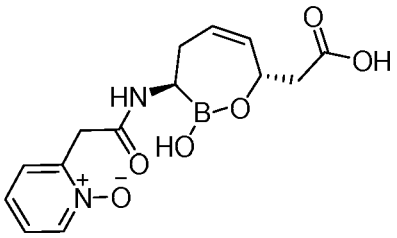
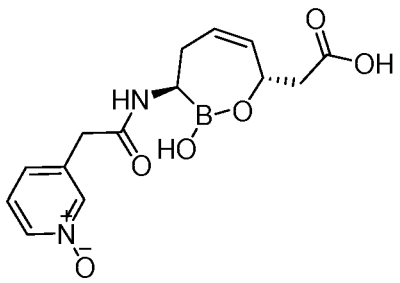
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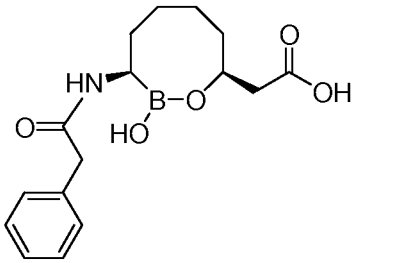
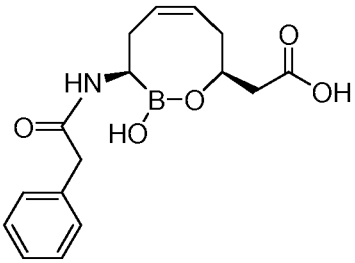
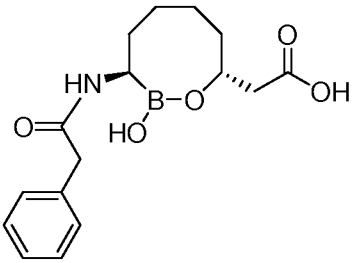
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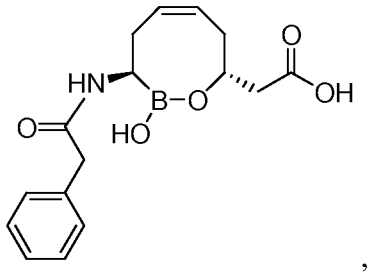
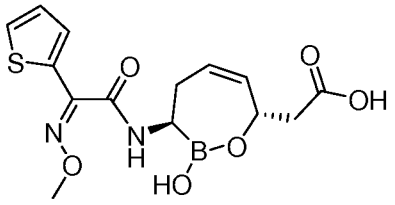
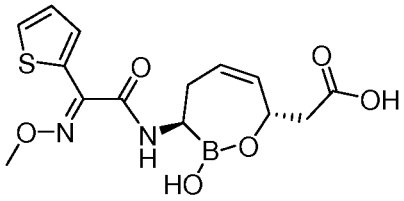
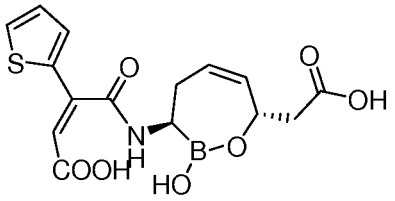
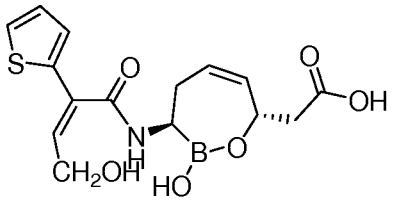
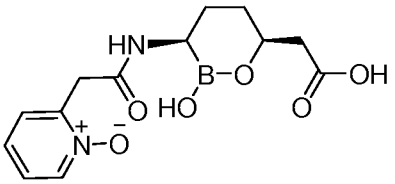
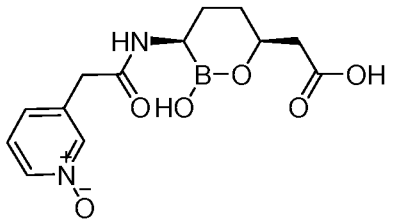
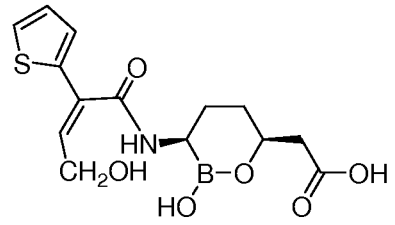
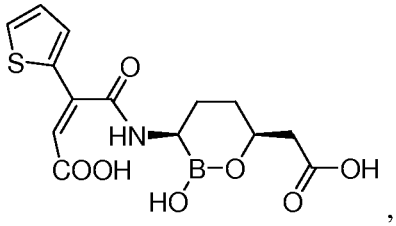
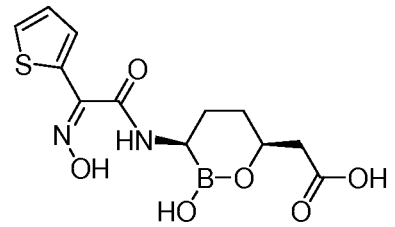
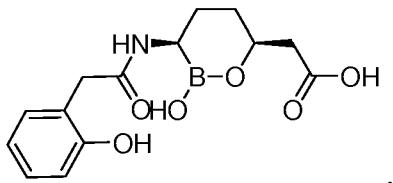
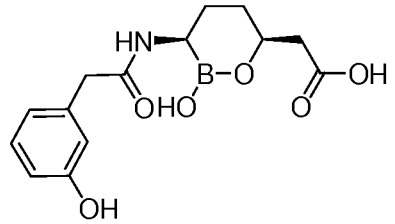
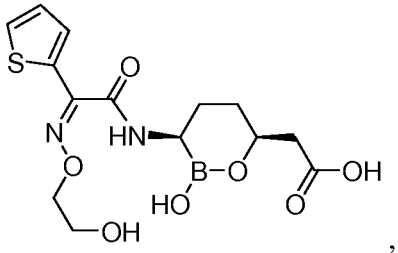
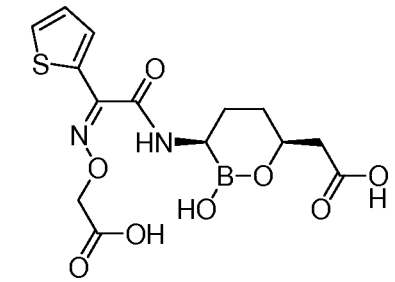
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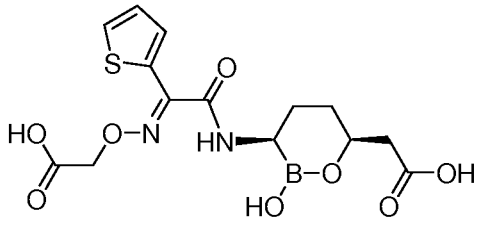
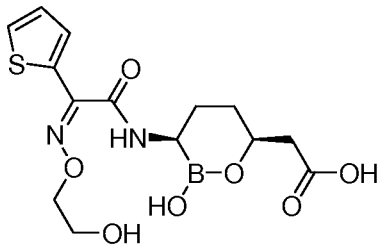
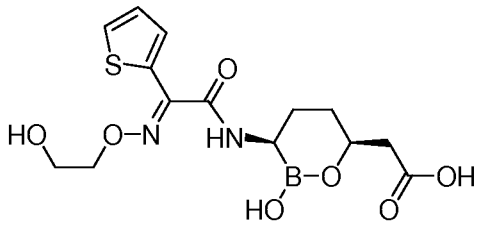
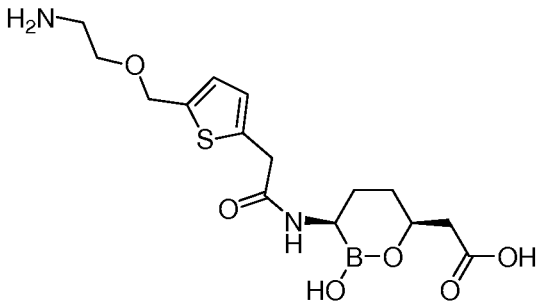
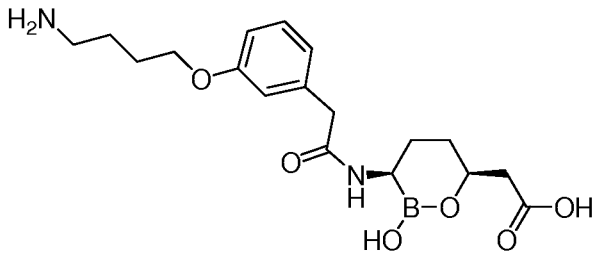
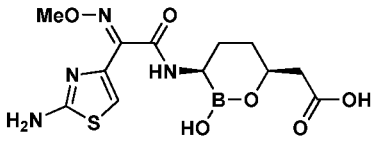
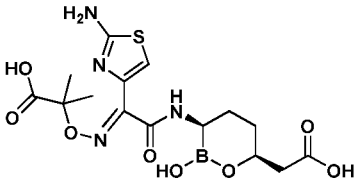
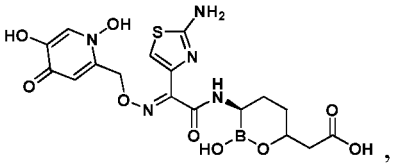
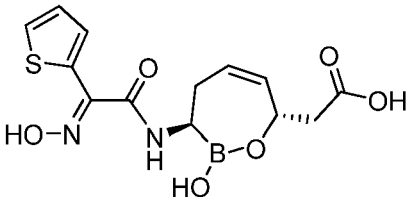
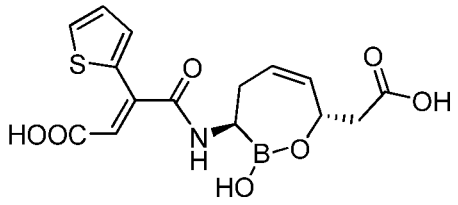
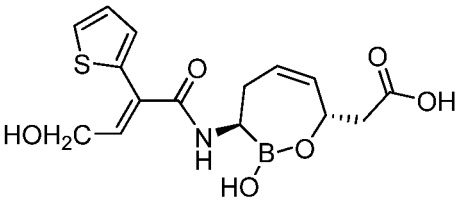
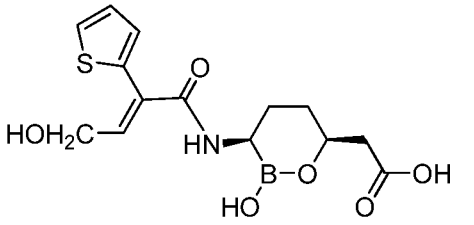
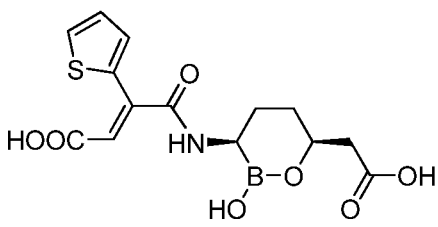
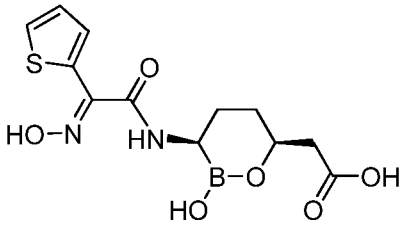

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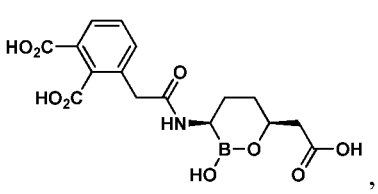
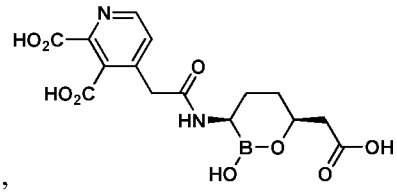
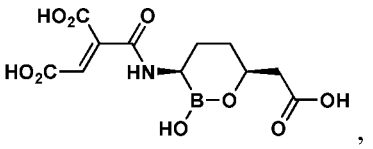
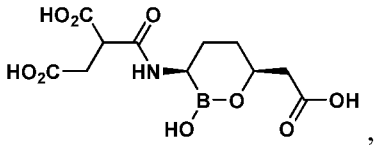
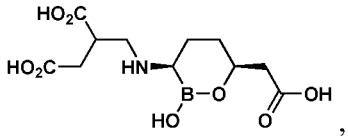
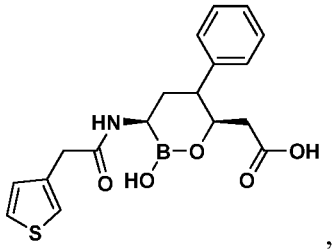
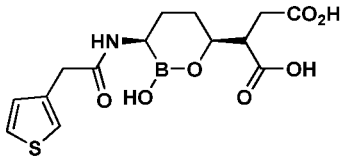
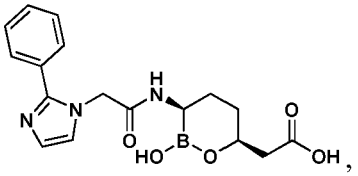
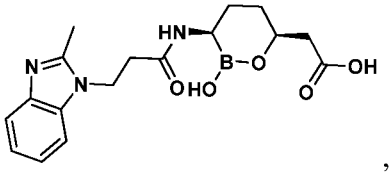
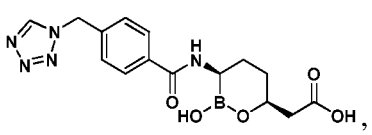
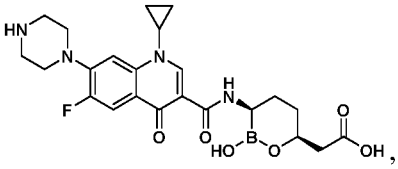
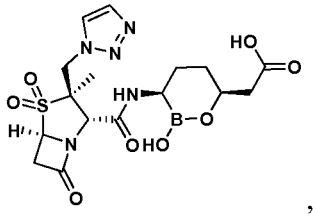
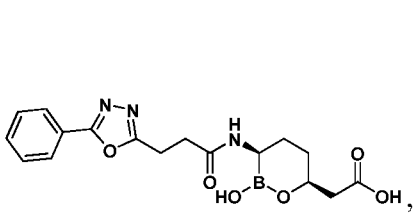
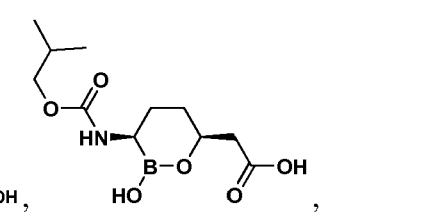
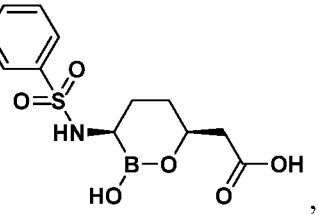
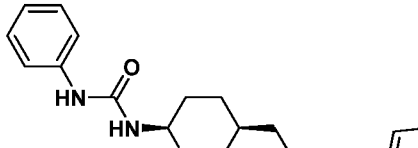
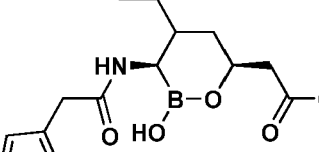
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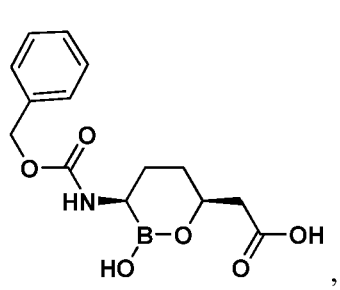

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, or a pharmaceutically acceptable salt thereof.

[0072] Some embodiments include compounds selected from the group consisting of:


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or a pharmaceutically acceptable salt thereof.

Definitions

[0073] Terms and substituents are given their ordinary meaning unless defined otherwise, and may be defined when introduced and retain their definitions throughout

unless otherwise specified, and retain their definitions whether alone or as part of another group unless otherwise specified.

[0074] As used herein, "alkyl" means a branched, or straight chain saturated chemical group containing only carbon and hydrogen, such as methyl, isopropyl, isobutyl, sec-butyl and pentyl. In various embodiments, alkyl groups can either be unsubstituted or substituted with one or more substituents, e.g., halogen, hydroxyl, substituted hydroxyl, acyloxy, amino, substituted amino, amido, cyano, nitro, guanidino, amidino, mercapto, substituted mercapto, carboxy, sulfonyloxy, carbonyl, benzyloxy, aryl, heteroaryl, carbocyclyl, heterocyclyl, or other functionality that may be suitably blocked with a protecting group. Typically, alkyl groups will comprise 1 to 20 carbon atoms, 1 to 9 carbon atoms, preferably 1 to 6, and more preferably 1 to 5 carbon atoms.

[0075] As used herein, "alkenyl" means a straight or branched chain chemical group containing only carbon and hydrogen and containing at least one carbon-carbon double bond, such as 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like. In various embodiments, alkenyls can either be unsubstituted or substituted with one or more substituents, e.g., halogen, hydroxyl, substituted hydroxyl, acyloxy, amino, substituted amino, amido, cyano, nitro, guanidino, amidino, mercapto, substituted mercapto, carboxy, sulfonyloxy, carbonyl, benzyloxy, aryl, heteroaryl, carbocyclyl, heterocyclyl, or other functionality that may be suitably blocked with a protecting group. Typically, alkenyl groups will comprise 2 to 20 carbon atoms, 2 to 9 carbon atoms, preferably 2 to 6, and more preferably 2 to 5 carbon atoms.

[0076] As used herein, "alkynyl" means a straight or branched chain chemical group containing only carbon and hydrogen and containing at least one carbon-carbon triple bond, such as 1-propynyl, 1-butynyl, 2-butynyl, and the like. In various embodiments, alkynyls can either be unsubstituted or substituted with one or more substituents, e.g., halogen, hydroxyl, substituted hydroxyl, acyloxy, amino, substituted amino, amido, cyano, nitro, guanidino, amidino, mercapto, substituted mercapto, carboxy, sulfonyloxy, carbonyl, benzyloxy, aryl, heteroaryl, carbocyclyl, heterocyclyl, or other functionality that may be suitably blocked with a protecting group. Typically, alkynyl groups will comprise 2 to 20 carbon atoms, 2 to 9 carbon atoms, preferably 2 to 6, and more preferably 2 to 5 carbon atoms.

[0077] As used herein, "carbocyclyl" means a non-aromatic cyclic ring system containing only carbon atoms in the ring system backbone, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexenyl. Carbocyclyls may include

multiple fused rings. Carbocyclyls may have any degree of saturation provided that at least one ring in the ring system is not aromatic. In various embodiments, carbocyclyl groups can either be unsubstituted or substituted with one or more substituents, e.g., halogen, alkoxy, acyloxy, amino, amido, cyano, nitro, hydroxyl, mercapto, carboxy, carbonyl, benzyloxy, aryl, heteroaryl, or other functionality that may be suitably blocked with a protecting group. Typically, carbocyclyl groups will comprise 3 to 10 carbon atoms, preferably 3 to 6.

[0078] As used herein, "cycloalkyl" means a fully saturated carbocyclyl ring system. Examples include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0079] As used herein, "cycloalkenyl" means a carbocyclyl ring system having at least one double bond. An example is cyclohexenyl.

[0080] As used herein, "lower alkyl" means a subset of alkyl, and thus is a hydrocarbon substituent, which is linear, or branched. Preferred lower alkyls are of 1 to about 4 carbons, and may be branched or linear. Examples of lower alkyl include butyl, propyl, isopropyl, ethyl, and methyl. Likewise, radicals using the terminology "lower" refer to radicals preferably with 1 to about 4 carbons in the alkyl portion of the radical.

[0081] As used herein, "aryl" means an aromatic radical having a single-ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) with only carbon atoms present in the ring backbone. In various embodiments, aryl groups can either be unsubstituted or substituted with one or more substituents, e.g., amino, cyano, hydroxyl, lower alkyl, haloalkyl, alkoxy, nitro, halo, mercapto, carboxy, carbonyl, benzyloxy, aryl, heteroaryl, and other substituents. Some embodiments include substitution with an alkoxy group, which may be further substituted with one or more substituents, e.g., amino, cyano, hydroxyl, lower alkyl, haloalkyl, alkoxy, nitro, halo, mercapto, and other substituents. A preferred aryl is phenyl.

[0082] As used herein, the term "heteroaryl" means an aromatic radical having one or more heteroatom(s) (e.g., N, O, or S) in the ring backbone and may include a single ring (e.g., pyridine) or multiple condensed rings (e.g., quinoline). In various embodiments, heteroaryl groups can either be unsubstituted or substituted with one or more substituents, e.g., amino, cyano, hydroxyl, lower alkyl, haloalkyl, alkoxy, nitro, halo, mercapto, carboxy, carbonyl, benzyloxy, aryl, heteroaryl, and other substituents. Examples of heteroaryl include thienyl, pyrridyl, furyl, oxazolyl, oxadiazolyl, pyrollyl, imidazolyl, triazolyl, thiodiazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl, quinolinyl, quinazolinyl and others.

[0083] In these definitions it is contemplated that substitution on the aryl and heteroaryl rings is within the scope of certain embodiments. Where substitution occurs, the radical is called substituted aryl or substituted heteroaryl. Preferably one to three and more preferably one or two substituents occur on the aryl ring. Though many substituents will be useful, preferred substituents include those commonly found in aryl compounds, such as alkyl, cycloalkyl, hydroxy, alkoxy, cyano, halo, haloalkyl, mercapto and the like.

[0084] As used herein, "amide" or "amido" includes both RNR'CO- (in the case of R = alkyl, alkaminocarbonyl-) and RCONR'- (in the case of R = alkyl, alkyl carbonylamino-). "Amide" or "amido" includes a H-CON-, alkyl-CON-, carbocyclyl-CON-, aryl-CON-, heteroaryl-CON- or heterocyclyl-CON- group, wherein the alkyl, carbocyclyl, aryl or heterocyclyl group is as herein described.

[0085] As used herein, the term "ester" includes both ROCO- (in the case of R = alkyl, alkoxycarbonyl-) and RCOO- (in the case of R = alkyl, alkylcarbonyloxy-).

[0086] As used herein, "acyl" means an H-CO-, alkyl-CO-, carbocyclyl-CO-, aryl-CO-, heteroaryl-CO- or heterocyclyl-CO- group wherein the alkyl, carbocyclyl, aryl or heterocyclyl group is as herein described. Preferred acyls contain a lower alkyl. Exemplary alkyl acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, t-butylacetyl, butanoyl and palmitoyl.

[0087] As used herein, "halo or halide" is a chloro, bromo, fluoro or iodo atom radical. Chloro and fluoro are preferred halides. The term "halo" also contemplates terms sometimes referred to as "halogen", or "halide".

[0088] As used herein, "heterocyclyl" means a non-aromatic cyclic ring system comprising at least one heteroatom in the ring system backbone. Heterocyclyls may include multiple fused rings. Heterocyclyls may have any degree of saturation provided that at least one ring in the ring system is not aromatic. The heteroatom(s) may be present in either a non-aromatic or aromatic ring in the ring system. In various embodiments, heterocyclyls may be substituted or unsubstituted with one or more substituents, e.g., halogen, alkoxy, acyloxy, amino, amido, cyano, nitro, hydroxyl, mercapto, carboxy, carbonyl, benzyloxy, aryl, heteroaryl, and other substituents, and are attached to other groups via any available valence, preferably any available carbon or nitrogen. Preferred heterocycles are of 5-7 members. In six membered monocyclic heterocycles, the heteroatom(s) are selected from one up to three of O, N or S, and when the heterocycle is five membered, preferably it has one or two heteroatoms selected from O, N, or S. Examples of heterocyclyl include pyrrolidinyl, piperidinyl, azepanyl,

tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, thiepanyl, indolinyl and dihydrobenzofuranyl.

[0089] As used herein, "substituted amino" means an amino radical which is substituted by one or two alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl groups, wherein the alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl are defined as above.

[0090] As used herein, "substituted hydroxyl" means RO- group wherein R is an alkyl, an aryl, heteroaryl, cycloalkyl or a heterocyclyl group, wherein the alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl are defined as above.

[0091] As used herein, "substituted thiol" means RS- group wherein R is an alkyl, an aryl, heteroaryl, cycloalkyl or a heterocyclyl group, wherein the alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl are defined as above.

[0092] As used herein, "sulfonyl" means an alkylSO_2, arylSO_2, heteroarylSO_2, carbocyclylSO_2, or heterocyclyl-SO_2 group wherein the alkyl, carbocyclyl, aryl, heteroaryl or heterocyclyl are defined as above.

[0093] As used herein, "sulfamido" means an alkyl-N-$S(O)_2N$-, aryl-$NS(O)_2N$-, heteroaryl-$NS(O)_2N$-, carbocyclyl-$NS(O)_2N$ or heterocyclyl-$NS(O)_2N$- group wherein the alkyl, carbocyclyl, aryl, heteroaryl or heterocyclyl group is as herein described.

[0094] As used herein, "sulfonamido" means an alkyl-$S(O)_2N$-, aryl-$S(O)_2N$-, heteroaryl-$S(O)_2N$-, carbocyclyl-$S(O)_2N$- or heterocyclyl-$S(O)_2N$- group wherein the alkyl, carbocyclyl, aryl, heteroaryl or heterocyclyl group is as herein described.

[0095] As used herein, "ureido" means an alkyl-NCON-, aryl-NCON-, heteroaryl-NCON- , carbocyclyl-NCON-, heterocyclyl-NCON- group or heterocyclyl-CON- group wherein the heterocyclyl group is attached by a ring nitrogen, and wherein the alkyl, carbocyclyl, aryl, heteroaryl or heterocyclyl group is as herein described.

[0096] As used herein, "guanidino" means an alkyl-NC(=NR')N-, aryl-NC(=NR')N-, heteroaryl-NC(=NR')N-, carbocyclyl-NC(=NR')N- or heterocyclyl-NC(=NR')N- group wherein R' is an H, substituted or unsubstituted hydroxyl, CN, alkyl, aryl, heteroaryl or a heterocyclyl group, wherein the alkyl, carbocyclyl, aryl, heteroaryl or heterocyclyl group is as herein described.

[0097] As used herein, a substituted group is derived from the unsubstituted parent group in which there has been an exchange of one or more hydrogen atoms for another atom or group. When substituted, the substituent group(s) is (are) substituted with one or more substituent(s) individually and independently selected from C_1-C_6 alkyl,

C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_3-C_7 carbocycle (optionally substituted with halo, alkyl, alkoxy, carboxyl, haloalkyl, CN, $-SO_2$-alkyl, $-CF_3$, and $-OCF_3$), C_1-C_6 heteroalkyl, 5-7 membered heterocyclyl (e.g., tetrahydrofuryl) (optionally substituted with halo, alkyl, alkoxy, carboxyl, CN, $-SO_2$-alkyl, $-CF_3$, and $-OCF_3$), aryl (optionally substituted with halo, alkyl, aryl optionally substituted with C_1-C_6 alkyl, arylalkyl, alkoxy, carboxyl, CN, $-SO_2$-alkyl, $-CF_3$, and $-OCF_3$), arylalkyl (optionally substituted with halo, alkyl, alkoxy, aryl, carboxyl, CN, $-SO_2$-alkyl, $-CF_3$, and $-OCF_3$), heteroaryl (optionally substituted with halo, alkyl, alkoxy, aryl, aralkyl, carboxyl, CN, $-SO_2$-alkyl, $-CF_3$, and $-OCF_3$), heteroarylalkyl (optionally substituted with halo, alkyl, alkoxy, aryl, carboxyl, CN, $-SO_2$-alkyl, $-CF_3$, and $-OCF_3$), halo (e.g., chloro, bromo, iodo and fluoro), cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl (i.e., ether), aryloxy, sulfhydryl (mercapto), halo(C_1-C_6)alkyl (e.g., $-CF_3$), C_1-C_6 alkylthio, arylthio, amino ($-NH_2$), mono- and di-(C_1-C_6)alkyl amino, quaternary ammonium salts, amino(C_1-C_6)alkoxy (e.g, $-O(CH_2)_4NH_2$), amino(C_1-C_6)alkoxyalkyl (e.g., $-CH_2O(CH_2)_2NH_2$), hydroxy(C_1-C_6)alkylamino, amino(C_1-C_6)alkylthio (e.g, $-S(CH_2)_2NH_2$), cyanoamino, nitro, carbamyl, oxo (=O), carboxy, glycolyl, glycyl, hydrazino, guanidinyl, sulfamyl, sulfonyl, sulfinyl, thiocarbonyl, thiocarboxy, C-amide, N-amide, N-carbamate, O-carbamate, and urea. Wherever a group is described as "optionally substituted" that group can be substituted with the above substituents.

[0098] In some embodiments, substituted group(s) is (are) substituted with one or more substituent(s) individually and independently selected from C_1-C_6 alkyl, C_3-C_7 carbocycle, amino ($-NH_2$), amino(C_1-C_6)alkoxy, carboxyl, oxo (=O), C_1-C_6 alkylthio, amino(C_1-C_6)alkylthio, guanidinyl, aryl, 5-7 membered heterocyclyl, heteroarylalkyl, hydroxy, halo, amino(C_1-C_6)alkoxy, and amino(C_1-C_6)alkoxyalkyl.

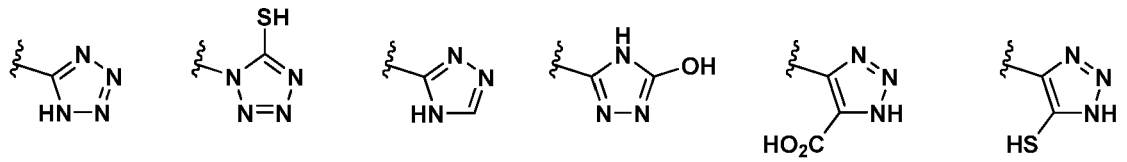
[0099] In some embodiments, substituted group(s) is (are) substituted with one or more substituent(s) individually and independently selected from C_1-C_6 alkyl, amino ($-NH_2$), amino(C_1-C_6)alkoxy, carboxyl, oxo (=O), C_1-C_6 alkylthio, amino(C_1-C_6)alkylthio, guanidinyl, hydroxy, halo, amino(C_1-C_6)alkoxy, and amino(C_1-C_6)alkoxyalkyl.

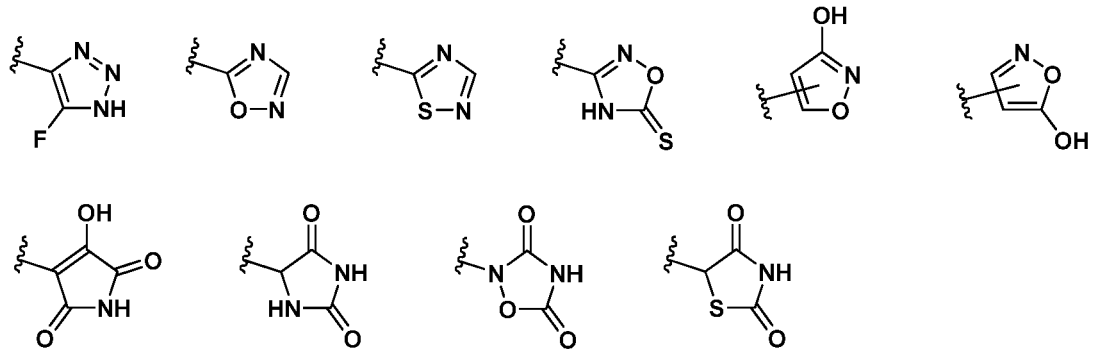
[0100] In some embodiments, substituted group(s) is (are) substituted with one or more substituent(s) individually and independently selected from C_1-C_6 alkyl, amino ($-NH_2$), carboxyl, oxo (=O), guanidinyl, hydroxy, and halo.

[0101] It is to be understood that certain radical naming conventions can include either a mono-radical or a di-radical, depending on the context. For example,

where a substituent requires two points of attachment to the rest of the molecule, it is understood that the substituent is a di-radical. For example, a substituent identified as alkyl that requires two points of attachment includes di-radicals such as $–CH_2–$, $–CH_2CH_2–$, $–CH_2CH(CH_3)CH_2–$, and the like. Other radical naming conventions clearly indicate that the radical is a di-radical. For example, as used herein, "alkylene" means a branched, or straight chain saturated di-radical chemical group containing only carbon and hydrogen, such as methylene, isopropylene, isobutylene, sec-butylene, and pentylene, that is attached to the rest of the molecule via two points of attachment. As used herein, "alkenylene" means a straight or branched chain di-radical chemical group containing only carbon and hydrogen and containing at least one carbon-carbon double bond, such as 1-propenylene, 2-propenylene, 2-methyl-1-propenylene, 1-butenylene, and 2-butenylene, that is attached to the rest of the molecule via two points of attachment.

[0102] As used herein, "isosteres" of a chemical group are other chemical groups that exhibit the same or similar properties. For example, tetrazole is an isostere of carboxylic acid because it mimics the properties of carboxylic acid even though they both have very different molecular formulae. Tetrazole is one of many possible isosteric replacements for carboxylic acid. Other carboxylic acid isosteres contemplated include $-SO_3H$, $-SO_2HNR^9$, $-PO_2(R^9)_2$, $-PO_3(R^9)_2$, $-CONHNHSO_2R^9$, $-COHNSO_2R^9$, and $–CONR^9CN$, where R^9 is as defined above. In addition, carboxylic acid isosteres can include 5-7 membered carbocycles or heterocycles containing any combination of CH_2, O, S, or N in any chemically stable oxidation state, where any of the atoms of said ring structure are optionally substituted in one or more positions. The following structures are non-limiting examples of carbocyclic and heterocyclic isosteres contemplated. The atoms of said ring structure may be optionally substituted at one or more positions with R^9 as defined above.



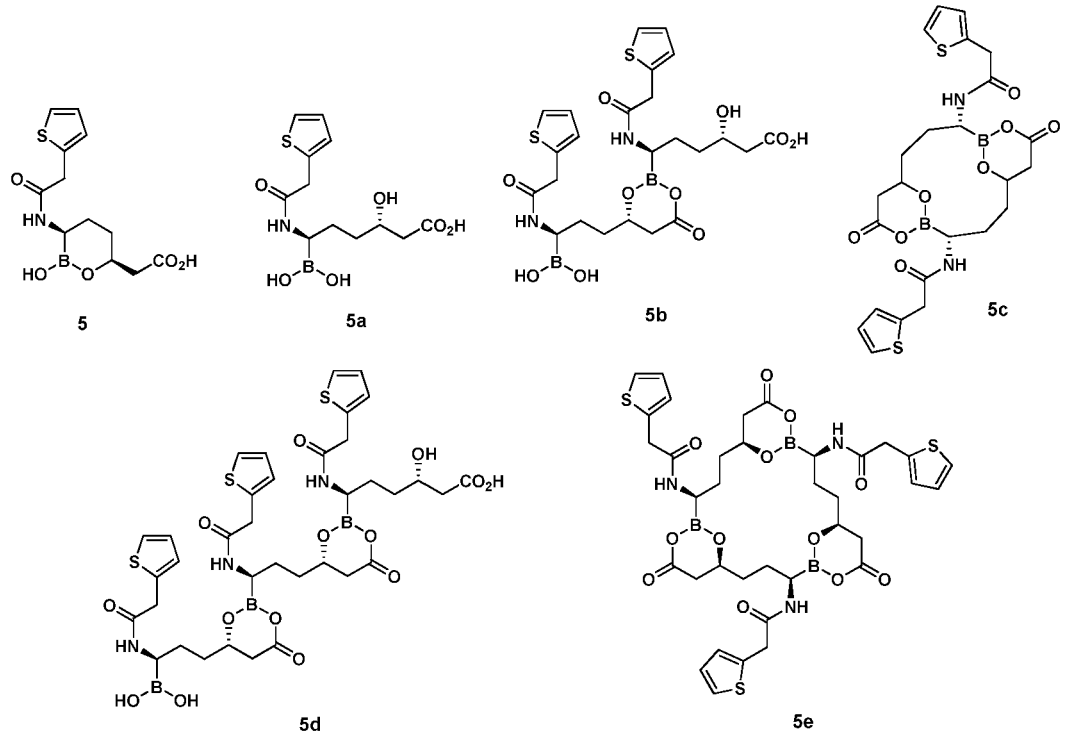


[0103] It is also contemplated that when chemical substituents are added to a carboxylic isostere, the compound retains the properties of a carboxylic isostere. It is contemplated that when a carboxylic isostere is optionally substituted with one or more moieties selected from R^9 as defined above, then the substitution and substitution position is selected such that it does not eliminate the carboxylic acid isosteric properties of the compound. Similarly, it is also contemplated that the placement of one or more R^9 substituents upon a carbocyclic or heterocyclic carboxylic acid isostere is not a substitution at one or more atom(s) that maintain(s) or is/are integral to the carboxylic acid isosteric properties of the compound, if such substituent(s) would destroy the carboxylic acid isosteric properties of the compound.

[0104] Other carboxylic acid isosteres not specifically exemplified in this specification are also contemplated.

[0105] The skilled artisan will recognize that some structures described herein may be resonance forms or tautomers of compounds that may be fairly represented by other chemical structures, even when kinetically; the artisan recognizes that such structures are only a very small portion of a sample of such compound(s). Such compounds are considered within the scope of the structures depicted, though such resonance forms or tautomers are not represented herein.

[0106] In some embodiments, due to the facile exchange of boron esters, the compounds described herein may convert to or exist in equilibrium with alternate forms. Accordingly, in some embodiments, the compounds described herein may exist in combination with one or more of these forms. For example, Compound **5** may exist in combination with one or more open-chain form (**5a**), dimeric form (**5b**), cyclic dimeric form (**5c**), trimeric form (**5d**), cyclic trimeric form (**5e**), and the like.



[0107] The compounds provided herein may encompass various stereochemical forms. The compounds also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

[0108] The term "agent" or "test agent" includes any substance, molecule, element, compound, entity, or a combination thereof. It includes, but is not limited to, e.g., protein, polypeptide, peptide or mimetic, small organic molecule, polysaccharide, polynucleotide, and the like. It can be a natural product, a synthetic compound, or a chemical compound, or a combination of two or more substances. Unless otherwise specified, the terms "agent", "substance", and "compound" are used interchangeably herein.

[0109] The term "analog" is used herein to refer to a molecule that structurally resembles a reference molecule but which has been modified in a targeted and controlled manner, by replacing a specific substituent of the reference molecule with an alternate substituent. Compared to the reference molecule, an analog would be expected, by one skilled in the art, to exhibit the same, similar, or improved utility. Synthesis and

screening of analogs, to identify variants of known compounds having improved characteristics (such as higher binding affinity for a target molecule) is an approach that is well known in pharmaceutical chemistry.

[0110] The term "mammal" is used in its usual biological sense. Thus, it specifically includes humans, cattle, horses, dogs, cats, rats and mice but also includes many other species.

[0111] The term "microbial infection" refers to the invasion of the host organism, whether the organism is a vertebrate, invertebrate, fish, plant, bird, or mammal, by pathogenic microbes. This includes the excessive growth of microbes that are normally present in or on the body of a mammal or other organism. More generally, a microbial infection can be any situation in which the presence of a microbial population(s) is damaging to a host mammal. Thus, a mammal is "suffering" from a microbial infection when excessive numbers of a microbial population are present in or on a mammal's body, or when the effects of the presence of a microbial population(s) is damaging the cells or other tissue of a mammal. Specifically, this description applies to a bacterial infection. Note that the compounds of preferred embodiments are also useful in treating microbial growth or contamination of cell cultures or other media, or inanimate surfaces or objects, and nothing herein should limit the preferred embodiments only to treatment of higher organisms, except when explicitly so specified in the claims.

[0112] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. In addition, various adjuvants such as are commonly used in the art may be included. These and other such compounds are described in the literature, e.g., in the Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press.

[0113] The term "pharmaceutically acceptable salt" refers to salts that retain the biological effectiveness and properties of the compounds of the preferred embodiments and, which are not biologically or otherwise undesirable. In many cases,

the compounds of the preferred embodiments are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Many such salts are known in the art, as described in WO 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein in its entirety).

[0114] "Solvate" refers to the compound formed by the interaction of a solvent and an EPI, a metabolite, or salt thereof. Suitable solvates are pharmaceutically acceptable solvates including hydrates.

[0115] "Subject" as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate.

[0116] A therapeutic effect relieves, to some extent, one or more of the symptoms of the infection, and includes curing an infection. "Curing" means that the symptoms of active infection are eliminated, including the elimination of excessive members of viable microbe of those involved in the infection. However, certain long-term or permanent effects of the infection may exist even after a cure is obtained (such as extensive tissue damage).

[0117] "Treat," "treatment," or "treating," as used herein refers to administering a pharmaceutical composition for prophylactic and/or therapeutic purposes.

The term "prophylactic treatment" refers to treating a patient who is not yet infected, but who is susceptible to, or otherwise at risk of, a particular infection, whereby the treatment reduces the likelihood that the patient will develop an infection. The term "therapeutic treatment" refers to administering treatment to a patient already suffering from an infection.

Administration and Pharmaceutical Compositions

[0118] Some embodiments include pharmaceutical compositions comprising: (a) a safe and therapeutically effective amount of the cyclic boronic acid ester derivative, or its corresponding enantiomer, diastereoisomer or tautomer, or pharmaceutically acceptable salt; and (b) a pharmaceutically acceptable carrier.

[0119] The cyclic boronic acid ester derivatives are administered at a therapeutically effective dosage, e.g., a dosage sufficient to provide treatment for the disease states previously described. While human dosage levels have yet to be optimized for the compounds of the preferred embodiments, generally, a daily dose for most of the cyclic boronic acid ester derivatives described herein is from about 0.25 mg/kg to about 120 mg/kg or more of body weight, from about 0.5 mg/kg or less to about 70 mg/kg, from about 1.0 mg/kg to about 50 mg/kg of body weight, or from about 1.5 mg/kg to about 10 mg/kg of body weight. Thus, for administration to a 70 kg person, the dosage range would be from about 17 mg per day to about 8000 mg per day, from about 35 mg per day or less to about 7000 mg per day or more, from about 70 mg per day to about 6000 mg per day, from about 100 mg per day to about 5000 mg per day, or from about 200 mg to about 3000 mg per day. The amount of active compound administered will, of course, be dependent on the subject and disease state being treated, the severity of the affliction, the manner and schedule of administration and the judgment of the prescribing physician.

[0120] Administration of the compounds disclosed herein or the pharmaceutically acceptable salts thereof can be via any of the accepted modes of administration for agents that serve similar utilities including, but not limited to, orally, subcutaneously, intravenously, intranasally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarilly, vaginally, rectally, or intraocularly. Oral and parenteral administrations are customary in treating the indications that are the subject of the preferred embodiments.

[0121] The compounds useful as described above can be formulated into pharmaceutical compositions for use in treatment of these conditions. Standard

pharmaceutical formulation techniques are used, such as those disclosed in Remington's The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (2005), incorporated by reference in its entirety.

[0122] In addition to the selected compound useful as described above, come embodiments include compositions containing a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances, which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction, which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration preferably to an animal, preferably mammal being treated.

[0123] Some examples of substances, which can serve as pharmaceutically-acceptable carriers or components thereof, are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

[0124] The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

[0125] The compositions described herein are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a compound that is suitable for administration to an animal, preferably mammal subject, in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be

administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded. The skilled artisan will recognize that the formulation does not specifically contemplate the entire course of therapy and such decisions are left for those skilled in the art of treatment rather than formulation.

[0126] The compositions useful as described above may be in any of a variety of suitable forms for a variety of routes for administration, for example, for oral, nasal, rectal, topical (including transdermal), ocular, intracerebral, intracranial, intrathecal, intra-arterial, intravenous, intramuscular, or other parental routes of administration. The skilled artisan will appreciate that oral and nasal compositions comprise compositions that are administered by inhalation, and made using available methodologies. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. Pharmaceutically-acceptable carriers include, for example, solid or liquid fillers, diluents, hydrotropies, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the inhibitory activity of the compound. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods described herein are described in the following references, all incorporated by reference herein: Modern Pharmaceutics, 4th Ed., Chapters 9 and 10 (Banker & Rhodes, editors, 2002); Lieberman *et al.*, Pharmaceutical Dosage Forms: Tablets (1989); and Ansel, Introduction to Pharmaceutical Dosage Forms 8th Edition (2004).

[0127] Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, with a maximum of about 90%, of the compound. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing

suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

[0128] The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for peroral administration is well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical, and can be readily made by a person skilled in the art.

[0129] Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

[0130] Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

[0131] Compositions described herein may optionally include other drug actives.

[0132] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[0133] A liquid composition, which is formulated for topical ophthalmic use, is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid should either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

[0134] For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions should preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

[0135] Preservatives that may be used in the pharmaceutical compositions disclosed herein include, but are not limited to, benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations disclosed herein. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

[0136] Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

[0137] Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. For many compositions, the pH will be between 4 and 9. Accordingly, buffers include acetate buffers, citrate buffers,

phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

[0138] In a similar vein, an ophthalmically acceptable antioxidant includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[0139] Other excipient components, which may be included in the ophthalmic preparations, are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

[0140] For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, co-solvent, emulsifier, penetration enhancer, preservative system, and emollient.

[0141] For intravenous administration, the compounds and compositions described herein may be dissolved or dispersed in a pharmaceutically acceptable diluent, such as a saline or dextrose solution. Suitable excipients may be included to achieve the desired pH, including but not limited to NaOH, sodium carbonate, sodium acetate, HCl, and citric acid. In various embodiments, the pH of the final composition ranges from 2 to 8, or preferably from 4 to 7. Antioxidant excipients may include sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA. Other non-limiting examples of suitable excipients found in the final intravenous composition may include sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran. Further acceptable excipients are described in Powell, et al., Compendium of Excipients for Parenteral Formulations, *PDA J Pharm Sci and Tech* **1998**, *52* 238-311 and Nema et al., Excipients and Their Role in Approved Injectable Products: Current Usage and Future Directions, *PDA J Pharm Sci and Tech* **2011**, *65* 287-332, both of which are incorporated herein by reference in their entirety. Antimicrobial agents may also be included to achieve a bacteriostatic or fungistatic solution, including but not limited to phenylmercuric nitrate, thimerosal, benzethonium chloride, benzalkonium chloride, phenol, cresol, and chlorobutanol.

[0142] The resulting composition may be infused into the patient over a period of time. In various embodiments, the infusion time ranges from 5 minutes to continuous infusion, from 10 minutes to 8 hours, from 30 minutes to 4 hours, and from 1 hour to 3 hours. In one embodiment, the drug is infused over a 3 hour period. The

infusion may be repeated at the desired dose interval, which may include, for example, 6 hours, 8 hours, 12 hours, or 24 hours.

[0143] The compositions for intravenous administration may be provided to caregivers in the form of one more solids that are reconstituted with a suitable diluent such as sterile water, saline or dextrose in water shortly prior to administration. Reconstituted concentrated solutions may be further diluted into a parenteral solutions haing a volume of from about 25 to about 1000 ml, from about 30 ml to about 500 ml, or from about 50 ml to about 100 ml. In other embodiments, the compositions are provided in solution ready to administer parenterally. In still other embodiments, the compositions are provided in a solution that is further diluted prior to administration. In embodiments that include administering a combination of a compound described herein and another agent, the combination may be provided to caregivers as a mixture, or the caregivers may mix the two agents prior to administration, or the two agents may be administered separately.

[0144] The actual dose of the active compounds described herein depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

Kits for Intravenous Administration

[0145] Some embodiments include a kit comprising a compound described herein and an additional agent, such as an antimicrobial agent. In one embodiment, both components are provided in a single sterile container. In the case of solids for reconstitution, the agents may be pre-blended and added to the container simultaneously or may be dry-powder filled into the container in two separate steps. In some embodiments, the solids are sterile crystalline products. In other embodiment, the solids are lyophiles. In one embodiment, both components are lyophilized together. Non-limiting examples of agents to aid in lyophilization include sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran. One embodiment includes non-sterile solids that are irradiated either before or after introduction into the container.

[0146] In the case of a liquid, the agents may be dissolved or dispersed in a diluent ready for administration. In another embodiment, the solution or dispersion may be further diluted prior to administration. Some embodiments include providing the liquid in an IV bag. The liquid may be frozen to improve stability.

[0147] In one embodiment, the container includes other ingredients such as a pH adjuster, a solubilizing agent, or a dispersing agent. Non-limiting examples of pH adjusters include NaOH, sodium carbonate, sodium acetate, HCl, and citric acid.

[0148] The molar ratio of compound described herein to additional agent (e.g., antibacterial agent) may be from about 10:1 to 1:10, 8:1 to 1:8, 5:1 to 1:5, 3:1 to 1:3, 2:1 to 1:2, or about 1:1. In various embodiments the amount of compound described herein may be from 100 mg to 5 g, 500 mg to 2 g, or about 1 g. Similarly, in various embodiments the amount of additional agent may be from 100 mg to 5 g, 500 mg to 2 g, or about 1 g.

[0149] In an alternative embodiment, the two components may be provided in separate containers. Each container may include a solid, solution, or dispersion. In such embodiments, the two containers may be provided in a single package or may be provided separately. In one embodiment, the compound described herein is provided as a solution while the additional agent (e.g., antibacterial agent) is provided as a solid ready for reconstitution. In one such embodiment, the solution of the compound desribed herein is used as the diluent to reconstitute the other agent.

Methods of Treatment

[0150] Some embodiments of the present invention include methods of treating bacterial infections with the compounds and compositions comprising cyclic boronic acid ester derivatives described herein. Some methods include administering a compound, composition, pharmaceutical composition described herein to a subject in need thereof. In some embodiments, a subject can be an animal, e.g., a mammal, a human. In some embodiments, the bacterial infection comprises a bacteria described herein. As will be appreciated from the foregoing, methods of treating a bacterial infection include methods for preventing bacterial infection in a subject at risk thereof.

[0151] Further embodiments include administering a combination of compounds to a subject in need thereof. A combination can include a compound, composition, pharmaceutical composition described herein with an additional medicament.

[0152] Some embodiments include co-administering a compound, composition, and/or pharmaceutical composition described herein, with an additional medicament. By "co-administration," it is meant that the two or more agents may be found in the patient's bloodstream at the same time, regardless of when or how they are

actually administered. In one embodiment, the agents are administered simultaneously. In one such embodiment, administration in combination is accomplished by combining the agents in a single dosage form. When combining the agents in a single dosage form, they may be physically mixed (e.g, by co-dissolution or dry mixing) or may form an adduct or be covalently linked such that they split into the two or more active ingredients upon administration to the patient. In another embodiment, the agents are administered sequentially. In one embodiment the agents are administered through the same route, such as orally. In another embodiment, the agents are administered through different routes, such as one being administered orally and another being administered i.v.

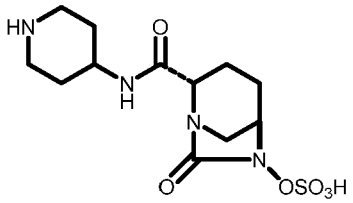
[0153] Examples of additional medicaments include an antibacterial agent, antifungal agent, an antiviral agent, an anti-inflammatory agent and an anti-allergic agent.

[0154] Some embodiments include co-administration of a compound, composition or pharmaceutical composition described herein with an antibacterial agent such as a β-lactam. Examples of such β-lactams include Amoxicillin, Ampicillin (e.g., Pivampicillin, Hetacillin, Bacampicillin, Metampicillin, Talampicillin), Epicillin, Carbenicillin (Carindacillin), Ticarcillin, Temocillin, Azlocillin, Piperacillin, Mezlocillin, Mecillinam (Pivmecillinam), Sulbenicillin, Benzylpenicillin (G), Clometocillin, Benzathine benzylpenicillin, Procaine benzylpenicillin, Azidocillin, Penamecillin, Phenoxymethylpenicillin (V), Propicillin, Benzathine phenoxymethylpenicillin, Pheneticillin, Cloxacillin (e.g., Dicloxacillin, Flucloxacillin), Oxacillin, Methicillin, Nafcillin, Faropenem, Biapenem, Doripenem, Ertapenem, Imipenem, Meropenem, Panipenem, Tomopenem, Razupenem, Cefazolin, Cefacetrile, Cefadroxil, Cefalexin, Cefaloglycin, Cefalonium, Cefaloridine, Cefalotin, Cefapirin, Cefatrizine, Cefazedone, Cefazaflur, Cefradine, Cefroxadine, Ceftezole, Cefaclor, Cefamandole, Cefminox, Cefonicid, Ceforanide, Cefotiam, Cefprozil, Cefbuperazone, Cefuroxime, Cefuzonam, Cefoxitin, Cefotetan, Cefmetazole, Loracarbef, Cefixime, Ceftazidime, Ceftriaxone, Cefcapene, Cefdaloxime, Cefdinir, Cefditoren, Cefetamet, Cefmenoxime, Cefodizime, Cefoperazone, Cefotaxime, Cefpimizole, Cefpiramide, Cefpodoxime, Cefsulodin, Cefteram, Ceftibuten, Ceftiolene, Ceftizoxime, Flomoxef, Latamoxef, Cefepime, Cefozopran, Cefpirome, Cefquinome, Ceftobiprole, Ceftaroline, CXA-101, RWJ-54428, MC-04,546, ME1036, BAL30072, SYN 2416, Ceftiofur, Cefquinome, Cefovecin, Aztreonam, Tigemonam, Carumonam, RWJ-442831, RWJ-333441, and RWJ-333442.

[0155] Preferred embodiments include β-lactams such as Ceftazidime, Biapenem, Doripenem, Ertapenem, Imipenem, Meropenem, ME1036, Tomopenem, Razupenem, and Panipenem.

[0156] Some embodiments include co-administration of the compounds, compositions and/or pharmaceutical compositions described herein with an additional agent, wherein the additional agent comprises a monobactam. Examples of monobactams include aztreonam, tigemonam, BAL 30072, SYN 2416 (BAL19764), and carumonam.

[0157] Some embodiments include co-administration of the compounds, compositions and/or pharmaceutical compositions described herein with an additional agent, wherein the additional agent comprises a Class A, B, C, or D beta-lactamase inhibitor. An example of a class B beta lactamase inhibitor includes ME1071 (Yoshikazu Ishii *et al*, "*In Vitro* Potentiation of Carbapenems with ME1071, a Novel Metallo-ß-Lactamase Inhibitor, against Metallo-ß-lactamase Producing Pseudomonas aeruginosa Clinical Isolates." Antimicrob. Agents Chemother. doi:10.1128/AAC.01397-09 (July 2010)). Other examples of beta-lactamase inhibitors administred as an additional agent include clavulanic acid, tazobactam, sulbactam, avibactam (NXL-104), MK-7655, and BAL29880. MK-7655 has the following structure:



MK-7655

Indications

[0158] The compounds and compositions comprising cyclic boronic acid ester derivatives described herein can be used to treat bacterial infections. Bacterial infections that can be treated with the compounds, compositions and methods described herein can comprise a wide spectrum of bacteria. Example organisms include gram-positive bacteria, gram-negative bacteria, aerobic and anaerobic bacteria, such as *Staphylococcus, Lactobacillus, Streptococcus, Sarcina, Escherichia, Enterobacter, Klebsiella, Pseudomonas, Acinetobacter, Mycobacterium, Proteus, Campylobacter, Citrobacter, Nisseria, Baccillus, Bacteroides, Peptococcus, Clostridium, Salmonella, Shigella, Serratia, Haemophilus, Brucella* and other organisms.

[0159] More examples of bacterial infections include *Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas acidovorans, Pseudomonas*

alcaligenes, Pseudomonas putida, Stenotrophomonas maltophilia, Burkholderia cepacia, Aeromonas hydrophilia, Escherichia coli, Citrobacter freundii, Salmonella typhimurium, Salmonella typhi, Salmonella paratyphi, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Francisella tularensis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia alcalifaciens, Providencia rettgeri, Providencia stuartii, Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Yersinia intermedia, Bordetella pertussis, Bordetella parapertussis, Bordetella bronchiseptica, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus ducreyi, Pasteurella multocida, Pasteurella haemolytica, Branhamella catarrhalis, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Borrelia burgdorferi, Vibrio cholerae, Vibrio parahaemolyticus, Legionella pneumophila, Listeria monocytogenes, Neisseria gonorrhoeae, Neisseria meningitidis, Kingella, Moraxella, Gardnerella vaginalis, Bacteroides fragilis, Bacteroides distasonis, Bacteroides 3452A homology group, Bacteroides vulgatus, Bacteroides ovalus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides eggerthii, Bacteroides splanchnicus, Clostridium difficile, Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium leprae, Corynebacterium diphtheriae, Corynebacterium ulcerans, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus intermedius, Staphylococcus hyicus subsp. hyicus, Staphylococcus haemolyticus, Staphylococcus hominis, or *Staphylococcus saccharolyticus*.

[0160] The following examples will further describe the present invention, and are used for the purposes of illustration only, and should not be considered as limiting.

EXAMPLES

General procedures

[0161] Materials used in preparing the cyclic boronic acid ester derivatives described herein may be made by known methods or are commercially available. It will

be apparent to the skilled artisan that methods for preparing precursors and functionality related to the compounds claimed herein are generally described in the literature including, for example, procedures described in US7271186 and WO2009064414, each of which is incorporated by reference in its entirety. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. The skilled artisan given the literature and this disclosure is well equipped to prepare any of the compounds.

[0162] It is recognized that the skilled artisan in the art of organic chemistry can readily carry out manipulations without further direction, that is, it is well within the scope and practice of the skilled artisan to carry out these manipulations. These include reduction of carbonyl compounds to their corresponding alcohols, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic, etherifications, esterification and saponification and the like. These manipulations are discussed in standard texts such as March Advanced Organic Chemistry (Wiley), Carey and Sundberg, Advanced Organic Chemistry (incorporated herein by reference in its entirety) and the like.

[0163] The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus avoiding any undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many of these manipulations can be found for example in T. Greene and P. Wuts Protecting Groups in Organic Synthesis, 4th Ed., John Wiley & Sons (2007), incorporated herein by reference in its entirety.

[0164] The following example schemes are provided for the guidance of the reader, and represent preferred methods for making the compounds exemplified herein. These methods are not limiting, and it will be apparent that other routes may be employed to prepare these compounds. Such methods specifically include solid phase based chemistries, including combinatorial chemistry. The skilled artisan is thoroughly equipped to prepare these compounds by those methods given the literature and this disclosure. The compound numberings used in the synthetic schemes depicted below are meant for those specific schemes only, and should not be construed as or confused with same numberings in other sections of the application.

[0165] Trademarks used herein are examples only and reflect illustrative materials used at the time of the invention. The skilled artisan will recognize that

variations in lot, manufacturing processes, and the like, are expected. Hence the examples, and the trademarks used in them are non-limiting, and they are not intended to be limiting, but are merely an illustration of how a skilled artisan may choose to perform one or more of the embodiments of the invention.

[0166] (^{1}H) nuclear magnetic resonance spectra (NMR) were measured in the indicated solvents on either a Bruker NMR spectrometer (Avance TM DRX500, 500 MHz for 1H) or Varian NMR spectrometer (Mercury 400BB, 400 MHz for 1H). Peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak multiplicities are denoted as follows, s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sex, sextet; sep, septet; non, nonet; dd, doublet of doublets; td, triplet of doublets; m, multiplet.

[0167] The following abbreviations have the indicated meanings:

n-BuLi	= *n*-butyllithium
t-Bu	= *tert*-butyl
DCM	= dichloromethane
DMF	= N,N-dimethylformamide
DIPEA	= diisopropylethylamine
EDCI	= 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
ESBL	= extended-spectrum β-lactamase
ESIMS	= electron spray mass spectrometry
EtOAc	= ethyl acetate
EtOH	= ethanol
HATU	= 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCl	= hydrochloric acid
HOBt	= hydroxybenzotriazole
Im	= imidazole
LiHMDS	= lithium bis(trimethylsilyl)amide
MeCN	= acetonitrile
$NaHCO_3$	= sodium bicarbonate
Na_2SO_4	= sodium sulfate
NMM	= N-methylmorpholine
NMR	= nuclear magnetic resonance

Pd/C = palladium on carbon

TBDMSCl = *tert*-butyldimethylsilyl chloride

TBS = *tert*-butyldimethylsilyl

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin layer chromatography

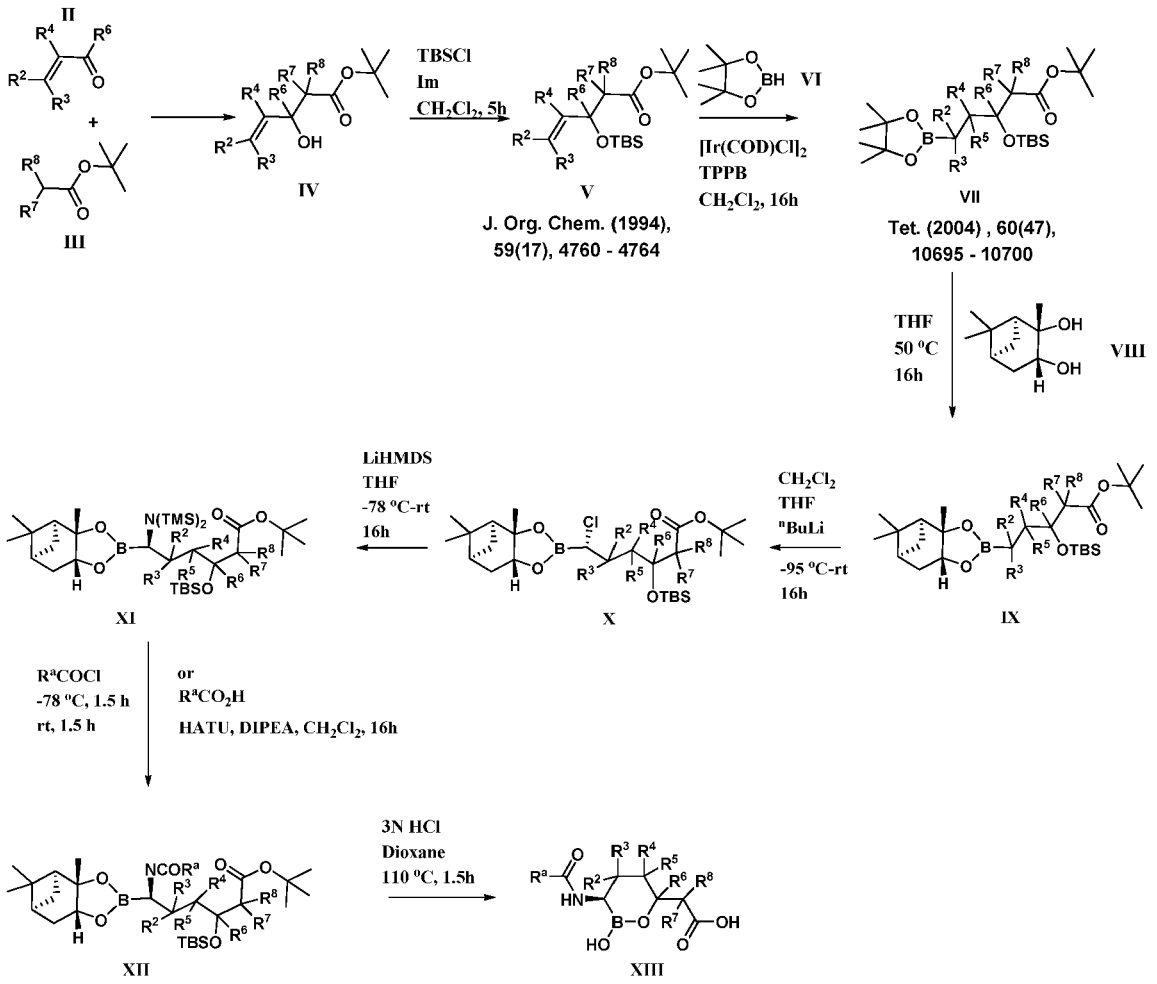
TMS = trimethylsilyl

TPPB = tris(pentafluorophenyl)borane monohydrate

[0168] The following example schemes are provided for the guidance of the reader, and collectively represent an example method for making the compounds provided herein. Furthermore, other methods for preparing compounds described herein will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

[0169] Compounds of formula I where R^1 is an acylamino group and X is a carboxylic acid can be prepared as depicted in Scheme 1.

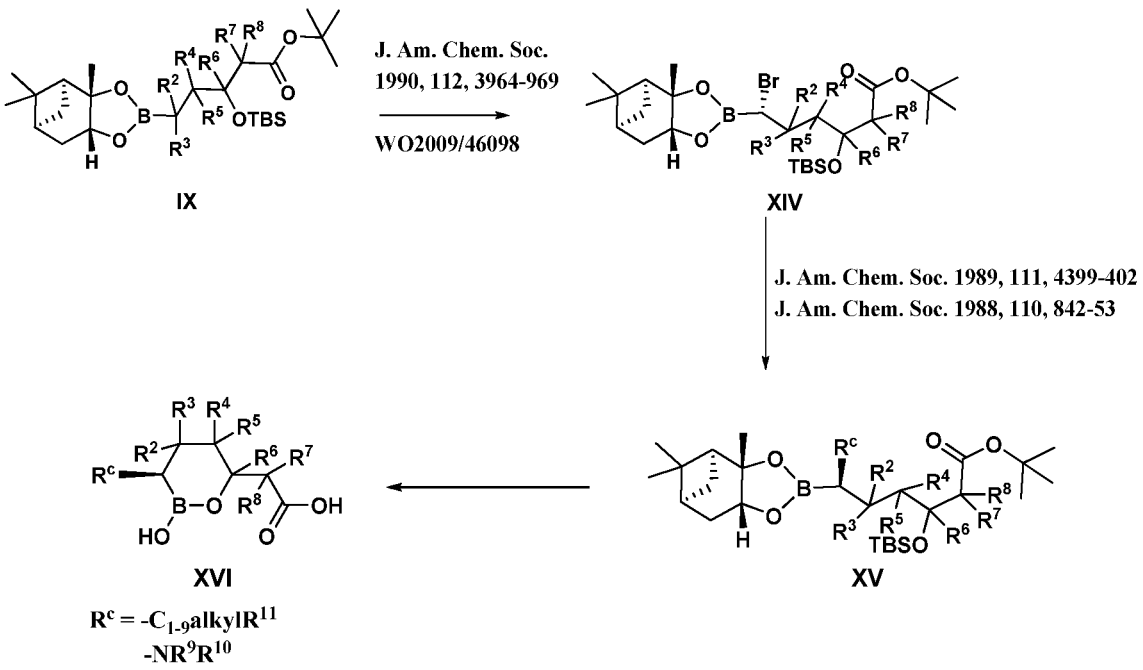
Scheme 1



[0170] The addition of enolates to substituted α,β-unsaturated ketones or aldehydes to form β-hydroxy esters is a well-known reaction (Scheme 1). Substituents R^7 and R^8 of formula **I** may be controlled by use of the appropriate α-mono or di-substituted ester **III**. Similarly, substituents R^2, R^3, and R^4 may be controlled by use of the appropriate substituted substituted α,β-unsaturated ketones or aldehydes analog **II**. Precursors of structure **IV**, where R^6 and R^7 or R^8 are combined together, may be made following the known procedures [*J. Am. Chem. Soc.* (**1982**), *104*, 1735-7, *Tetrahedron Lett.* (**2003**), *44*, 1259-62]. The β-hydroxy ester of structure **IV** is protected with an acid-sensitive protecting group, affording **V**; this selection allows simultaneous deprotection of the boronate ester and hydroxyl protecting group in the final step, resulting in a cyclized product. The pinacol boronate **VII** is formed from substituted **V** using iridium catalysis [*Tetrahedron* (**2004**), *60*, 10695-700]. Trans-esterification was readily achieved with optically active pinane diol **VIII** to result in **IX** [*Tetrahedron: Asymmetry*, (**1997**), *8*, 1435-40]. Transesterification may also be achieved from the catechol ester analog of

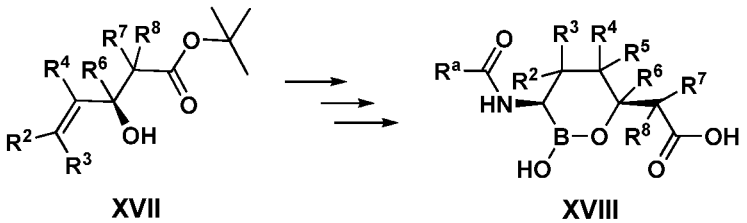
VII. Such catechol esters can be made by reaction of **V** with commercially available catechol borane [*Tetrahedron* **(1989)**, *45*, 1859-85]. Homologation of **IX** to give chloromethylene addition product **X** with good stereocontrol may be achieved via Matteson reaction conditions (WO0946098). The chloro derivative **X** can be utilized to introduce a substituted amine group at the C3-position of the oxaborinane-2-ol. Stereospecific substitution with hexamethyldisilazane gives the corresponding bis(trimethylsilyl) amide **XI** which may be reacted in situ with an acid chloride to result directly in analogs of structure **XII**. Such analogs of **XII** can also be made via coupling of the bis-TMS amine with commercially available carboxylic acids under typical amide coupling conditions (e.g., carbodiimide or HATU coupling). Compounds of Formula 1 where R^1 is substituted with $-N(R^9)C(=O)C(=NOR^9)R^9$ may be synthesized from corresponding carboxylic acids via coupling of **XI** to **XII** as in scheme 1. Such carboxylic acids can be made by following the procedures described U.S. Patent No. 5,888,998, U.S. Application Publication No. 2004/0019203, and U.S. Patent No. 4,822,786, all of which are incorporated herein by reference in their entirety. Simultaneous deprotection of the pinane ester, the tert-butyldimethylsilyloxy group and the tert-butyl ester group and concomitant cyclization are achieved by heating with dilute HCl, affording the desired oxaborinane derivatives of structure **XIII**. This transformation may also be achieved by treatment with BCl_3 or BBr_3. Alternatively, the deprotection may be attained via trans-esterification with isobutyl boronic acid in presence of dilute HCl (WO09064413).

Scheme 2



[0171] Compounds of structure **XVI** where R^1 of Formula I is an alkyl, aralkyl or aminoaryl group may be made from bromo intermediate **XIV** as shown in Scheme 2 [*J. Organomet. Chem.* (**1992**), *431*, 255-70]. Such bromo derivatives may be made as analogously to the chloro compounds of Scheme 1, utilizing dibromomethane [*J. Am. Chem. Soc.* (**1990**), *112*, 3964-969]. Displacement of the bromo group in **XIV** can be achieved by α-alkoxy substituted alkyllithium agents [*J. Am. Chem. Soc.* (**1989**), *111*, 4399-402; *J. Am. Chem. Soc.* (**1988**), *110*, 842-53] or organomagnesium reagents (WO0946098) or by the sodium salt of alkyl or aryl carbamate derivatives [*J. Org. Chem.* (**1996**), *61*, 7951-54], resulting in **XV**. Cyclization of **XV** to afford **XVI** may be achieved under the conditions described in Scheme 1.

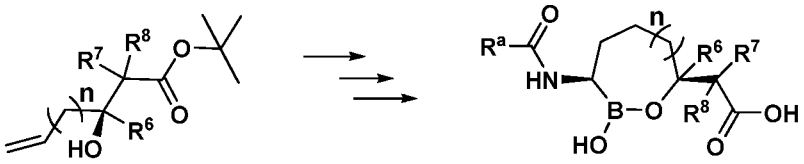
Scheme 3



[0172] Compounds of formula **XIII** and **XVI** are mixtures of 3,6-cis- and 3,6-trans-isomers. These analogs can be made in enantiomerically pure form as single isomers by starting (as in Scheme 1) with a single enantiomer (**XVII**), as shown in Scheme 3. A variety of methods to prepare such enantiomerically pure β-hydroxy esters

are known in literature, for example via resolution [*Org. Lett.*, **(2008)**, *10*, 3907-09] or stereoselective synthesis [*Tetrahedron*, **(2000)**, *56*, 917–47]. Such single isomers result in enantiomerically pure cis-compounds **XIII** or **XVI** when used in the sequences depicted in Schemes 1 and 2.

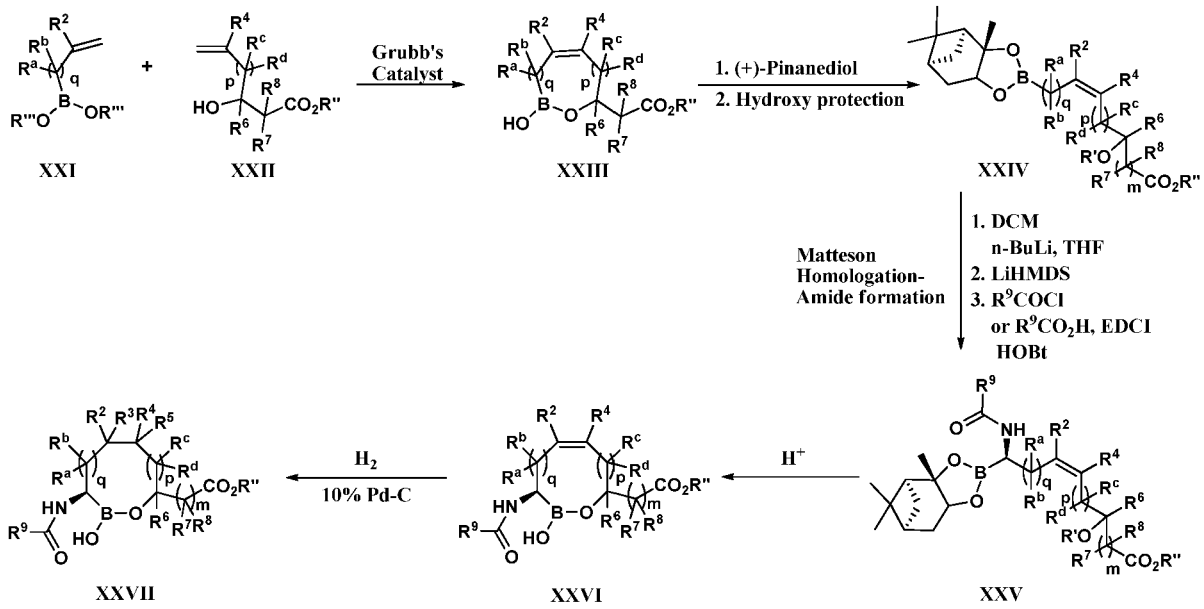
Scheme 4



XIX **XX**

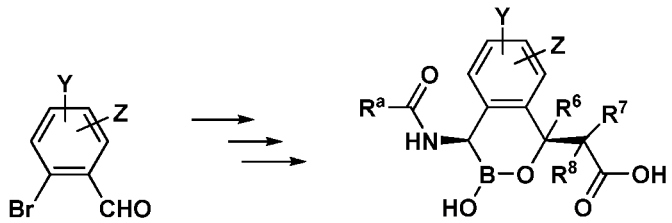
[0173] The sequence shown in Scheme 1 also allows for varied ring sizes in formula **I** such as 7- and 8-membered rings. For example, a seven-membered analog **XX** where n = 1 can be achieved by using the corresponding allyl intermediate (**XIX**) as a starting material (Scheme 4). Such allyl derivatives as **XIX** can be made utilizing one of several well known β-hydroxy ester preparations [*Tetrahedron* (**2007**), *63*, 8336–50]. Intermediate XIX where n = 2 can be prepared as described in Scheme 1 to give corresponding 8-membered compound of structure XX starting from pent-4-ene-1-al [*J. Med. Chem.* (**1998**), *41(6)*, 965-972].

Scheme 5



[0174] Compounds of formula **XXVI** and **XXVII** can be made following the sequence depicted in Scheme 5. Ring-Closing Metathesis reaction with boronated olefins (**XXI**) and olefin substituted β-hydroxy esters (**XXII**) result in cyclic boronates of formula **XXIII**. Such cyclic boronates (**XXIII**) undergo ready esterification with (+)-pinane diol to give required Matteson reaction precursors upon protection of the resulting alcohol with groups such as t-butyldimethylsilyl- or benzyl or trityl. Matteson homologation followed by amide formation result in compounds of formula **XXV** with high stereoselectivity, as described above. Acid mediated hydrolysis of compounds of **XXV** upon deprotection give cyclic boronate (**XXVI**). Double bond substitution of XXVI can be further modified to other analogs such as saturated cyclic boronate (**XXVII**) by catalytic hydrogenation. The above sequence can be utilized to make 7- or 8- membered rings with double bond at a desired position by varying p and q of **XXI** and **XXII**.

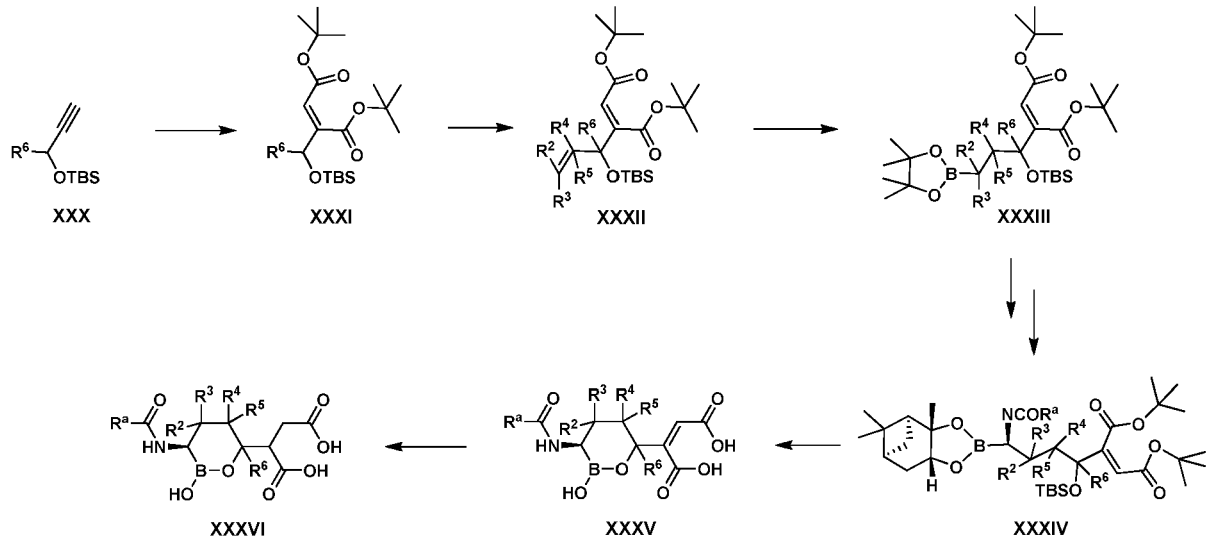
Scheme 6



XXVIII XXIX

[0175] Compounds of formula **I** where R^2 and R^4 taken together form an aryl ring can be made from commercially available substituted aryl precursors as **XXVIII**. Substitution of the bromine atom by a boronate ester may be done under palladium catalyzed conditions [*Tetrahedron* (**2002**), *58*, 9633–95]. The steps of hydroxy ester formation, α-amidoboronate preparation and cyclization can be attained by synthetic steps analogous to those in Scheme 1 to give compounds **XXIX**.

Scheme 7



XXX XXXI XXXII XXXIII XXXIV XXXV XXXVI

[0176] Compounds of formula I where R^7 and R^8 are substituted as maleate (**XXXV**) or succinate (**XXXVI**) may be made following the sequence shown in Scheme 7. Maleate intermediates such as **XXXII** can be transformed to analogs **XXXV** analogously to the steps in Scheme 1. Analogs of **XXXV** can be further transformed to the corresponding succinic acids of structure **XXXVI** by catalytic hydrogenation. Maleate intermediate **XXXII** may be assembled from intermediate **XXXI** by successive deprotection of the TBS group, oxidation to the aldehyde, addition of vinyl Grignard and reprotection as a TBS ether. Intermediate **XXXI** may be formed from a protected

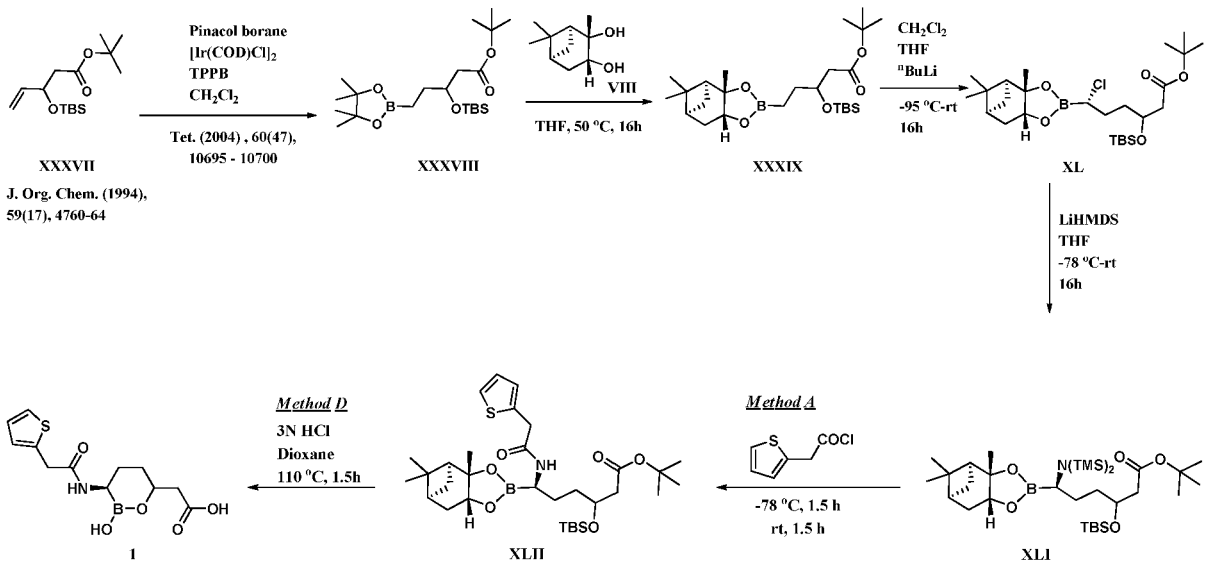
propargylic alcohol **XXX** following methods known in the literature [*Tetrahedron,* **(2002)**, *58*, 6545–54].

Compounds of Formula I where X is a carboxylic acid isostere can be prepared following the protocols described in the literature (*see J. Med. Chem.* 2011, 54, 2529-2591, which is incorporated herein by reference in its entirety).

Illustrative Compound Examples

[0177] Synthesis of 2-((3R)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-1,2-oxaborinan-6-yl)acetic acid. An example synthesis of **1** is depicted in Scheme 8 and Example 1.

Scheme 8



Example 1

Step 1

[0178] A round-bottom flask charged with $[Ir(cod)Cl]_2$ (350 mg, 0.52 mmol) and 1,4-bis(diphenylphosphanyl)butane (446 mg, 1.04 mmol) was flushed with argon. DCM (60 mL), pinacolborane (3 mL, 21 mmol) and *tert*-butyl-3-(tert-butyldimethylsilyloxy)pent-4-enoate **XXXVII** [*J. Org. Chem.*, (**1994**) , *59(17)* , 4760 – 4764] (5 g, 17.48 mmol) in 5 mL of DCM were added successively at room temperature. The mixture was then stirred at room temperature for 16h. The reaction was quenched with MeOH (3 mL) and water (10 mL), the product was extracted with ether, and dried.

Chromatography on silica gel (100% DCM→50% EtOAc/DCM gave *tert*-butyl 3-(*tert*-butyldimethylsilyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate **XXXVIII** (5.5 g, 13.2 mmol, 75.5%yield).

Step 2

[0179] To a solution of *tert*-butyl 3-(*tert*-butyldimethylsilyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate **XXXVIII** (5.4 g, 13 mmol) in THF (25 mL) was added (1 S,2S,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptane-2,3-diol (2.4 g, 14.3 mol) at room temperature. The reaction mixture was stirred for 16 h and then was concentrated under vacuum. The residue was purified by column chromatography (100% hexane→40% EtOAc/hexane) on silica gel to give 1-(*tert*-butoxy)-3-[(*tert*-butyldimethylsilyl)oxy]-1-oxo-6-[(2S,6R)-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo [6.1.1.02,6]decan-4-yl]hexan-3-yl **XXXIX** (5.5 g, 11 mmol, 84.6% yield).

Step 3

[0180] To a solution of DCM (1.5 mL, 23.6 mmol) in THF (30 mL) at -100 °C was added 2.5 M n-butyl lithium in hexane (5.19 mL, 12.98 mmol) slowly under nitrogen and down the inside wall of the flask whilst maintaining the temperature below -90°C. The resulting white precipitate was stirred for 30 minutes before the addition of 1-(*tert*-butoxy)-3-[(*tert*-butyldimethylsilyl)oxy]-1-oxo-6-[(2S,6R)-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo [6.1.1.02,6]decan-4-yl]hexan-3-yl **XXXIX** (5.5 g, 11 mmol) in THF (10 mL) at -90°C. Zinc chloride (23.6 mL, 0.5 M in diethyl ether, 11.86 mmol) was then added to the reaction mixture at -90°C and then the reaction was allowed to warm to room temperature where it was stirred for 16 h. The reaction was quenched with a saturated solution of ammonium chloride and the phases were separated. The aqueous phase was then extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The concentrated material was then chromatographed (100% hexane → 50% EtOAc/hexane) to obtain 6-(*tert*-butoxy)-4-[(*tert*-butyldimethylsilyl)oxy]-1-chloro-6-oxo-1-[(2S,6R)-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.02,6]decan-4-yl]hexyl **XL** (5.6 g, 10.5 mmol, 95.4% yield).

Step 4-5

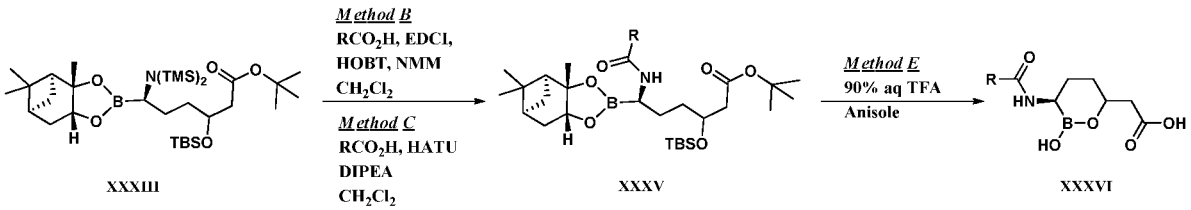
[0181] Chloro intermediate **XL** (1.2 g, 2.33 mmol) in THF (10 mL) was cooled to -78°C under nitrogen. A solution of LiHMDS (2.33 mL, 1.0 M in THF, 2.33 mmol) was added slowly and the reaction flask was then allowed to warm to room temperature where it was stirred for 16 h. ***Method A:*** The resulting was cooled to -78°C and 5-thiopheneacetyl chloride was added and the solution stirred at -78°C for 1.5 h. Then, the cooling bath was removed and the solution stirred at ambient temperature for 1.5 h. The reaction was quenched with water and extracted twice with EtOAc. The organic layers were combined, washed with water, brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow solid as crude product. The residue was chromatographed on a silica column (100% DCM→40% EtOAc/DCM) to afford 570 mg of 6-(*tert*-butoxy)-4-[(*tert*-butyldimethylsilyl)oxy]-6-oxo-1-(thiophen-2-ylacetamido)-1-[(2S,6R)-2,9,9- trimethyl-3,5-dioxa-4- boratricyclo[6.1.1.02,6]decan-4-yl]hexylidyne **XLII** as a white solid (570 mg, 0.92 mmol, 39.5% yield).

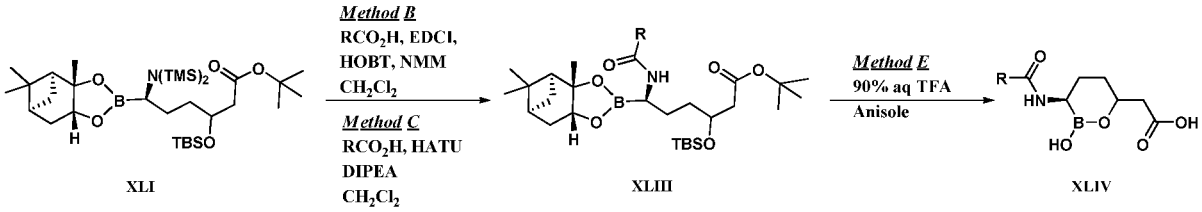
Step 6

[0182] ***Method D:*** To a solution of amide **XLII** (250 mg, 0.40 mmol) in 1,4-dioxane (10 mL) was added 10 mL of 3 N HCI. The mixture was heated to 110°C for 90 min. The solution was cooled and diluted with 10 mL of water and extracted twice with 10 mL of diethyl ether. The aqueous layer was concentrated to afford a sticky residue as crude product. The residue was rinsed with 5 mL of water, dissolved in 10% MeCN-water and lyophilized to afford 2-((3R)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-1,2-oxaborinan-6-yl)acetic acid **1** as white powder (100 mg, 0.337 mmol, 84.1% yield). ^1H NMR (CD_3OD) δ ppm 0.94-1.35 (m, 1H), 1.35-1.54 (m, 1H), 1.54-1.68 (m, 1H), 1.68-2.00 (m, 1H), 2.20-2.67 (m, 3H), 3.93 (s, 1H), 3.98 (s, 1H), 4.02-4.23 (m, 2H), 6.98-7.05 (m, 2H), 7.32-7.36 (m, 1H); ESIMS found for $C_{12}H_{16}BNO_5S$ *m/z* 280 (100%) (M-H_2O)+.

[0183] Alternative procedures for Steps 5 and 6 are shown in Scheme 9.

Scheme 9





XLI XLIII XLIV

Step5, Method B

[0184] To a solution of the acid (0.36 mmol) in DCM (10 mL) at 0°C under nitrogen was added EDCI (86 mg, 0.45 mmol) and HOBT (48 mg, 0.36 mmol). After stirring at 0°C for 30 minutes, a solution of the bis-silyl amide intermediate **XLI** (0.3 mmol) in DCM (2 mL) followed by *N*-methyl-morpholine (65 µL, 0.6 mmol) were sequentially added at 0°C. The reaction flask was then allowed to warm to room temperature. After stirring at room temperature overnight, the reaction mixture was washed with water, then brine, dried (Na_2SO_4), filtered and concentrated under vacuum. The residue was purified by column chromatography to produce intermediate **XLIII**.

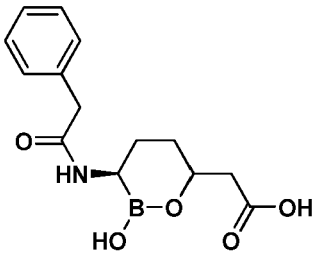
Step5, Method C

[0185] A solution of bis-silyl amide **XLI** (0.5 mmol) and acid in dry DCM (10 mL) were cooled to 0°C. Then DIPEA (1.5 mmol) was added drop wise followed HATU (0.75 mmol). The mixture was then allowed to warm to room temperature. After TLC has indicated complete conversion (~3h) of the starting materials, the reaction was diluted with additional DCM (20 mL). The reaction mixture was washed with water (3×5 mL), brine (10 mL), and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to flash column chromatography to produce intermediate **XLIII**.

Step 6, Method E

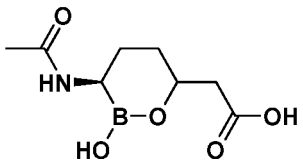
[0186] To a solution of amide **(XLIII)** (0.1 mmol) in dichloroethane (2 mL) at 0^0C was treated with pre-cooled 90% aq. TFA (4 mL) and stirred at room temperature for 3 hrs. The reaction mixture was evaporated in vacuo, azeotroped with MeCN (3 X 5 mL) and the residue was triturated with ether (5 mL). The product separated was filtered, dissolved in dioxane-water mixture and freeze dried to give the final product **XLIV** as a fluffy solid.

[0187] The following compounds are prepared in accordance with the procedure described in the above Example 1 using methods A and D.



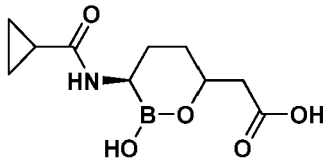
2

[0188] 2-((3R)-2-hydroxy-3-(2-phenylacetamido)-1,2-oxaborinan-6-yl)acetic acid **2**. ^{1}H NMR (CD_3OD) δ ppm 0.82-1.33 (m, 1H), 1.33-1.51 (m, 1H), 1.51-1.68 (m, 1H), 1.69-2.00 (m, 1H), 2.14-2.34 (m, 1H), 2.34-2.69 (m, 2H), 3.74-3.76 (m, 2H), 3.98-4.20 (m, 1H), 7.22-7.41 (m, 5H); ESIMS found for C14H18BNO5 m/z 274 (100%) $(M-H_2O)^+$.



3

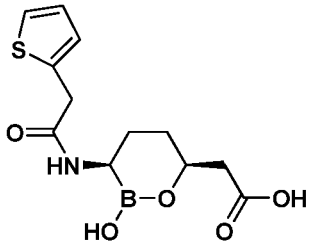
[0189] 2-((3R)-3-acetamido-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **3**. ^{1}H NMR (CD_3OD) δ ppm 1.07-1.36 (m, 1H), 1.36-1.59 (m, 1H), 1.59-1.73 (m, 1H), 1.73-2.09 (m, 1H), 2.15-2.16 (d, 3H), 2.35-2.69 (m, 3H), 4.01-4.23 (m, 1H); ESIMS found for $C_8H_{14}BNO_5$ *m/z* 198 (100%) $(M-H_2O)^+$.



4

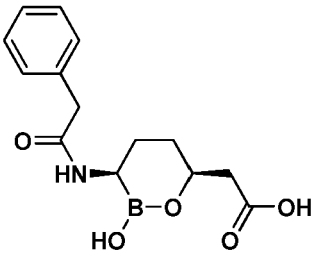
[0190] 2-((3R)-3-(cyclopropanecarboxamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **4**. ^{1}H NMR (CD_3OD) δ ppm 0.98-1.32 (m, 5H), 1.32-1.67 (m, 2H), 1.67-2.06 (m, 2H), 2.27-2.66 (m, 3H), 3.98-4.16 (m, 1H); ESIMS found for $C_{10}H_{16}BNO_5$ *m/z* 224 (100%) $(M-H_2O)^+$.

[0191] The following compounds are prepared starting from enantiomerically pure (R)-tert-butyl 3-hydroxypent-4-enoate (J. Am. Chem. Soc. 2007, 129, 4175-4177) in accordance with the procedure described in the above Example 1.



5

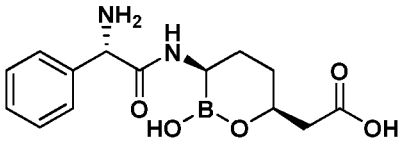
[0192] 2-((3R,6S)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-1,2-oxaborinan-6-yl)acetic acid **5**. ^{1}H NMR (CD_3OD) δ ppm 0.97-1.11 (q, 1H), 1.47-1.69 (m, 2H), 1.69-1.80 (m, 1H), 2.21-2.33 (td, 1H), 2.33-2.41 (dd, 1H), 2.58-2.67 (m, 1H), 3.97 (s, 2H), 4.06-4.14 (m, 1H), 6.97-7.04 (m, 1H), 7.04-7.08 (m, 1H), 7.34-7.38 (dd, 1H); ESIMS found for $C_{12}H_{16}BNO_5S$ *m/z* 280 (100%) $(M-H_2O)^+$.



6

[0193] 2-((3R,6S)-2-hydroxy-3-(2-phenylacetamido)-1,2-oxaborinan-6-yl)acetic acid **6**. ^{1}H NMR (CD_3OD) δ ppm 0.86-1.02 (m, 1H), 1.44-1.53 (dd, 1H), 1.53-1.66 (td, 1H), 1.68-1.78 (m, 1H), 2.17-2.26 (dd, 1H), 2.26-2.36 (dd, 2H), 3.75 (s, 2H), 4.02-4.12 (m, 1H), 7.22-7.40 (m, 5H); ESIMS found for $C_{14}H_{18}BNO_5$ *m/z* 274 (100%) $(M-H_2O)^+$.

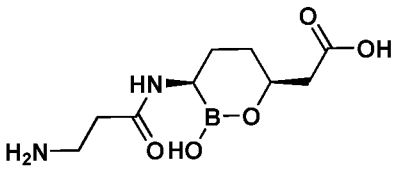
[0194] The following compounds are prepared in accordance with the procedure described in the above Example 1 starting from enantiomerically pure (R)-tert-butyl 3-hydroxypent-4-enoate (J. Am. Chem. Soc. 2007, 129, 4175-4177) using methods B and D.



33

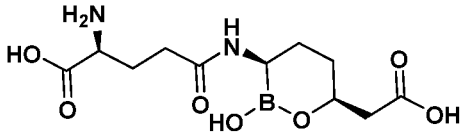
[0195] 2-((3R,6S)-3-((S)-2-amino-2-phenylacetamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **33** was isolated as the HCl salt. ^{1}H NMR (CD_3OD) δ ppm 1.24-1.27 (m, 1H), 1.51-1.72 (m, 3H), 2.45-2.50 (dd, *J*=5 Hz, *J*=5 Hz, 1H), 2.55-2.63 (dd,

J=2 Hz, *J*=3 Hz, 1H), 3.66-3.71 (m, 1H), 4.38-4.53 (m, 1H), 4.99-5.09 (d, 1H), 7.48-7.56 (m, 5H); ESIMS found for $C_{14}H_{19}BN_2O_5$ *m/z* 289 $(M-H_2O)^+$.



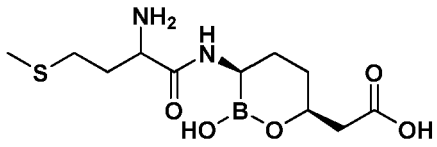
34

[0196] 2-((3R,6S)-3-(3-aminopropanamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **34** was isolated as the HCl salt. ^{1}H NMR (CD_3OD) δ ppm 1.24-1.29 (td, *J*=13 Hz. *J*=3 Hz, 1H), 1.55-1.62 (td, *J*=14 Hz, *J*=4 Hz, 1H), 1.68-1.72 (m, 1H), 1.79-1.82 (m, 1H), 2.43-2.47 (dd, *J*=6 Hz, *J*=6 Hz, 2H), 2.70-2.74 (m, 2H), 2.83-2.86 (t, *J*=7 Hz, 2H), 3.26-3.29 (t, *J*=7 Hz, 1H), 4.10-4.16 (m, 1H); ESIMS found for $C_9H_{17}BN_2O_5$ *m/z* 227 $(M-H_2O)^+$.



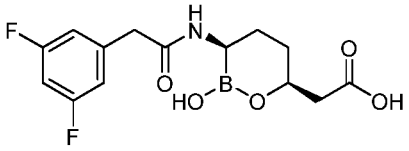
35

[0197] (S)-2-amino-5-((3R,6S)-6-(carboxymethyl)-2-hydroxy-1,2-oxaborinan-3-ylamino)-5-oxopentanoic acid **35** was isolated as the HCl salt. ^{1}H NMR (CD_3OD) δ ppm 1.50-1.66 (m, 2H), 1.66-1.84 (m, 2H), 2.10-2.20 (sex, *J*=8 Hz 1H), 2.20-2.29 (m, 1H), 2.40-2.47 (m, 2H), 2.55-2.59 (q, *J*=7 Hz 1H), 2.69-2.75 (m, 1H), 2.94-2.98 (td, *J*=9 Hz, *J*=2 Hz 1H), 3.99-4.12 (m, 2H); ESIMS found for $C_{11}H_{19}BN_2O_7$ *m/z* 302.8 (M+H).



41

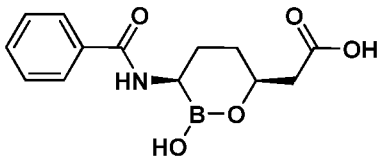
[0198] 2-((3R,6S)-3-(2-amino-4-(methylthio)butanamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **41** was isolated as the HCl salt. ^{1}H NMR (CD_3OD) δ ppm 1.45-1.65 (m, 1H), 1.65-1.75 (m, 1H), 1.75-1.86 (m, 1H), 1.86-2.05 (m, 1H), 2.09-2.20 (m, 4H), 2.46-2.73 (m, 6H), 2.84-2.86 (t, *J*=6 Hz, 1H), 3.99-4.02 (t, *J*=7 Hz, 1H), 4.38-4.46 (m, 1H); ESIMS found for $C_{11}H_{21}BN_2O_5S$ *m/z* 287 $(M-H_2O)^+$.



66

[0199] 2-((3R,6S)-3-(2-(3,5-difluorophenyl)acetamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **66** was isolated as the HCl salt. ^{1}H NMR (CD_3OD) δ ppm 0.98-1.07 (q, *J*=13 Hz, 1H), 1.55-1.68 (m, 2H), 1.73-1.79 (dd, *J*=6 Hz, *J*=3 Hz, 1H), 2.22-2.26 (dd, *J*=15 Hz, *J*=6 Hz, 1H), 2.33-2.38 (dd, *J*=13 Hz, *J*=7 Hz, 1H), 2.62-2.63 (m, 1H), 3.78 (s, 2H), 4.05-4.12 (m, 1H), 6.88-5.93 (tt, *J*=5 Hz, *J*=2 Hz, 1H), 6.97-7.01 (dd, *J*=5 Hz, *J*=2 Hz, 2H); ESIMS found for $C_{14}H_{16}BF_2NO_5$ *m/z* 310.1 $(M\text{-}H_2O)^+$.

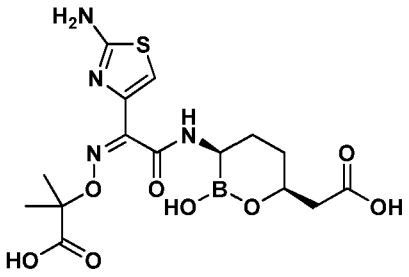
[0200] The following compounds are prepared in accordance with the procedure described in the above Example 1 starting from enantiomerically pure (R)-tert-butyl 3-hydroxypent-4-enoate (J. Am. Chem. Soc. 2007, 129, 4175-4177) using methods A and E.



37

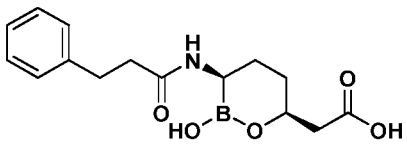
[0201] 2-((3R,6S)-3-benzamido-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **37**. ^{1}H NMR (CD_3OD) δ ppm 1.10-1.19 (q, *J*=11 Hz, 1H), 1.60-1.65 (dd, *J*=14 Hz, *J*=3 Hz, 1H), 1.71-1.80 (td, *J*=9 Hz, *J*=3 Hz, 1H), 1.91-1.96 (d, *J*=14 Hz, 1H), 2.32-2.38 (dd, *J*=15 Hz, *J*=6 Hz, 1H), 2.44-2.49 (dd, *J*=15 Hz, *J*=7 Hz, 1H), 2.82-2.84 (d, *J*=4 Hz, 1H), 4.10-4.17 (m, 1H), 7.57-7.60 (t, *J*=8 Hz, 2H), 7.70-7.73 (t, *J*=8 Hz, 1H), 8.00-8.02 (d, *J*=8 Hz 2H); ESIMS found for $C_{13}H_{16}BNO_5$ *m/z* 260 $(M\text{-}H_2O)^+$.

[0202] The following compounds are prepared in accordance with the procedure described in the above Example 1 starting from enantiomerically pure (R)-tert-butyl 3-hydroxypent-4-enoate (J. Am. Chem. Soc. 2007, 129, 4175-4177) using methods B and E.



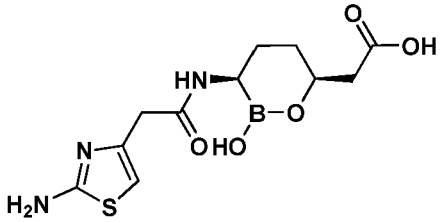
36

[0203] 2-((Z)-1-(2-aminothiazol-4-yl)-2-((3R,6S)-6-(carboxymethyl)-2-hydroxy-1,2-oxaborinan-3-ylamino)-2-oxoethylideneaminooxy)-2-methylpropanoic acid **36** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.60 (s, 3H), 1.61 (s, 3H), 1.62-1.75 (m, 2H), 1.77-1.82 (m, 1H), 1.86-1.91 (m, 1H), 2.55-2.58 (t, *J*=6 Hz, 2H), 2.90-2.94 (t, *J*=6 Hz, 2H), 4.37-4.42 (m, 1H), 7.11 (s, 1H); ESIMS found for $C_{15}H_{21}BN_4O_8S$ *m/z* 411 $(M-H_2O)^+$.



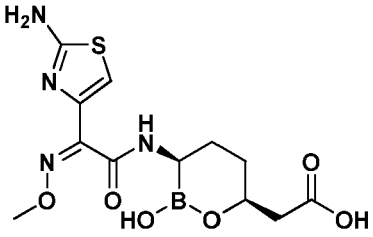
38

[0204] 2-((3R,6S)-2-hydroxy-3-(3-phenylpropanamido)-1,2-oxaborinan-6-yl)acetic acid **38**. ^{1}H NMR (CD_3OD) δ ppm 0.78-0.87 (q, *J*=13 Hz, 1H), 1.40-1.46 (dd, *J*=10 Hz, *J*=3 Hz, 1H), 1.54-1.62 (dt, *J*=8 Hz, *J*=4 Hz, 1H), 1.63-1.70 (d, *J*=13 Hz, 1H), 2.24-2.29 (dd, *J*=15 Hz, *J*=6 Hz, 1H), 2.36-2.40 (dd, *J*=8 Hz, *J*=3 Hz, 1H), 2.53-2.56 (d, *J*=3.2 Hz, 1H), 2.74-2.78 (t, *J*=7 Hz, 2H), 2.98-3.01 (t, *J*=6 Hz, 2H), 3.90-4.03 (m, 1H), 7.18-7.23 (m, 1H), 7.25-7.33 (m, 4H); ESIMS found for $C_{15}H_{20}BNO_5$ *m/z* 288 $(M-H_2O)^+$.



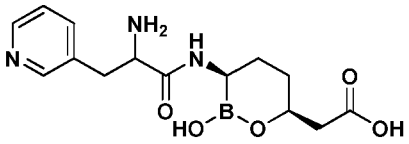
39

[0205] 2-((3R,6S)-3-(2-(2-aminothiazol-4-yl)acetamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **39** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.25-1.36 (m, 1H), 1.63-1.76 (m, 3H), 2.40-2.43 (d, *J*=6 Hz 2H), 2.68-2.70 (m, 1H), 3.72 (s, 2H), 4.17-4.21 (m, 1H), 6.69 (s, 1H); ESIMS found for $C_{11}H_{16}BN_3O_5S$ *m/z* 296.1 $(M-H_2O)^+$.



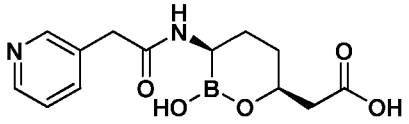
40

[0206] 2-((3R,6S)-3-((Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **40** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.56-1.67 (m, 2H), 1.76-1.81 (m, 1H), 1.86-1.90 (m, 1H), 2.50-2.54 (dd, *J*=17 Hz, *J*=6 Hz, 1H), 2.59-2.64 (dd, *J*=16 Hz, *J*=7 Hz, 1H), 2.86-2.90 (t, *J*=7 Hz, 1H), 4.22 (s, 3H), 4.34-4.37 (m, 1H), 7.86 (s, 1H); ESIMS found for $C_{12}H_{17}BN_4O_6S$ *m/z* 339.1 $(M\text{-}H_2O)^+$.



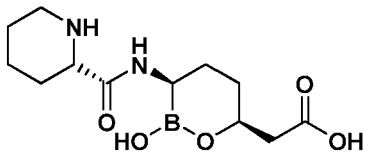
42

[0207] 2-((3R,6S)-3-(2-amino-3-(pyridin-3-yl)propanamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **42** was isolated as the TFA salt. ^{1}H NMR (CD_3OD/CF_3O_2D) δ ppm 1.43-1.56 (m, 2H), 1.72-1.83 (m, 2H), 2.37-2.42 (m, 1H), 2.53-2.57 (t, *J*=6 Hz, 1H), 2.89-2.93 (t, *J*=7 Hz, 1H), 3.37-3.43 (m, 2H), 4.17-4.21 (t, *J*=7 Hz, 1H), 4.41-4.46 (m, 1H), 8.06-8.10 (dd, *J*=6 Hz, *J*=3 Hz, 1H), 8.53-8.57 (t, *J*=17 Hz, 1H), 8.80-8.81 (brd, *J*=4 Hz, 1H), 8.84-8.87 (brd, *J*=6 Hz, 1H); ESIMS found for $C_{14}H_{20}BN_3O$= *m/z* 304.2 $(M\text{-}H_2O)^+$.



43

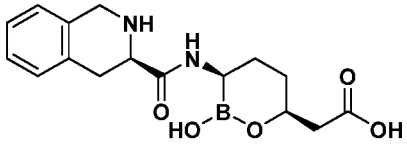
[0208] 2-((3R,6S)-2-hydroxy-3-(2-(pyridin-3-yl)acetamido)-1,2-oxaborinan-6-yl)acetic acid **43** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.15-1.20 (m, 1H), 1.59-1.63 (m, 1H), 1.68-1.74 (m, 2H), 2.29-2.34 (dd, *J*=15 Hz, *J*=6 Hz, 2H), 2.66-2.68 (m, 1H), 3.94 (s, 2H), 4.11-4.18 (m, 1H), 7.82-7.85 (dd, *J*=8 Hz, *J*=6 Hz, 1H), 8.30-8.32 (d, *J*=8 Hz, 1H), 8.68-8.70 (brd, *J*=5 Hz, 1H), 8.72-8.75 (brs, 1H); ESIMS found for $C_{13}H_{17}BN_2O5$ *m/z* 275 $(M\text{-}H_2O)^+$.



45

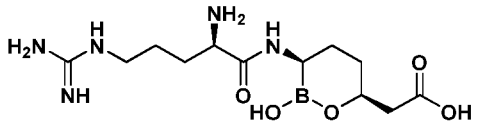
[0209] 2-((3R,6S)-2-hydroxy-3-((S)-piperidine-2-carboxamido)-1,2-oxaborinan-6-yl)acetic acid **45** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.44-1.51 (m, 1H), 1.54-1.80 (m, 5H), 1.80-1.91 (m, 2H), 1.91-1.98 (brd, *J*=12 Hz, 1H),

2.16-2.21 (dd, *J*=13 Hz, *J*=2 Hz, 1H), 2.49-2.57 (non, *J*=7 Hz, 2H), 2.75-2.78 (t, *J*=6 Hz, 1H), 2.98-3.03 (dt, *J*=13 Hz, *J*=3 Hz, 1H), 3.36-3.39 (d, *J*=13 Hz, 1H), 3.79-3.82 (dd, *J*=12 Hz, *J*=4 Hz, 1H), 4.34-4.38 (m, 1H); ESIMS found for $C_{12}H_{21}BN_2O_5$ m/z 267 $(M-H_2O)^+$.



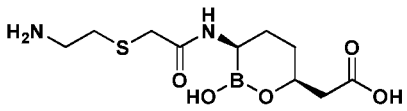
46

[0210] 2-((3R,6S)-2-hydroxy-3-((R)-1,2,3,4-tetrahydroisoquinoline-3-carboxamido)-1,2-oxaborinan-6-yl)acetic acid **46** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.43-1.51 (m, 1H), 1.56-1.63 (m, 1H), 1.75-1.83 (m, 1H), 1.86-1.94 (m, 1H), 2.46-2.57 (dq, *J*=16 Hz, *J*=6 Hz, 2H), 2.82-2.86 (t, *J*=7 Hz, 1H), 3.18-3.24 (dd, *J*=17 Hz, *J*=12 Hz, 1H), 3.36-3.41 (dd, *J*=17 Hz, *J*=5 Hz, 1H), 4.21-4.24 (dd, *J*=18 Hz, *J*=13 Hz, 1H), 4.36-4.40 (m, 1H), 4.42 (s, 2H), 7.23-7.25 (m, 1H), 7.27-7.33 (m, 3H); ESIMS found for $C_{16}H_{21}BN_2O_5$ *m/z* 315 $(M-H_2O)^+$.



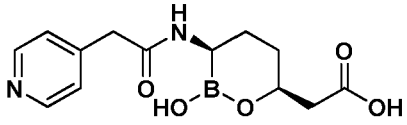
47

[0211] Following method E while the compound is still in 90% aq. trifluoroacetic acid (10 mL), 10% Pd/C (50 mg) was added. The reaction mixture was stirred under hydrogen for 6 h, filtered through Celite and rinsed with dichloroethane (10 mL). The filtrate was concentrated under vacuum and azeotroped with dichloroethane (2 X 10 mL). Triturating with ether resulted in a precipitate which was filtered and washed with ether (5 mL) and dried to give 2-((3R,6S)-3-((R)-2-amino-5-guanidinopentanamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **47** as the TFA salt (50 mg) as an off-white solid. ^{1}H NMR (CD_3OD) δ ppm 1.39-1.46 (m, 1H), 1.52-1.58 (m, 1H), 1.66-1.77 (m, 2H), 1.77-1.84 (m, 1H), 1.87-1.95 (m, 3H), 2.34-2.38 (dd, *J*=17 Hz, *J*=3 Hz, 1H), 2.63-2.68 (dd, *J*=17 Hz, *J*=7 Hz, 1H), 2.94-2.97 (dd, *J*=10 Hz, *J*=6 Hz, 1H), 3.20-3.24 (dt, *J*=7 Hz, *J*=2 Hz, 2H), 3.86-3.88 (t, *J*=6 Hz, 1H), 4.27-4.31 (m, 1H); ESIMS found for $C_{12}H_{24}BN_5O_5$ *m/z* 312.2 $(M-H_2O)^+$.



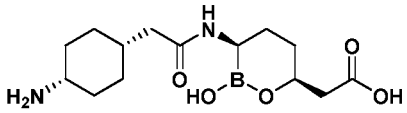
48

[0212] 2-((3R,6S)-3-(2-(2-aminoethylthio)acetamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **48** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.38-1.46 (m, 1H), 1.46-1.54 (m, 1H), 1.71-1.78 (m, 1H), 1.84-1.92 (m, 1H), 2.30-2.34 (dd, *J*=16 Hz, *J*=4 Hz, 1H), 2.56-2.61 (dd, *J*=16 Hz, *J*=6 Hz, 1H), 2.80-2.83 (t, *J*=6 Hz, 1H), 2.89-2.97 (non, *J*=7 Hz, 2H), 3.17-3.24 (non, *J*=5 Hz, 2H), 3.37 (s, 2H), 4.15-4.20 (m, 1H); ESIMS found for $C_{10}H_{19}BN_2O_5S$ *m/z* 273 $(M\text{-}H_2O)^+$.



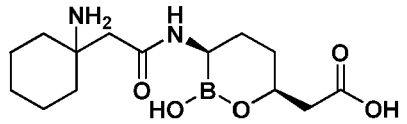
49

[0213] 2-((3R,6S)-2-hydroxy-3-(2-(pyridin-4-yl)acetamido)-1,2-oxaborinan-6-yl)acetic acid **49** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.17-1.27 (m, 1H), 1.60-1.67 (m, 1H), 1.67-1.76 (m, 2H), 2.32-2.43 (m, 2H), 2.68-2.70 (t, *J*=4 Hz, 2H), 3.22-3.26 (t, *J*=7 Hz, 1H), 4.15-4.21 (m, 1H), 7.94-7.96 (d, *J*=7 Hz, 2H), 8.75-8.79 (d, *J*=6 Hz, 2H); ESIMS found for $C_{13}H_{17}BN_2O_5$ *m/z* 275.1 $(M\text{-}H_2O)^+$.



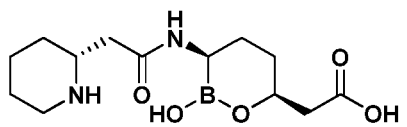
50

[0214] 2-((3R,6S)-3-(2-(4-aminocyclohexyl)acetamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **50** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.15-1.25 (m, 1H), 1.44-1.88 (m, 10H), 2.05-2.13 (m, 1H), 2.19-2.21 (d, *J*=8 Hz, 1H), 2.30-2.36 (dd, *J*=6 Hz, 1H), 2.38-2.47 (m, 3H), 2.61-2.63 (brd, *J*=3 Hz, 1H), 3.18-3.22 (t, *J*=7 Hz, 1H), 4.04-4.11 (m, 1H); ESIMS found for $C_{14}H_{25}BN_2O_5$ *m/z* 295.1 $(M\text{-}H_2O)^+$.



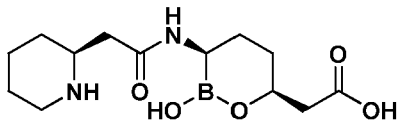
51

[0215] 2-((3R,6S)-3-(2-(1-aminocyclohexyl)acetamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **51** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.23-1.34 (m, 1H), 1.34-1.48 (m, 1H), 1.48-1.86 (m, 12H), 2.40-2.50 (m, 2H), 2.65-2.83 (m, 2H), 3.22-3.26 (t, *J*=7 Hz, 1H), 4.11-4.18 (m, 1H); ESIMS found for $C_{14}H_{25}BN_2O_5$ *m/z* 295 $(M\text{-}H_2O)^+$.



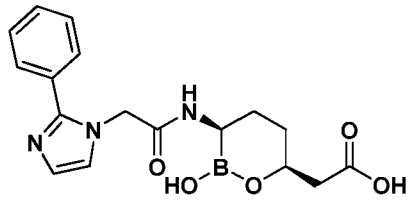
52

[0216] 2-((3R,6S)-2-hydroxy-3-(2-((R)-piperidin-2-yl)acetamido)-1,2-oxaborinan-6-yl)acetic acid **52** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.27-1.37 (m, 1H), 1.49-1.80 (m, 7H), 1.86-2.00 (brdd, *J*=11 Hz, 3H), 2.44-2.46 (d, *J*=6 Hz, 2H), 2.61-2.65 (m, 1H), 2.72-2.73 (d, *J*=6 Hz, 1H), 3.03-3.09 (t, *J*=13 Hz, 1H), 3.41-3.45 (d, *J*=13 Hz, 1H), 3.47-3.56 (m, 1H), 4.15-4.21 (m, 1H); ESIMS found for $C_{13}H_{23}BN_2O_5$ *m/z* 281 $(M-H_2O)^+$.



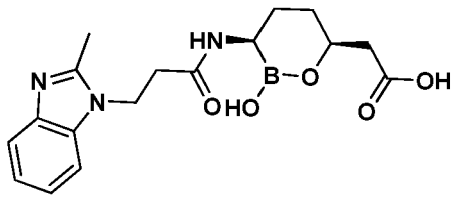
53

[0217] 2-((3R,6S)-2-hydroxy-3-(2-((S)-piperidin-2-yl)acetamido)-1,2-oxaborinan-6-yl)acetic acid **53** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.26-1.35 (m, 1H), 1.48-1.59 (m, 1H), 1.59-1.68 (m, 2H), 1.68-1.81 (m, 3H), 1.87-2.00 (m, 3H), 2.45-2.47 (d, *J*=7 Hz, 2H), 2.65-2.67 (t, *J*=4 Hz, 1H), 2.74-2.76 (t, *J*=6 Hz, 2H), 3.03-3.08 (dt, *J*=13 Hz, *J*=3 Hz, 1H), 3.42-3.46 (brd, *J*=13 Hz, 1H), 3.47-3.55 (m, 1H), 4.12-4.19 (m, 1H); ESIMS found for $C_{13}H_{23}BN_2O_5$ *m/z* 298.1 (M+H).



54

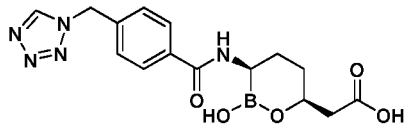
[0218] 2-((3R,6S)-2-hydroxy-3-(2-(2-phenyl-1H-imidazol-1-yl)acetamido)-1,2-oxaborinan-6-yl)acetic acid **54** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.36-1.44 (m, 1H), 1.44-1.54 (m, 1H), 1.66-1.80 (m, 2H), 2.15 (s, 1H), 2.48-2.51 (m, *J*=6 Hz, 1H), 2.72-2.75 (t, *J*=7 Hz, 1H), 4.33-4.39 (m, 1H), 4.94-5.05 (m, 2H), 7.65-7.76 (m, 7H); ESIMS found for $C_{17}H_{20}BN_3O_5$ *m/z* 358.2 (M+H).



55

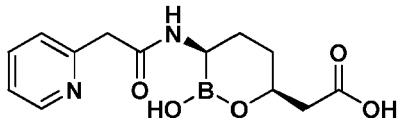
[0219] 2-((3R,6S)-2-hydroxy-3-(3-(2-methyl-1H-benzo[d]imidazol-1-yl)propanamido)-1,2-oxaborinan-6-yl)acetic acid **55**. ^{1}H NMR (CD_3OD) δ ppm 0.92-1.00

(m, 1H), 1.47-1.53 (m, 1H), 1.58-1.62 (m, 2H), 2.31-2.33 (d, *J*=7 Hz, 2H), 2.50-2.52 (t, *J*=4 Hz, 1H), 2.97 (s, 3H), 3.08-3.20 (m, 2H), 4.04-4.10 (m, 1H), 4.77-4.81 (t, *J*=6 Hz, 2H), 7.61-7.68 (m, 2H), 7.75-7.78 (d, *J*=7 Hz, 1H), 7.93-7.95 (d, *J*=7 Hz, 1H); ESIMS found for $C_{17}H_{22}BN_3O_5$ *m/z* 342.2 $(M\text{-}H_2O)^+$.



56

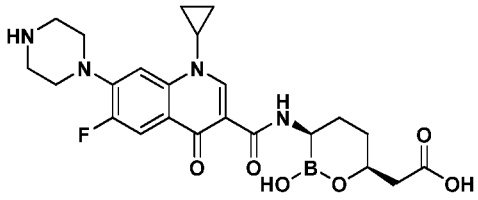
[0220] 2-((3R,6S)-3-(4-((1H-tetrazol-1-yl)methyl)benzamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **56**. ^1H NMR (CD_3OD) δ ppm 1.10-1.21 (m, 1H), 1.58-1.64 (m, 1H), 1.70-1.79 (m, 1H), 1.89-1.96 (m, 1H), 2.31-2.36 (dd, *J*=15 Hz, *J*=6 Hz, 1H), 2.41-2.47 (m, 1H), 2.80-2.83 (brd, *J*=4 Hz, 1H), 4.11-4.17 (m, 1H), 5.83 (s, 2H), 7.53-7.55 (d, *J*=8 Hz, 2H), 8.02-8.05 (d, *J*=8 Hz, 2H), 9.30 (s, 1H); ESIMS found for $C_{15}H_{18}BN_5O_5$ *m/z* 342.0 $(M\text{-}H_2O)^+$.



57

[0221] 2-((3R,6S)-2-hydroxy-3-(2-(pyridin-2-yl)acetamido)-1,2-oxaborinan-6-yl)acetic acid **57** was isolated as the TFA salt. ^1H NMR (CD_3OD) δ ppm 1.21-1.32 (m, 1H), 1.59-1.67 (m, 2H), 1.67-1.75 (m, 2H), 2.29-2.40 (m, 3H), 2.67-2.72 (m, 1H), 4.14-4.21 (m, 1H), 7.62-7.66 (t, *J*=6 Hz, 1H), 7.70-7.73 (d, *J*=8 Hz, 1H), 8.14-8.18 (t, *J*=8 Hz, 1H), 8.65-8.67 (d, *J*=5 Hz, 1H); ESIMS found for $C_{13}H_{17}BN_2O_5$ *m/z* 275.1 $(M\text{-}H_2O)^+$.

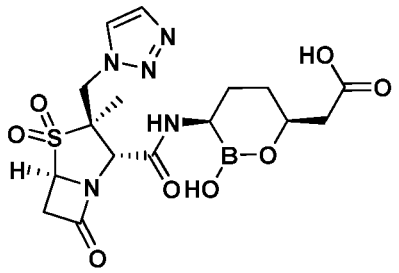
[0222] The following compounds are prepared in accordance with the procedure described in the above Example 1 using methods C and E.



58

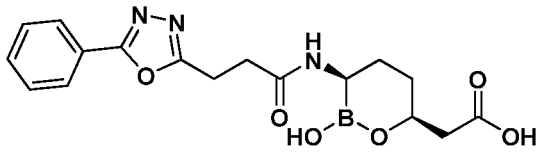
[0223] 2-((3R,6S)-3-(1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **58** was isolated as the TFA salt. ^1H NMR (CD_3OD) δ ppm 1.14-1.29 (m, 3H), 1.39-1.44 (brd, *J*=7 Hz, 2H), 1.56-1.63 (dd, *J*=14 Hz, *J*=3 Hz, 1H), 1.70-1.80 (m, 1H), 1.92-1.99 (d, *J*=14 Hz, 1H), 2.33-2.38 (dd, *J*=15 Hz, *J*=6 Hz, 1H), 2.43-2.48 (dd, *J*=15 Hz, *J*=7 Hz, 1H), 2.85-

2.86 (d, *J*=3 Hz, 1H), 3.46-3.52 (m, 4H), 3.59-3.64 (m, 4H), 3.73-3.79 (m, 1H), 4.08-4.15 (m, 1H), 7.66-7.67 (d, J=7 Hz, 1H), 8.00-8.03 (d, J=13 Hz, 1H), 8.81 (s, 1H); ESIMS found for $C_{23}H_{28}BFN_4O_6$ *m/z* 469.2 $(M-H_2O)^+$.



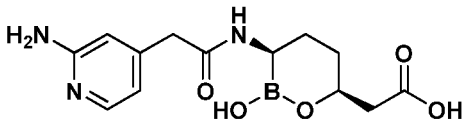
59

[0224] 2-[(3R,6S)-2-hydroxy-3-[(2S,3S,5R)-3-methyl-4,4,7- trioxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4λ^6- thia-1-azabicyclo[3.2.0]heptane-2-amido]-1,2- oxaborinan-6-yl] acetic acid **59**. ^{1}H NMR (CD_3OD) δ ppm 1.43 (s, 3H), 1.49-1.57 (m, 1H), 1.72-1.81 (m, 3H), 2.51-2.56 dd, *J*=15 Hz, *J*=6 Hz, 1H), 2.62-2.67 (dd, *J*=15 Hz, *J*=8 Hz, 1H), 2.80-2.84 (m, 1H), 3.41-3.44 (dd, *J*=17 Hz, *J*=2 Hz, 1H), 3.63-3.67 (dd, *J*=16 Hz, *J*=5 Hz, 1H), 4.37-4.44 (m, 1H), 4.61 (s, 1H), 4.90-4.94 (dd, *J*=5 Hz, *J*=2 Hz, 1H), 5.16-5.19 (d, *J*=15 Hz, 1H), 5.25-5.28 (d, *J*=15 Hz, 1H), 7.77 (s, 1H), 8.07 (s, 1H); ESIMS found for $C_{16}H_{22}BN_5O_8S$ *m/z* 438 $(M-H_2O)^+$.



60

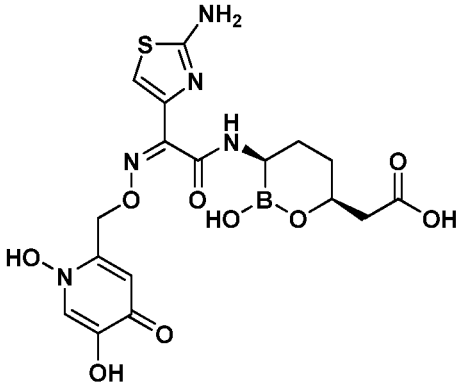
[0225] 2-((3R,6S)-2-hydroxy-3-(3-(5-phenyl-1,3,4-oxadiazol-2-yl)propanamido)-1,2-oxaborinan-6-yl)acetic acid **60**. ^{1}H NMR (CD_3OD) δ ppm 1.10-1.21 (m, 1H), 1.50-1.58 (dd, *J*=14 Hz, *J*=3 Hz, 1H), 1.59-1.68 (dt, *J*=11 Hz, *J*=5 Hz, 1H), 1.74-1.81 (brd, *J*=13 Hz, 1H), 2.22-2.26 (dd, *J*=15 Hz, *J*=6 Hz, 1H), 2.30-2.34 (dd, *J*=15 Hz, *J*=7 Hz, 1H), 2.63-2.64 (d, *J*=4 Hz, 1H), 3.01-3.12 (sex, *J*=7 Hz, 2H), 3.33-3.43 (sex, *J*=7 Hz, 2H), 4.03-4.09 (m, 1H), 7.54-7.62 (m, 3H), 8.03-8.05 (d, *J*=8 Hz, 2H); ESIMS found for $C_{17}H_{20}BN_3O_6$ *m/z* 356.1 $(M-H_2O)^+$.



61

[0226] 2-((3R,6S)-3-(2-(2-aminopyridin-4-yl)acetamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **61** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm

1.58-1.66 (m, 1H), 1.67-1.78 (m, 3H), 2.31-2.36 (dd, *J*=15 Hz, *J*=6 Hz, 1H), 2.39-2.44 (dd, *J*=15 Hz, *J*=7 Hz, 1H), 2.65-2.68 (t, *J*=4 Hz, 1H), 4.12-4.19 (m, 1H), 6.85-6.87 (d, *J=7* Hz, 1H), 6.99 (s, 1H), 7.81-7.82 (d, *J=7* Hz, 1H); ESIMS found for $C_{13}H_{18}BN_3O_5$ *m/z* 290.1 $(M\text{-}H_2O)^+$.

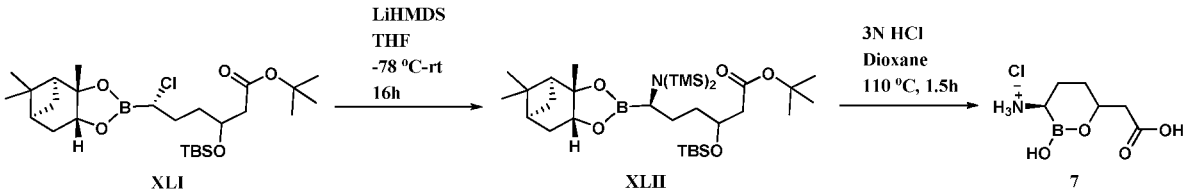


62

[0227] Following method E, the reaction mixture was evaporated in vacuo, azeotroped with MeCN (3 X 5 mL) and the residue was triturated with ether (5 mL). The precipitate was filtered, dissolved in dioxane-water mixture and freeze dried to get 2-((3R)-3-((Z)-2-(2-aminothiazol-4-yl)-2-((1,5-dihydroxy-4-oxo-1,4-dihydropyridin-2-yl) methoxyimino)acetamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **62** as the TFA (25 mg) salt as a fluffy solid. ESIMS found for $C_{17}H_{20}BN_5O_9S$ *m/z* 464.0 $(M\text{-}H_2O)^+$.

[0228] Synthesis of 2-((3R)-3-amino-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid hydrochloride **7**. An example synthesis of **7** is depicted in Scheme 10 and Example 2.

Scheme 10



Example 2

Step 1

[0229] 6-(tert-butoxy)-4-[(tert-butyldimethylsilyl)oxy]-1-chloro-6-oxo-1-[(2S,6R)-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.02,6]decan-4-yl]hexane **XLI** (515 mg, 0.97 mmol) in THF (5 mL) was cooled to -78°C under nitrogen. A solution of LiHMDS (1 mL, 1.0 M in THF, 1 mmol, 1.0 eq) was added slowly and the reaction flask

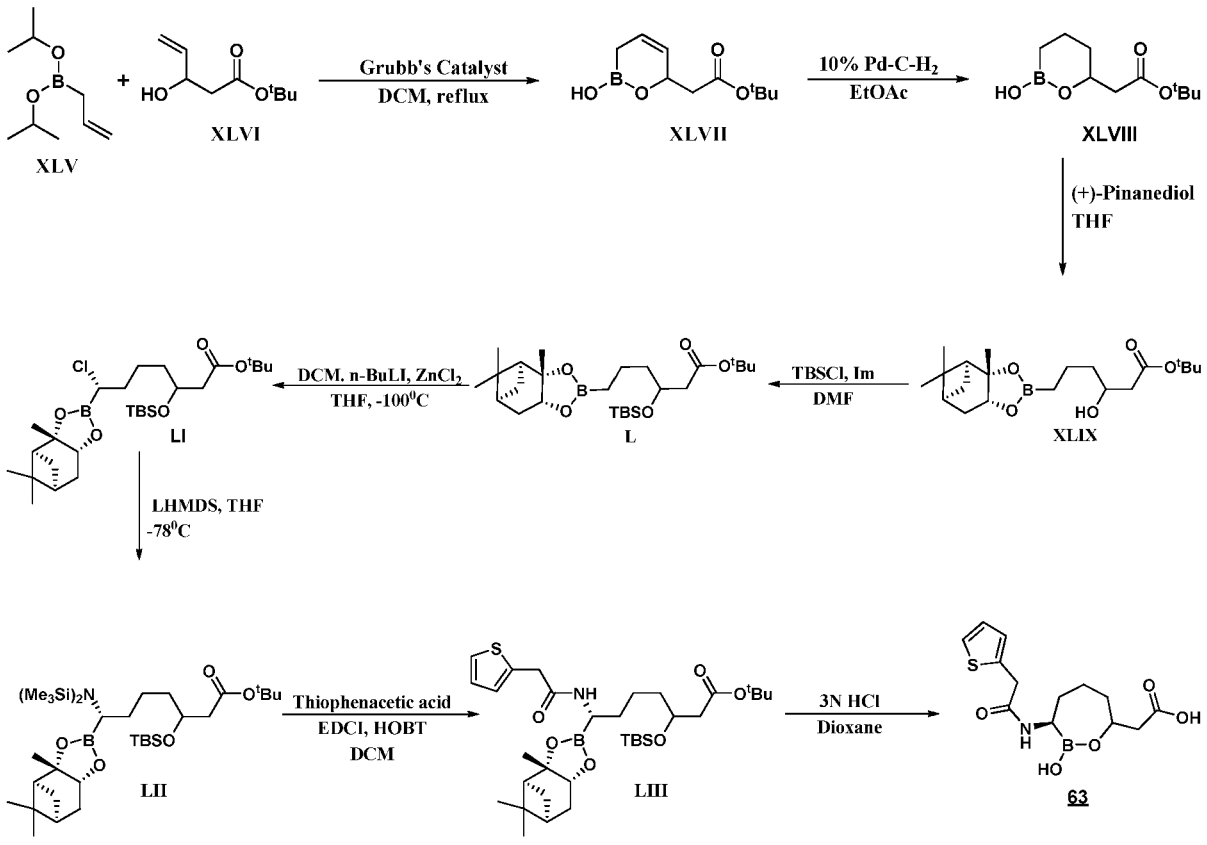
was then allowed to warm to room temperature where it was stirred for 16 h. The yellow solution was concentrated under reduced pressure to give an oil. After hexane (10 mL) was added to the oil, a precipitate formed. This was then filtered through Celite and the filtrate concentrated under reduced pressure to give 1-[bis(trimethylsilyl)amino]-6-(tert-butoxy)-4-[(tert-butyldimethylsilyl)oxy]-6-oxo-1-[(2S,6R)-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.02,6]decan-4-yl]hexyl **XLII**.

Step 2

[0230] The procedure is identical to that found in Example 1 method D. Compound **7** was isolated as a white powder (120 mg, 0.573 mmol, 59.1% yield). ^{1}H NMR (CD_3OD) δ ppm 1.43-1.66 (m, 1H), 1.66-1.79 (m, 1H), 1.79-1.97 (m, 1H), 1.97-2.30 (m, 1H), 2.40-2.71 (m, 3H), 4.34-4.54 (m, 1H); ESIMS found for $C_6H_{12}BNO_4$ *m/z* 174 (63%) (M+H).

[0231] Synthesis of 2-((3R)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-1,2-oxaborepan-7-yl)acetic acid **63**. An example synthesis of **63** is depicted in Scheme 11 and Example 3.

Scheme 11



Example 3

Step 1

[0232] To a solution of *tert*-butyl 3-hydroxypent-4-enoate, **XLVI** (674 mg, 3.92 mmol) in DCM (15 mL) was added diisopropylallylboronate **XLV**(2 g, 11.76 mmol) via syringe. To the mixture was then added Grubbs' first generation catalyst (260 mg, 0.31 mmol, 7.5 mol%) and the vessel was purged with argon. The reaction was heated at 65 °C under nitrogen for 18h. The mixture was concentrated under vacuum and the residue was purified by flash column chromatography (100% hexane→30% EtOAc/hexane) to afford *tert*-butyl 2-(2-hydroxy-3,6-dihydro-2H-1,2-oxaborinin-6-yl)acetate **XLVII** (770 mg, 3.63 mmol, 92.7% yield).

Step 2

[0233] To a solution of *tert*-butyl 2-(2-hydroxy-3,6-dihydro-2H-1,2-oxaborinin-6-yl)acetate **XLVII** (670 mg, 3.16 mmol) in EtOAc (45 mL) was added 10% Pd/C (135 mg). The vessel was evacuated by applying vacuum and flushed with hydrogen gas. The reaction was stirred under hydrogen for 2 h. The mixture was filtered through a Celite pad and which was washed with additional EtOAc (15 mL). Concentration of the filtrate gave pure *tert*-butyl 2-(2-hydroxy-1,2-oxaborinan-6-yl)acetate **XLVIII** (641 mg, 3.00 mmol, 94.8% yield).

Step 3

[0234] To a solution of *tert*-butyl 2-(2-hydroxy-1,2-oxaborinan-6-yl)acetate **XLVIII** (641 mg, 3.00 mmol) in THF (20 mL) was added (1 S,2S,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptane-2,3-diol (509 mg, 3 mol) at room temperature. The reaction mixture was stirred for 16 h and concentrated under vacuum. The residue was purified by column chromatography (100% hexane→40% EtOAc/hexane) on silica gel to give *tert*-butyl 3-hydroxy-6-[(1R,2R,6S,8R)-6,9,9- trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.$0^{2,6}$]decan-4-yl]hexanoate **XLIX** (790 mg, 2.16 mmol, 71.9% yield).

Step 4

[0235] To a solution of alcohol **XLIX** (790 mg, 2.16 mmol) in DMF (7.5 mL) was added imidazole (548 mg, 8.06 mmol) followed by TBDMSCl (580 mg, 3.87 mol). The reaction mixture was stirred at room temperature for 16 h and concentrated under vacuum. The white slurry was dissolved in 100 mL of EtOAc and washed with saturated

$NaHCO_3$ solution (20 mL), water (2 X 10 mL) and dried (Na_2SO_4). The organic extract was concentrated under vacuum and the residue was purified by column chromatography (100% hexane→30% EtOAc/hexane) on silica gel to give *tert*-butyl 3-[(*tert*-butyldimethylsilyl)oxy]-6- [(1R,2R,6S,8R)-6,9,9-trimethyl-3,5-dioxa-4- boratricyclo [6.1.1.$0^{2,6}$]decan-4-yl]hexanoate **L** (1 g, 2.08 mmol, 96.3% yield).

Step 5

[0236] To a solution of DCM (0.26 mL, 4.16 mmol) in THF (5 mL) at -100°C was added 2.5 M *n*-butyl lithium in hexane (1 mL, 2.5 mmol) slowly under nitrogen and down the inside wall of the flask whilst maintaining the temperature below -90°C. The resulting white precipitate was stirred for 30 minutes before the addition of **L** (1 g, 2.08 mmol) in THF (3 mL) at -90°C. Zinc chloride (5 mL, 0.5 M in THF, 2.5 mmol) was then added to the reaction mixture at -90°C and then the reaction was allowed to warm to room temperature where it was stirred for 16 h. The reaction was quenched with a saturated solution of ammonium chloride and the phases were separated. The aqueous phase was then extracted with diethyl ether (2 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The concentrated material was then chromatographed (100% hexane→20% EtOAc-hexane) to obtain *tert*-butyl (7S)-3-[(*tert*-butyldimethylsilyl)oxy]-7- chloro-7-[(1R,2R,6S,8R)-6,9,9-trimethyl-3,5-dioxa-4- boratricyclo[6.1.1.$0^{2,6}$]decan-4-yl]heptanoate **LI** (740 mg, 1.40 mmol, 67.2% yield).

Step 6

[0237] Chloro intermediate **LI** (727 mg, 1.37 mmol) in THF (7 mL) was cooled to -78°C under nitrogen. A solution of 1M LiHMDS solution in THF (1.37 mL, 1.37 mmol) was added slowly at -78°C. Upon completion of the addition, the reaction flask was allowed to warm to room temperature. After stirring at room temperature for 16 h, the reaction mixture was concentrated under vacuum and hexane (20 mL) was added. The precipitated lithium salts were filtered off through a Celite pad, rinsed with additional hexane and the combined filtrates were concentrated under vacuum to give crude *tert*-butyl (7S)-7-[bis(trimethylsilyl)amino]-3- [(*tert*-butyldimethylsilyl)oxy]-7-[(1R,2R,6S,8R)- 6,9,9-trimethyl-3,5-dioxa-4- boratricyclo[6.1.1.$0^{2,6}$]decan-4-yl]heptanoate **LII**.

Step 7

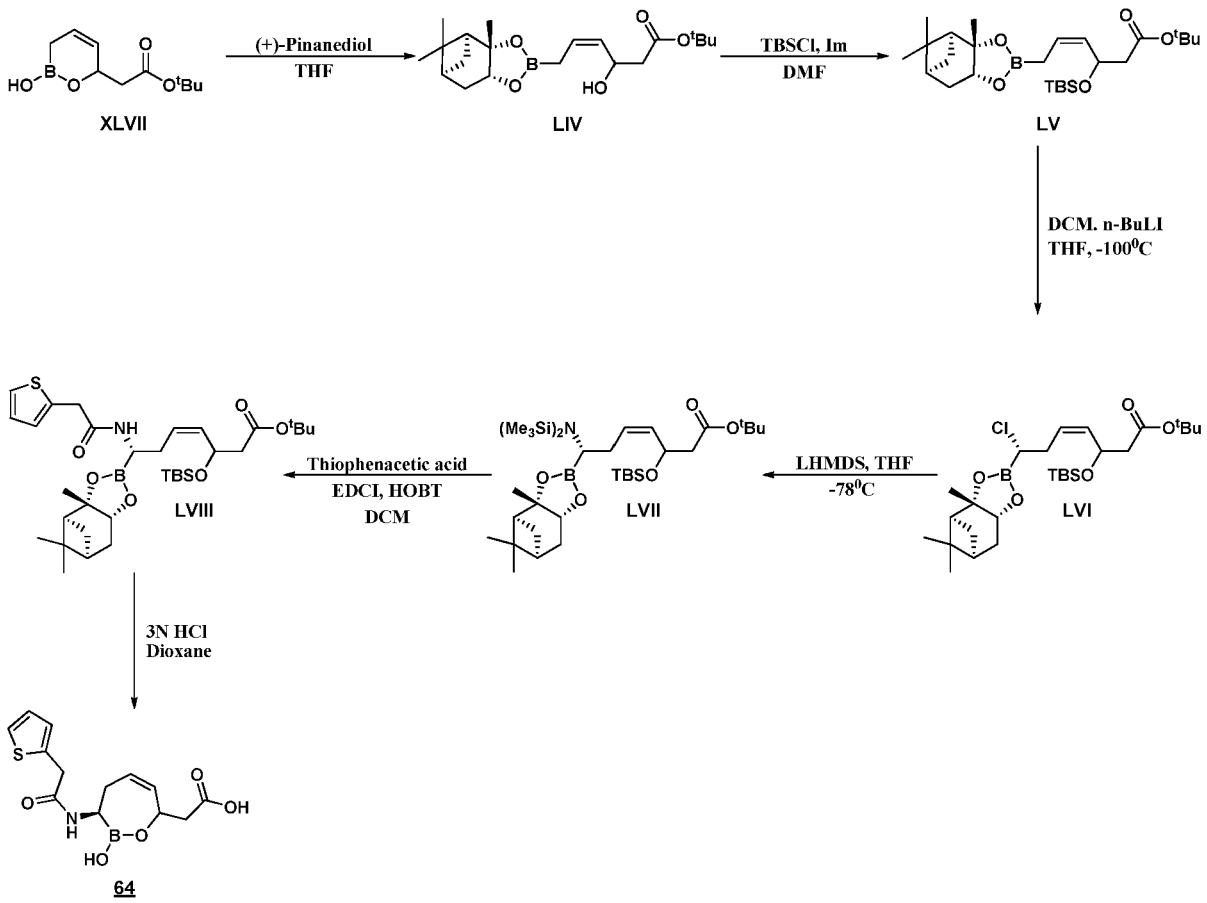
[0238] To a stirred solution of 2-thiophenacetic acid (232 mg, 1.64 mmol) in DCM (45 mL) at 0°C under nitrogen was added EDCI (391 mg, 2.05 mmol) and HOBT (221 mg, 1.64 mmol). After stirring at 0°C for 30 minutes, a solution of the bis-silyl amide **LII** intermediate (1.37 mmol) in DCM (10 mL) followed by *N*-methyl-morpholine (0.3 mL, 2.74 mmol) were sequentially added at 0°C. Upon completion of the addition, the reaction flask was allowed to warm to room temperature. After stirring at room temperature overnight, the reaction mixture was washed with water, dried and concentrated under vacuum. The residue was purified by column chromatography (100% DCM→50% EtOAc/DCM) to afford *tert*-butyl (7S)-3-[(*tert*-butyldimethylsilyl)oxy]-7-[2-(thiophen-2-yl)acetamido]-7-[(1R,2R,6S,8R)-6,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.$0^{2,6}$]decan-4-yl]heptanoate **LIII** (340 mg, 0.54 mmol, 39.4% yield for 2 steps).

Step 8

[0239] To a solution of amide **LIII** (300 mg, 0.47 mmol) in 1,4-dioxane (9 mL) was added 9 mL of 3 N HCl. The reaction mixture was heated at reflux for 90 minutes. The cooled reaction mixture was then diluted with water (10 mL) and extracted with diethyl ether (2 x 10 mL). The aqueous layer was concentrated to afford a sticky solid which was azeotroped with MeCN (3 X 10 mL). The residue was dissolved in 40% dioxane-water and lyophilized to afford 2-((3R)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-1,2-oxaborepan-7-yl)acetic acid **63** as an off-white solid (100 mg, 32.1 mmol, 68.4% yield). ^{1}H NMR (CD_3OD) δ ppm 1.21-1.38 (m, 2H), 1.42-1.60 (m, 2H), 1.60-1.72 (m, 1H), 1.80-1.94 (m, 1H), 2.32-2.47 (m, 2H), 2.54-2.58 (dd, *J*=15 Hz, *J*=6 Hz, 1H), 3.97-3.98 (d, *J*=8 Hz, 1H), 4.05 (s, 2H), 6.97-7.01 (m, 1H), 7.02-7.10 (m, 1H), 7.33-7.37 (m, 1H); ESIMS found for $C_{13}H_{18}BNO_5S$ *m/z* 294.0 $(M\text{-}H_2O)^+$.

[0240] Synthesis of 2-((3R)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-2,3,4,7-tetrahydro-1,2-oxaborepin-7-yl)acetic acid **64**. An example synthesis of **64** is depicted in Scheme 12 and Example 4.

Scheme 12



Example 4

Step 1

[0241] To a stirred solution of *tert*-butyl 2-(2-hydroxy-3,6-dihydro-2H-1,2-oxaborinin-6-yl)acetate **XLVII** (770 mg, 4.58 mmol) in THF (25 mL) was added (1 S,2S,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptane-2,3-diol (980 mg, 4.58 mmol) at room temperature. The reaction mixture was stirred for 16 h and concentrated under vacuum. The residue was purified by column chromatography (100% hexane→30% EtOAc/hexane) on silica gel to give *tert*-butyl (4Z)-3-hydroxy-6-[(1R,2R,6S,8R)-6,9,9-trimethyl-3,5-dioxa-4- boratricyclo[6.1.1.$0^{2,6}$]decan-4-yl]hex-4-enoate **LIV** (1 g, 2.75 mmol, 59.9% yield).

Step 2

[0242] To a solution of alcohol **LIV** (650 mg, 1.78 mmol) in DMF (10 mL) was added imidazole (484 mg, 7.12 mmol) followed by TBDMSCl (534 mg, 3.56 mol). The reaction mixture was stirred at room temperature for 16 h and concentrated under

vacuum. The white slurry was dissolved in 100 mL of EtOAc and washed with water (2 X 10 mL), brine and dried (Na_2SO_4). The organic extract was concentrated under vacuum and the residue was purified by column chromatography (100% hexane→20% EtOAc/hexane) on silica gel to give *tert*-butyl (4Z)-3-[(*tert*-butyldimethylsilyl)oxy]-6-[(1R,2R,6S,8R)-6,9,9-trimethyl-3,5-dioxa-4- boratricyclo[6.1.1.$0^{2,6}$]decan-4-yl]hex-4-enoate **LV** (800 mg, 1.67 mmol, 93.9% yield).

Step 3

[0243] To a solution of DCM (0.3 mL, 4.68 mmol) in THF (8 mL) at -100°C was added 2.5 M *n*-butyl lithium in hexane (1.12 mL, 2.8 mmol) slowly under nitrogen and down the inside wall of the flask whilst maintaining the temperature below -90°C. The resulting white precipitate was stirred for 30 minutes before the addition of **LV** (1.12 g, 2.34 mmol) in THF (3 mL) at -90°C and the reaction was allowed to warm to room temperature where it was stirred for 16 h. The reaction was quenched with a saturated solution of ammonium chloride and the phases were separated. The aqueous phase was then extracted with diethyl ether (2 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The concentrated material was then chromatographed (100% hexane→20% EtOAc/hexane) to obtain *tert*-butyl (4Z,7S)-3-[(*tert*- butyldimethylsilyl)oxy]-7-chloro-7-[(1R,2R,6S,8R)- 6,9,9-trimethyl-3,5-dioxa-4- boratricyclo[6.1.1.$0^{2,6}$]decan-4-yl]hept-4- enoate **LVI** (820 mg, 1.56 mmol, 66.5% yield).

Step 4

[0244] Chloro intermediate **LVI** (790 mg, 1.49 mmol) in THF (10 mL) was cooled to -78°C under nitrogen. A solution of 1M LiHMDS solution in THF (1.5 mL, 1.5 mmol) was added slowly at -78°C. Upon completion of the addition, the reaction flask was allowed to warm to room temperature. After stirring at room temperature for 16 h, the reaction mixture was concentrated under vacuum and hexane (20 mL) was added. The precipitated lithium salts were filtered off through a Celite pad, rinsed with additional hexane and the combined filtrates were concentrated under vacuum to give crude *tert*-butyl (4Z,7S)-7-[bis(trimethylsilyl)amino]-3- [(*tert*-butyldimethylsilyl)oxy]-7-[(1R,2R,6S,8R)- 6,9,9-trimethyl-3,5-dioxa-4- boratricyclo[6.1.1.$0^{2,6}$]decan-4-yl]hept-4-enoate **LVII**.

Step 5

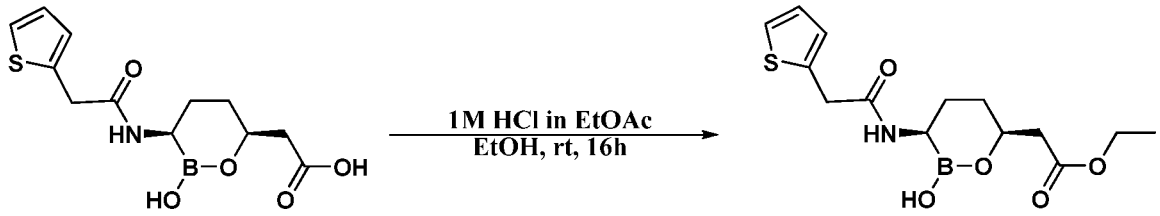
[0245] To a stirred solution of 2-thiophenacetic acid (252 mg, 1.78 mmol) in DCM (35 mL) at 0°C under nitrogen was added EDCI (426 mg, 2.23 mmol) and HOBT (240 mg, 1.78 mmol). After stirring at 0 °C for 30 minutes, a solution of the crude bis-silyl amide **LVII** intermediate in DCM (10 mL) followed by *N*-methyl-morpholine (0.32 mL, 3 mmol) were sequentially added at 0°C. Upon completion of the addition, the reaction flask was allowed to warm to room temperature. After stirring at room temperature overnight, the reaction mixture was washed with water, dried and concentrated under vacuum. The residue was purified by column chromatography (100% DCM→25% EtOAc/DCM) to afford *tert*-butyl (4Z,7S)-3-[(*tert*- butyldimethylsilyl)oxy]-7-[2-(thiophen-2- yl)acetamido]-7-[(1R,2R,6S,8R)-6,9,9-trimethyl-3,5- dioxa-4-boratricyclo[6.1.1.$0^{2,6}$]decan-4-yl]hept-4- enoate **LVIII** (600 mg, 0.95 mmol, 63.7% yield for 2 steps).

Step 6

[0246] A solution of amide **LVIII** (100 mg, 0.15 mmol) in anisole (5 mL) at 0^0C was treated with pre-cooled 90% aq trifluoroacetic acid (10 mL). The reaction mixture was warmed to room temperature and stirred for 16 h. The mixture was evaporated in vacuo, azeotroped with MeCN (3 X 5 mL). The residue was sonicated in water (10 mL) and ether (10 mL). The aqueous phase was separated, washed with ether (2 X 5 mL) and freeze dried to give fluffy solid 2-((3R)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-2,3,4,7-tetrahydro-1,2-oxaborepin-7-yl)acetic acid **64** (15 mg, 0.05 mmol, 32.3% yield). ^{1}H NMR (CD_3OD) δ ppm 2.23-2.35 (m, 2H), 2.40-2.61 (m, 2H), 2.76-2.83 (m, 1H), 3.96-4.03 (m, 1H), 4.10 (s, 2H), 5.34-5.40 (m, 1 H), 5.53-5.74 (m, 1H), 6.97-7.08 (m, 2H), 7.32-7.39 (m, 1H); ESIMS found for $C_{13}H_{16}BNO_5S$ *m/z* 292 $(M\text{-}H_2O)^+$.

[0247] Synthesis of ethyl 2-((3R,6S)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-1,2-oxaborinan-6-yl)acetate **65**. An example synthesis of **65** is depicted in Scheme 13 and Example 5.

Scheme 13



5 65

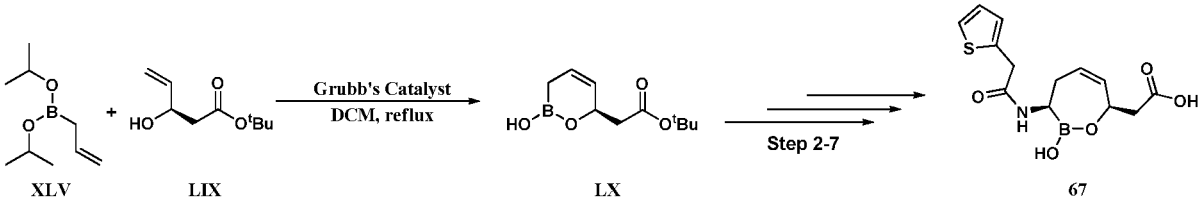
Example 5

Step 1

[0248] To a solution of **5** (400 mg, 1.35 mmol) in 4 mL of absolute ethanol was added anhydrous 1M HCl in EtOAc (4 mL, 4 mmol). The reaction was stirred at room temperature for 16 h. The mixture was then concentrated and azeotroped with acetonitrile (3 X 10 mL) to give a sticky solid. Ether (10 mL) was added to the azeotroped sticky solid and the resulting precipitate was filtered. The filtered solid was rinsed with additional ether (5 mL) and dried to give ethyl 2-((3R,6S)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-1,2-oxaborinan-6-yl)acetate **65** (300 mg, 0.92 mmol, 68.5% yield). ^{1}H NMR (CD_3OD) δ ppm 0.98-1.09 (q, *J*=14 Hz, 1H), 1.23-1.26 (t, *J*=7 Hz, 3H), 1.49-1.54 (dd, *J*=14 Hz, *J*=3 Hz, 1H), 1.57-1.64 (dt, *J*=11 Hz, *J*=2 Hz, 1H), 1.72-1.78 (brd, *J*=14 Hz, 1H), 2.24-2.28 (dd, *J*=15 Hz, *J*=6 Hz, 1H), 2.34-2.39 (dd, *J*=15 Hz, *J*=8 Hz, 1H), 2.63 (brs, 1H), 3.99 (s, 2H), 4.07-4.13 (q, *J*=4 Hz, 3H), 6.99-7.01 (t, *J*=4 Hz, 1H), 7.05-7.06 (d, *J*=3 Hz, 1H), 7.35-7.36 (dd, *J*=5 Hz, *J*=1.3 Hz, 1H); ESIMS found for $C_{14}H_{20}BNO_5S$ *m/z* 308.1 $(M\text{-}H_2O)^+$.

[0249] Synthesis of 2-((3R,7R)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-2,3,4,7-tetrahydro-1,2-oxaborepin-7-yl)acetic acid **67**. An example synthesis of **67** is depicted in Scheme 14 and Example 6.

Scheme 14



Example 6

Step 1

[0250] Prepared starting from enantiomerically pure (*R*)-*tert*-butyl 3-hydroxypent-4-enoate [*J. Am. Chem. Soc.* (**2007**), *129*, 4175-4177] in accordance with the procedure described in the above Step 1 of Example 3

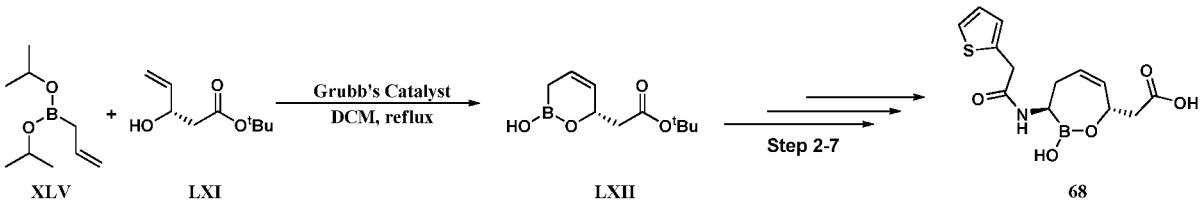
Steps 2-7

[0251] Prepared in accordance with the procedure described in the above Steps 1-6 of Example 4.

[0252] White fluffy solid (23 mg, 0.074 mmol, 47% yield). ^{1}H NMR (CD_3OD) δ ppm 2.29-2.31 (m, 1H), 2.40-2.68 (m, 4H), 4.10 (m, 2H), 4.74-4.82 (m, 1H), 5.35-5.38 (m, 1H), 5.53-5.58 (m, 1H), 6.98-7.05 (m, 2H), 7.32-7.36 (m, 1H); ESIMS found for $C_{13}H_{16}BNO_5S$ *m/z* 292 $(M\text{-}H_2O)^+$.

[0253] Synthesis of 2-((3R,7S)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-2,3,4,7-tetrahydro-1,2-oxaborepin-7-yl)acetic acid **68**. An example synthesis of **68** is depicted in Scheme 15 and Example 7.

Scheme 15



Example 7

Step 1

[0254] Prepared starting from enantiomerically pure (*S*)-*tert*-butyl 3-hydroxypent-4-enoate [*J. Med. Chem.*, (**2010**), *53*, 4654–4667] in accordance with the procedure described in the above Step 1 of Example 3

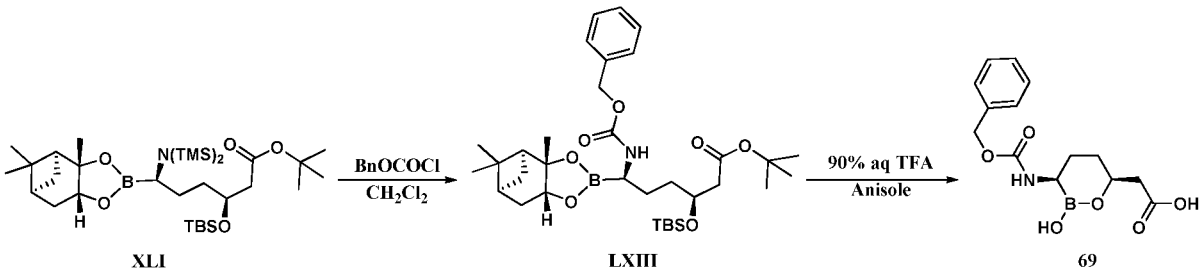
Steps 2-7

[0255] Prepared in accordance with the procedure described in the above Steps 1-6 of Example 4.

[0256] White fluffy solid (45 mg, 0.146 mmol, 39% yield). ^{1}H NMR (CD_3OD) δ ppm 2.15-2.18 (m, 1H), 2.29-2.38 (m, 2H), 2.66-2.72 (m, 2H), 3.88-3.91 (m, 1H) 4.00 (s, 2H), 5.24-5.27 (m, 1 H), 5.57-5.63 (m, 1H), 6.87-6.96 (m, 2H), 7.24-7.28 (m, 1H); ESIMS found for $C_{13}H_{16}BNO_5S$ *m/z* 292 $(M\text{-}H_2O)^+$.

[0257] Synthesis of 2-((3R,6S)-3-(benzyloxycarbonylamino)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **69**. An example synthesis of **69** is depicted in Scheme 16 and Example 8.

Scheme 16



XLI LXIII 69

Example 8

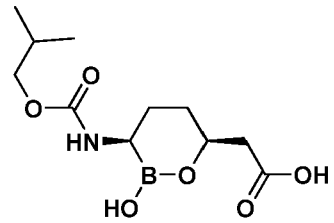
Step 1

[0258] A solution of bis-silyl amide **XLI** (0.2 mmol) in DCM (5 mL) was cooled to 0°C and benzyl chloroformate (0.056 mL, 0.4 mmol) was added. Then, the cooling bath was removed and the solution stirred at ambient temperature for 16 h. The reaction was quenched with water and extracted twice with EtOAc. The organic layers were combined, washed with water, brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow oil as crude product. The residue was chromatographed on a silica column (100% DCM→40% EtOAc/DCM) to afford carbamate **LXIII** (90 mg, 0.143 mmol, 71.5% yield).

Step 2

[0259] A solution of carbamate **LXIII** (70 mg, 0.11 mmol) in anisole (5 mL) at 0°C was treated with pre-cooled 90% aq trifluoroacetic acid (10 mL). The reaction mixture was warmed to room temperature and stirred for 16 h. The mixture was evaporated in vacuo, azeotroped with MeCN (3 X 5 mL). The residue was sonicated in water (10 mL) and ether (10 mL). The aqueous phase was separated, washed with ether (2 X 5 mL) and freeze dried to give 2-((3*R*,6*S*)-3-(benzyloxycarbonylamino)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **69** as a fluffy solid (10 mg, 0.033 mmol, 29.6% yield). ESIMS found for $C_{14}H_{18}BNO_6S$ *m/z* 289.9 $(M-H_2O)^+$.

[0260] The following compound is prepared in accordance with the procedure described in the above Example 8.

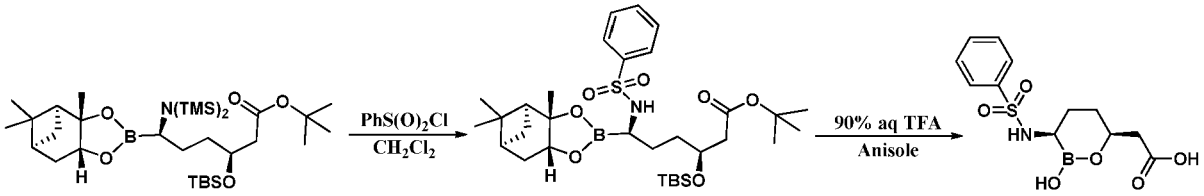


70

[0261] 2-((3R,6S)-2-hydroxy-3-(isobutoxycarbonylamino)-1,2-oxaborinan-6-yl)acetic acid **70** as a off-white solid (20 mg, 0.073 mmol, 27% yield). ^{1}H NMR (CD_3OD) δ ppm 0.95 (d, *J*=7 Hz, 6H), 1.62-1.67 (m, 1H), 1.70-1.75 (m, 2H), 1.87-1.90 (m, 2H), 2.42-2.60 (m, 3H), 3.77-3.86 (m, 2H), 4.35-4.38 (m, 1H); ESIMS found for $C_{11}H_{20}BNO_6S$ *m/z* 256 $(M-H_2O)^+$.

[0262] Synthesis of 2-((3R,6S)-2-hydroxy-3-(phenylsulfonamido)-1,2-oxaborinan-6-yl)acetic acid **71**. An example synthesis of **71** is depicted in Scheme 17 and Example 9.

Scheme 17



XLI LXIV 71

Example 9

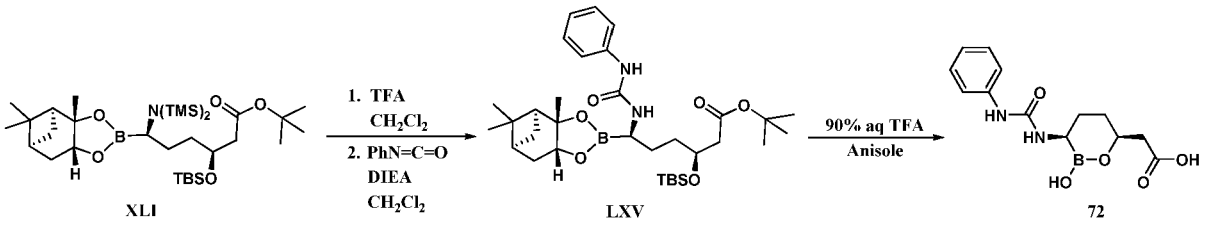
Step 1-2

[0263] Prepared in accordance with the procedure described in the above Steps 1-2 of Example 8.

[0264] Off-white solid (30 mg, 0.096 mmol, 43% yield). ^{1}H NMR (CD_3OD) δ ppm 1.57-1.83 (series of m, 4 H), 2.49-2.71 (series of m, 3H), 4.35-4.89 (m, 1H), 7.51-7.59 (m, 3H), 7.85-7.89 (m, 2H); ESIMS found for $C_{12}H_{16}BNO_6S$ *m/z* 296.1 $(M-H_2O)^+$.

[0265] Synthesis of 2-((3R,6S)-2-hydroxy-3-(3-phenylureido)-1,2-oxaborinan-6-yl)acetic acid **72**. An example synthesis of **72** is depicted in Scheme 18 and Example 10.

Scheme 18



Example 10

Step 1

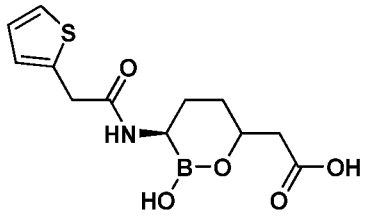
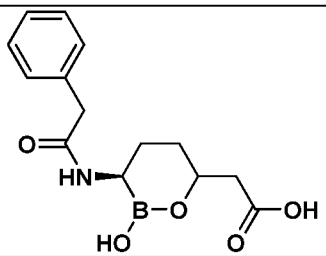
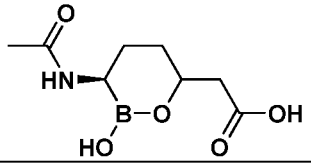
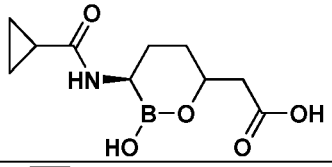
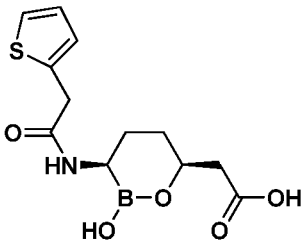
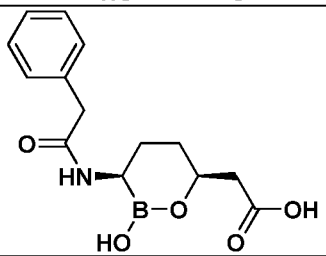
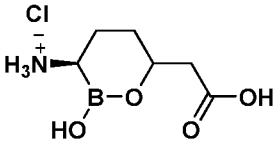
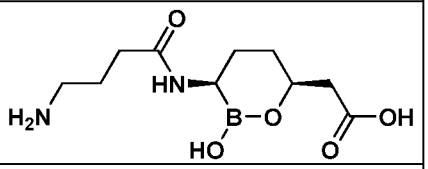
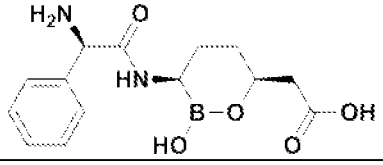
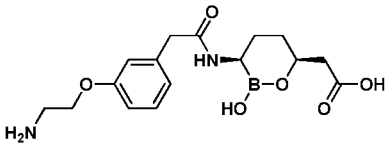
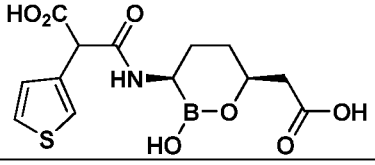
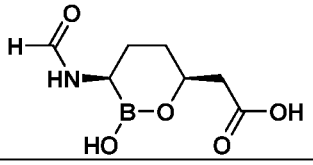
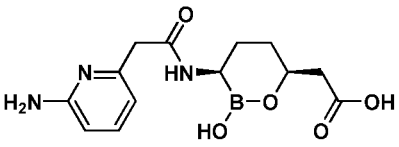
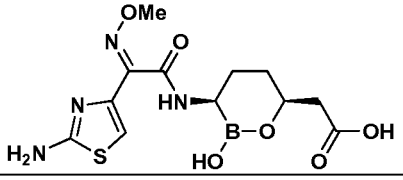
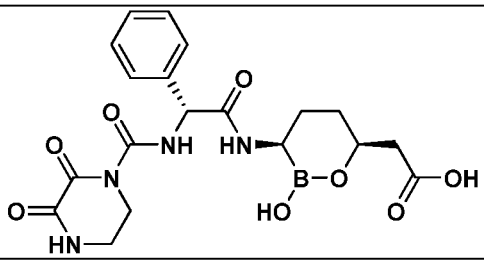
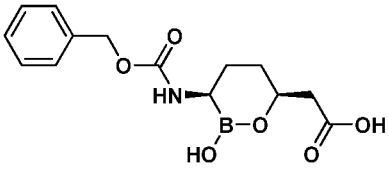
[0266] To a solution of bis-silyl amide **XLI** (0.2 mmol) in DCM (5 mL) at 0°C was added a solution of TFA in hexane (0.6 mmol). The reaction was stirred at 0°C for 20 min before adding phenyl isocayanate (0.04 mL, 0.4 mmol) followed by N,N-diisopropylethylamine (0.18 mL, 1 mmol). The cooling bath was then removed and the solution was stirred at ambient temperature for 16 h. The reaction was quenched with water and extracted twice with EtOAc. The organic layers were combined, washed with water, brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow oil as crude product. The residue was chromatographed on a silica column (100% DCM→25% EtOAc/DCM) to afford the pure urea (50 mg, 0.081 mmol, 40.7% yield).

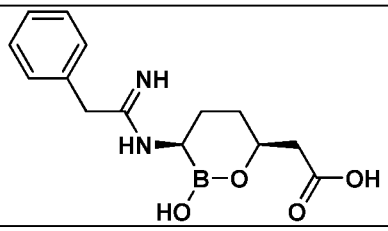
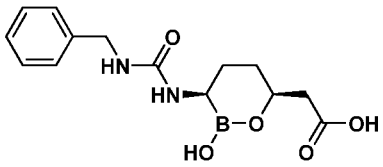
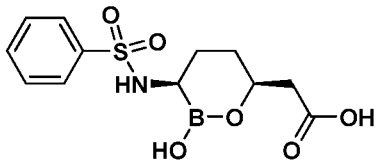
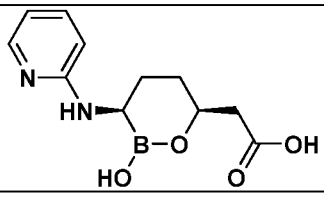
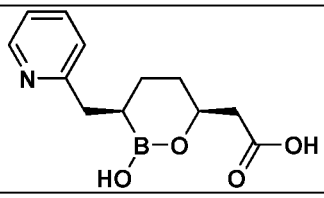
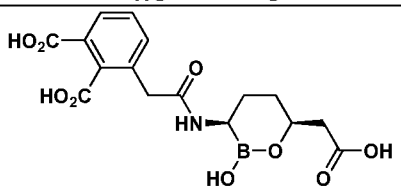
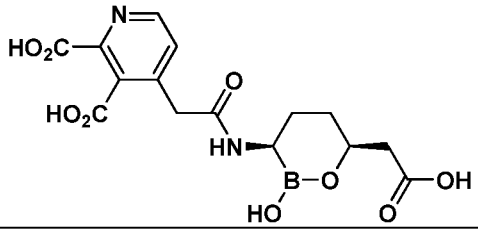
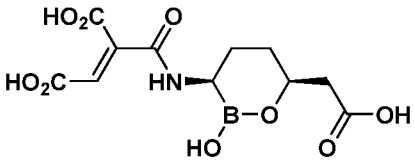
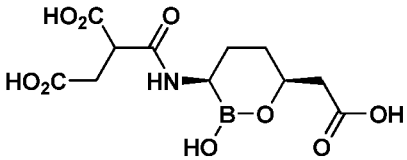
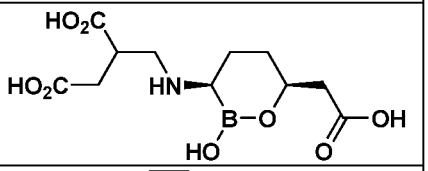
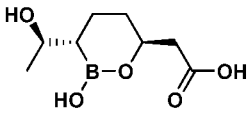
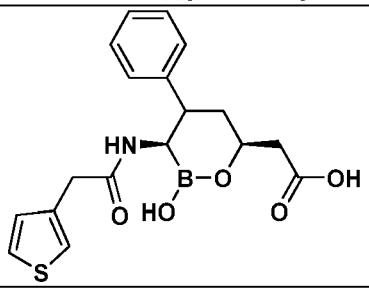
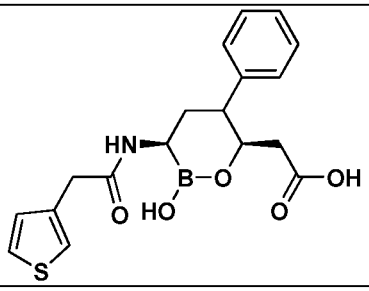
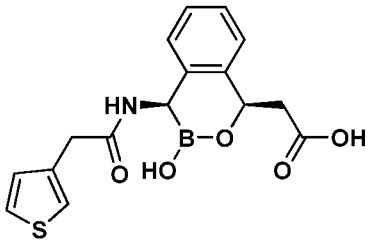
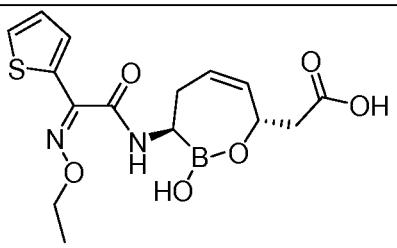
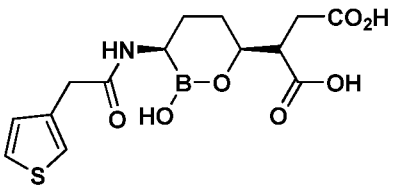
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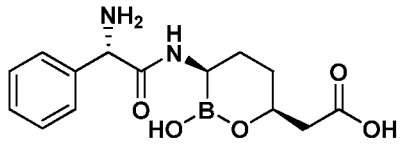
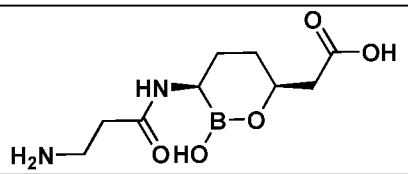
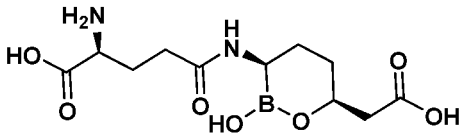
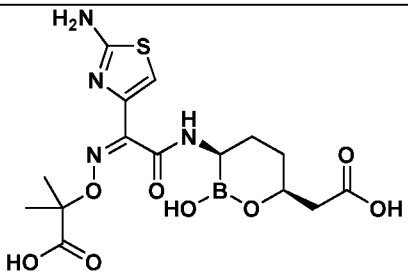
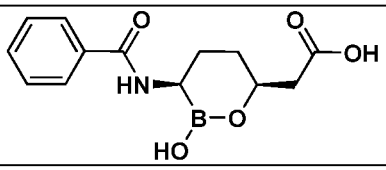
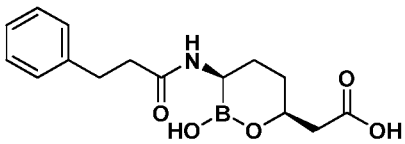
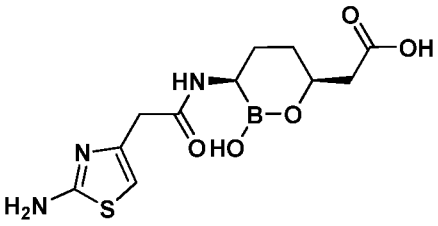
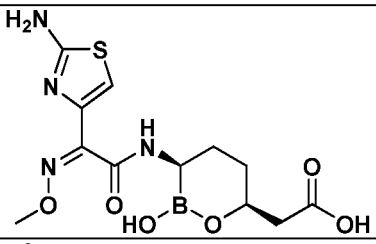
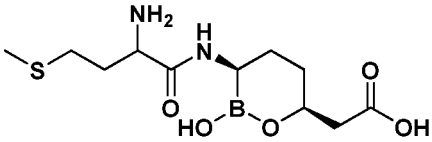
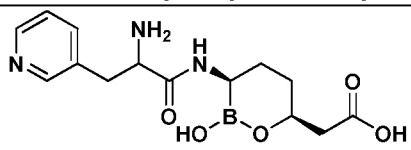
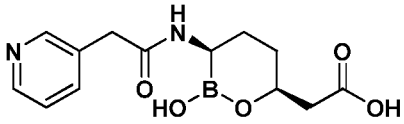
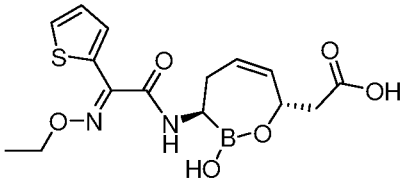
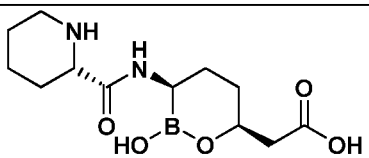
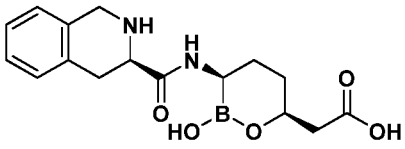
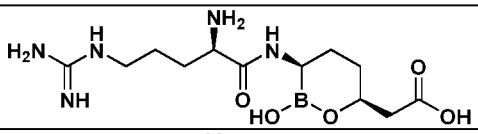
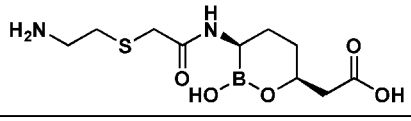
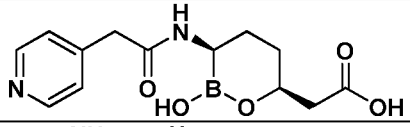
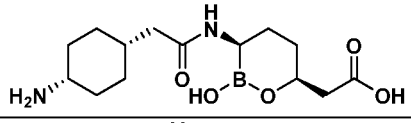
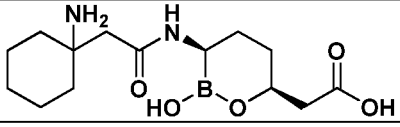
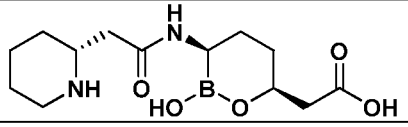
[0267] Deprotection was performed following the procedure described above in step 2 of example 8 to give 2-((3*R*,6*S*)-2-hydroxy-3-(3-phenylureido)-1,2-oxaborinan-6-yl)acetic acid **72** as a white solid (20 mg, 0.068 mmol, 86% yield). ^{1}H NMR (CD_3OD) δ ppm 1.24-1.31 (m, 1H), 1.56-1.64 (m, 2H) 1.78-1.81 (m, 1H), 2.36-2.40 (dd, *J*=15 Hz, *J*=6 Hz, 1H), 2.46-2.58 (dd, *J*=13 Hz, *J*=7 Hz, 1H), 2.68-2.71 (m, 1H), 4.07-4.12 (m, 1H), 7.15-7.18 (m, 1H), 7.34-7.37 (m, 4H); ESIMS found for $C_{13}H_{17}BN_2O_5$ *m/z* 275.1 $(M-H_2O)^+$.

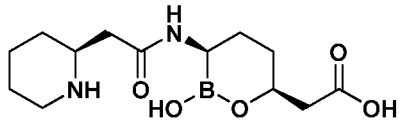
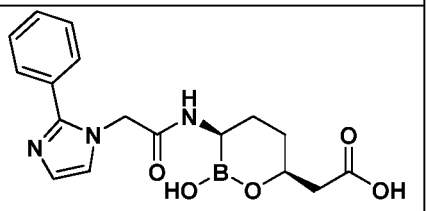
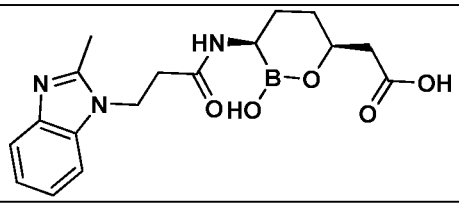
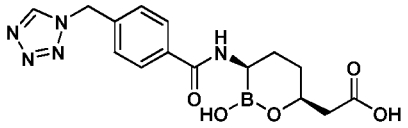
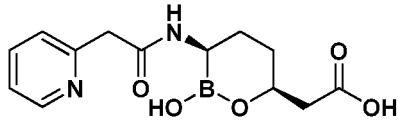
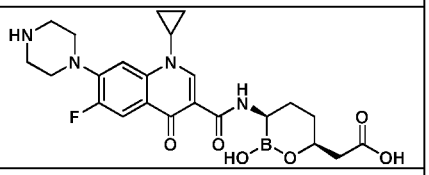
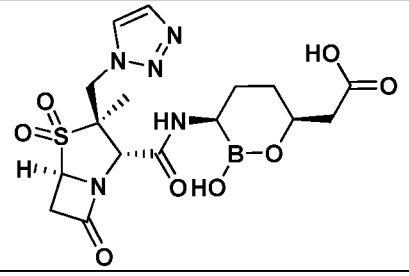
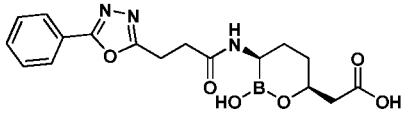
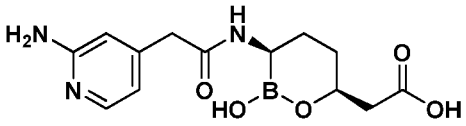
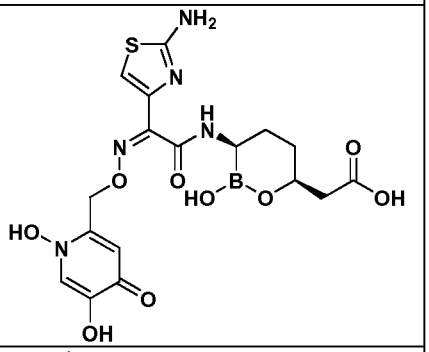
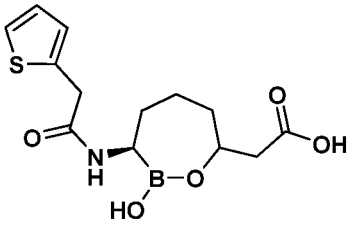
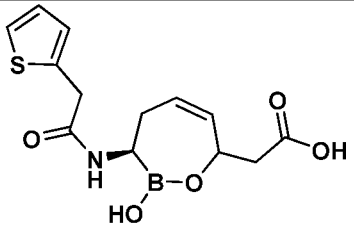
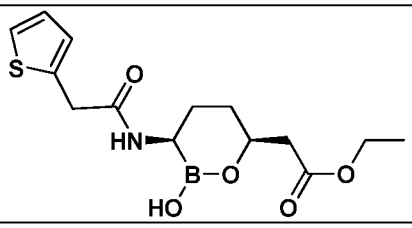
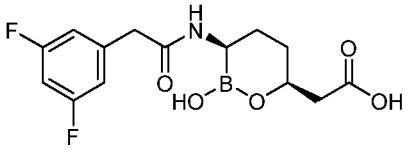
[0268] Illustrative compounds of Formula (I) are shown in Table 1. Some structures are shown with defined configurations at selected stereocenters but the shown stereochemistries are not meant to be limiting and all possible stereoisomers of the shown structures are to be considered encompassed herein. Compounds of any absolute and relative configurations at the stereocenters as well as mixtures of enantiomers and diastereoisomers of any given structure are also encompassed herein.

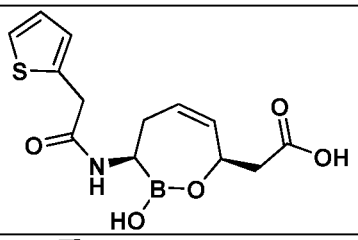
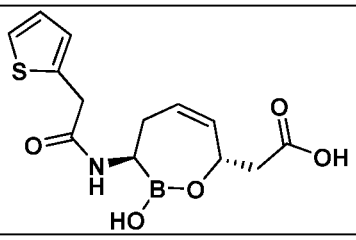
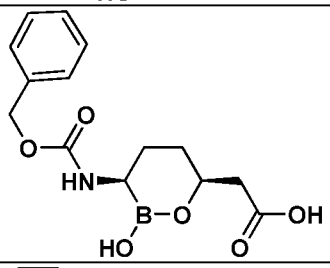
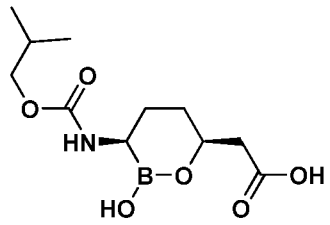
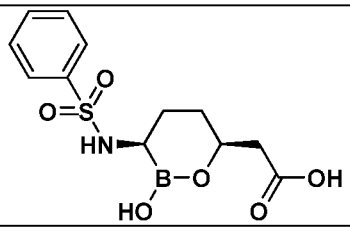
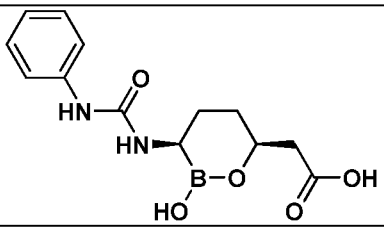
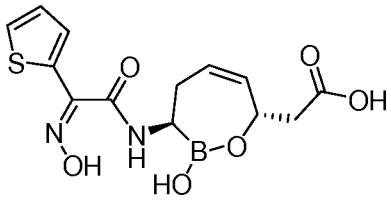
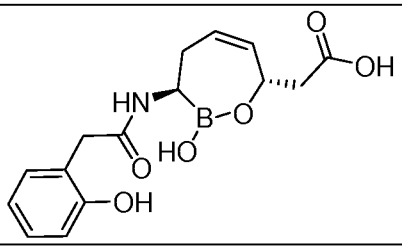
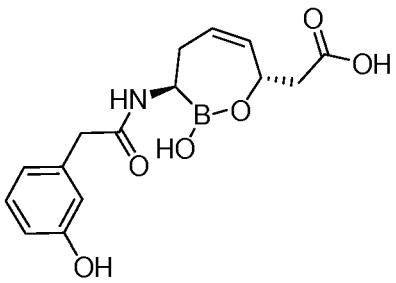
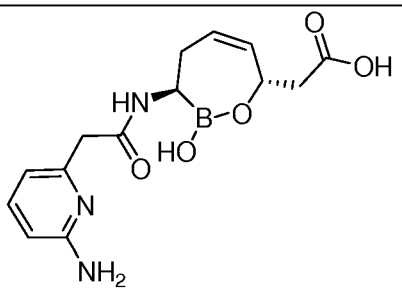
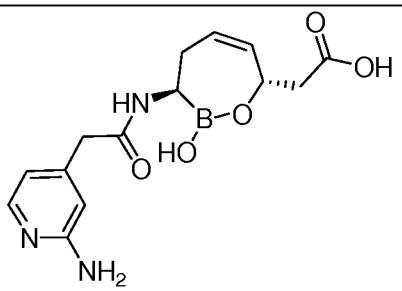
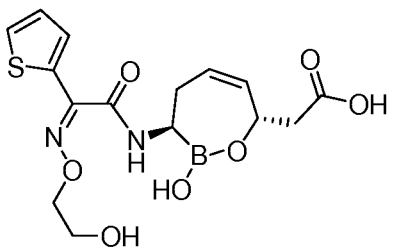
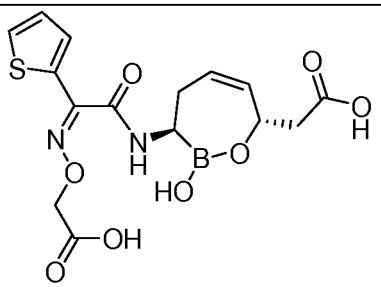
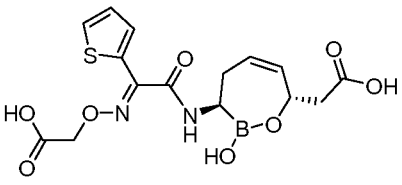
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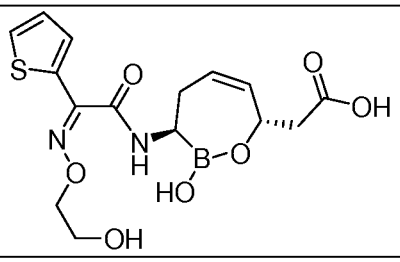
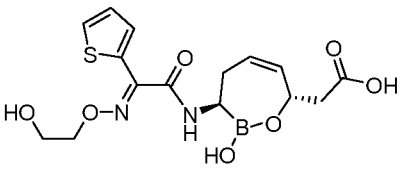
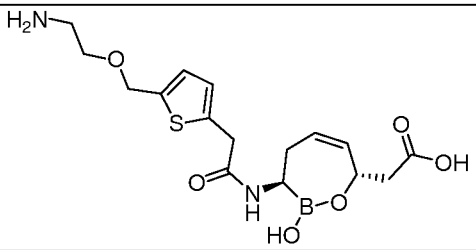
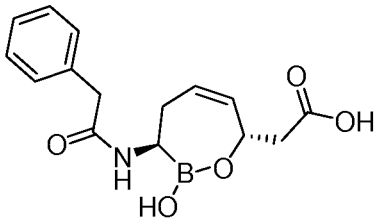
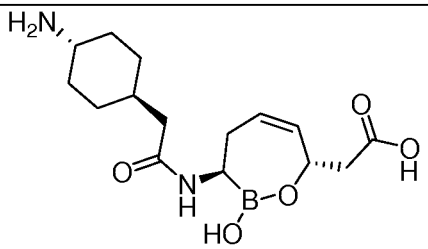
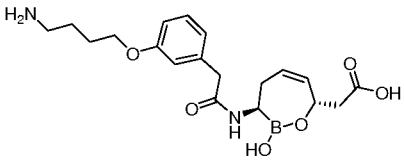
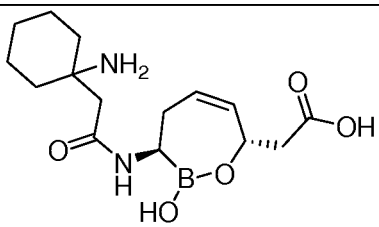
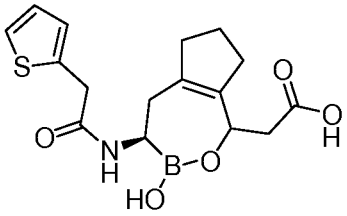
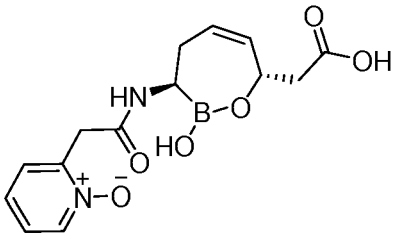
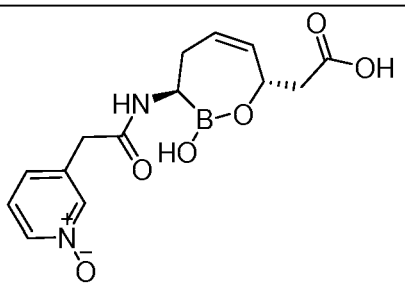
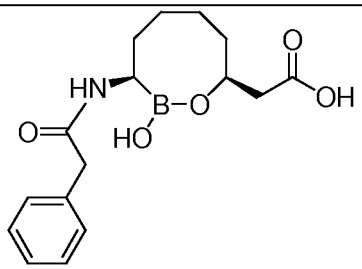
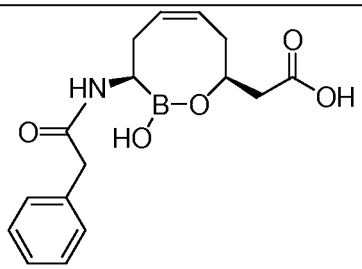
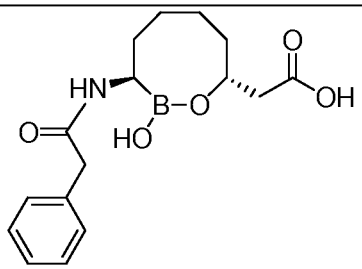
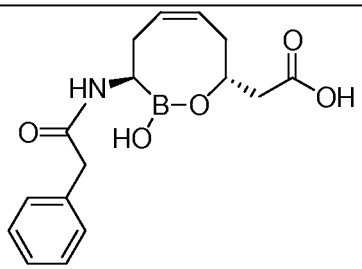
Example	Structure	Example	Structure
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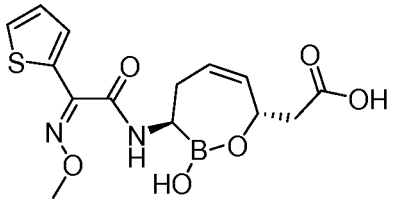
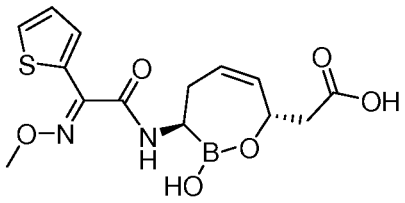
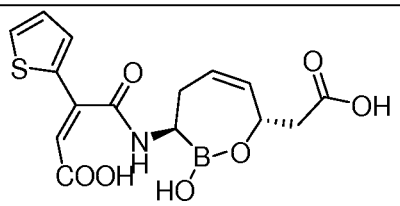
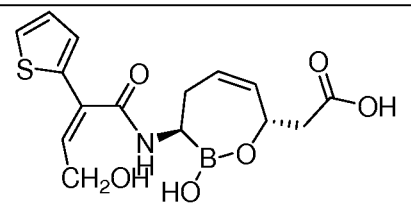
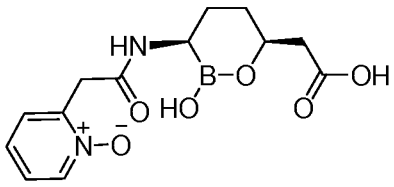
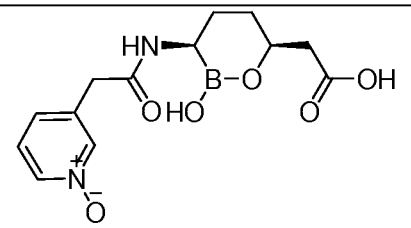
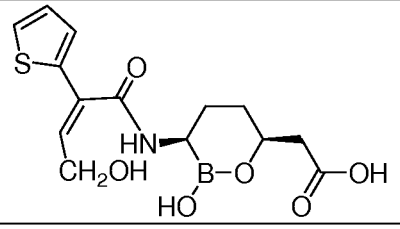
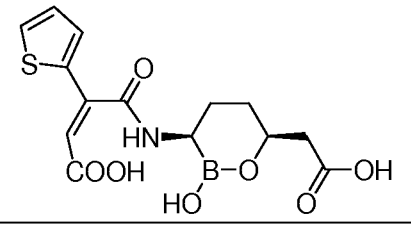
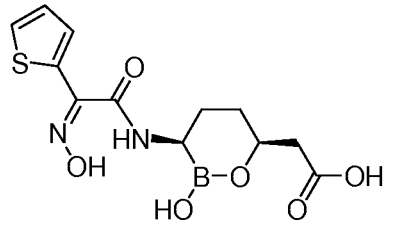
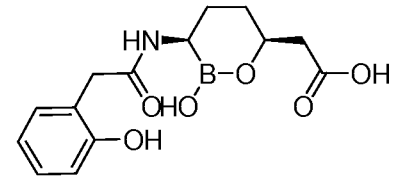
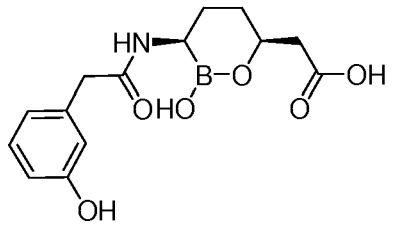
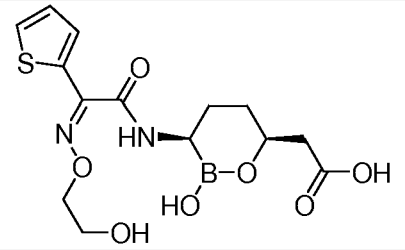
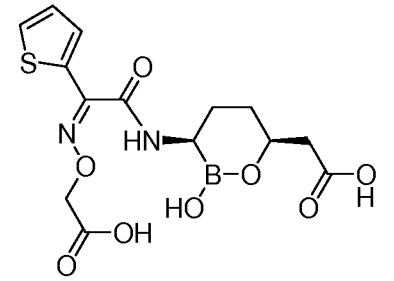
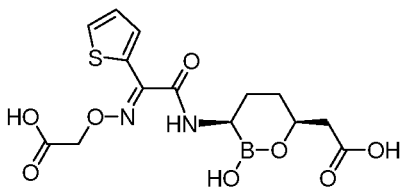
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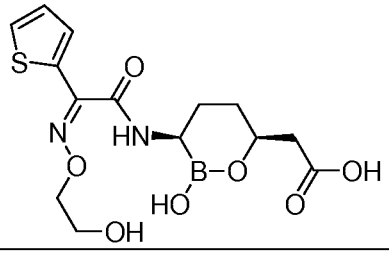
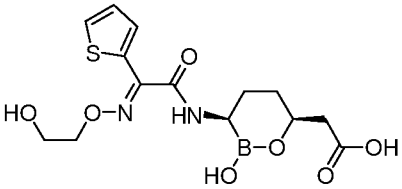
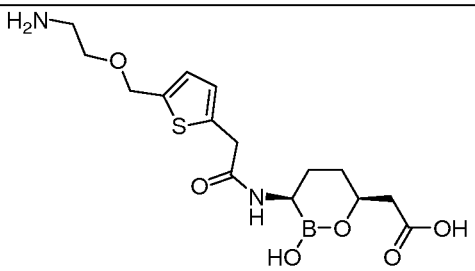
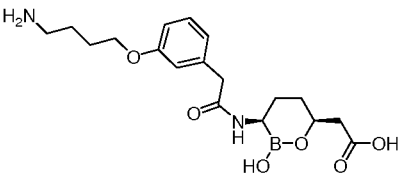
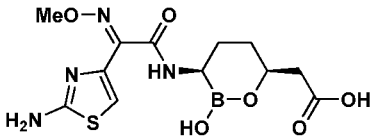
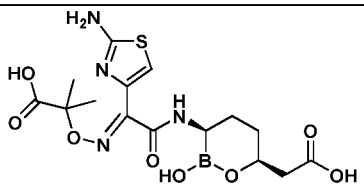
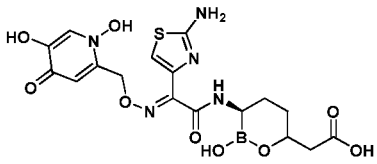
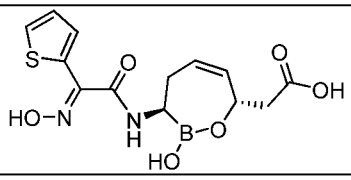
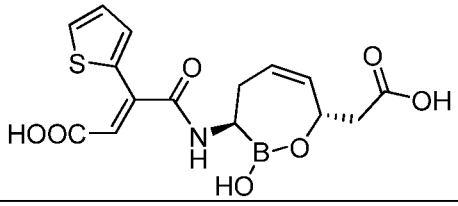
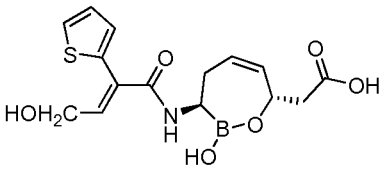
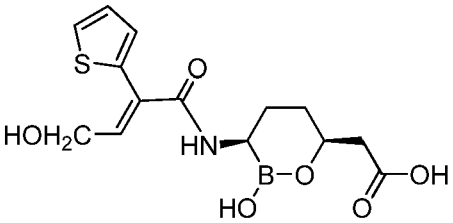
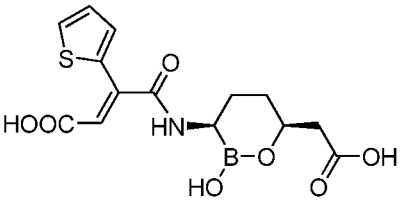
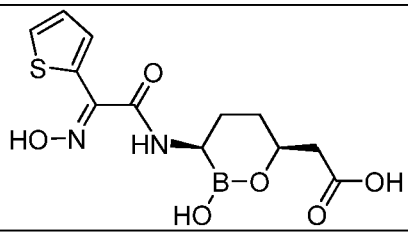
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Example	Structure	Example	Structure
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Example	Structure	Example	Structure
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Example	Structure	Example	Structure
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Example	Structure	Example	Structure
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107		108	

Example	Structure	Example	Structure
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113		114	
115		116	
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121			

Example 11

[0269] The potency and spectrum of β-lactamase inhibitors was determined by assessing their antibiotic potentiation activity.

[0270] The potentiation effect is observed by the reduction of the minimum inhibitory concentration of β-lactam antibiotics in the presence of β-lactamase inhibitors (BLIs). The activity of BLIs in combination with ceftazidime or biapenem is assessed by the checkerboard assay (Antimicrobial Combinations. In Antibiotics in Laboratory Medicine, Ed. Victor Lorian, M.D., Fourth edition, 1996, pp 333-338) using broth microdilution method performed as recommended by the NCCLS (National Committee for Clinical Laboratory Standards (NCCLS). 1997. Methods for Dilution of Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Fourth Edition; Approved Standard. NCCLS Document M7-A4, Vol 17 No.2). In this assay, multiple dilutions of two drugs, namely BLI and β-lactam (ceftazidime or biapenem), are being tested, alone and in combination, at concentrations equal to, above and below their respective minimal inhibitory concentrations (MICs). BLIs are solubilized in 10% DMSO at 10 mg/mL. Stock solutions are further diluted, according to the needs of a particular assay, in Mueller Hinton Broth (MHB). Stock solution can be stored at –80°C.

[0271] The checkerboard (CB) assay is performed in microtiter plates. Ceftazidime or biapenem are diluted in the x axis, each column containing a single concentration of antibiotic. BLIs are diluted in the y axis, each row containing an equal concentration of BLI. The result of these manipulations is that each well of the microtiter plate contains a unique combination of concentrations of the two agents. The assay is performed in MHB with a final bacterial inoculum of 5 x 105 CFU/mL (from an early-log phase culture). Microtiter plates are incubated during 20 h at 35°C and are read using a microtiter plate reader (Molecular Devices) at 650 nm as well as visual observation using a microtiter plate reading mirror. The MIC is defined as the lowest concentration of antibiotics, within the combination, at which the visible growth of the organism is completely inhibited. Activity of BLIs is reported at MPC8, or the minimal potentiation concentration to reduce the MIC of antibiotic 8-fold.

[0272] Ceftazidime potentiation is studied in strains of various bacteria that are resistant to ceftazidime due to expression of β-lactamase hydrolyzing enzymes. The panel of strains used in checkerboard experiments contains β-lactamases that belong to all the known classes of these enzymes: A, B, C and D. Activity of Compound 1 is tested at the maximum concentration of 40 μg/mL. At this concentration it shows no inhibition of growth of any bacteria tested, however at concentration as low as 0.6 μg/mL it reduced MICs to ceftazidime 8-fold in some bacteria (Table 2). Based on CB results, 1 has a broad-spectrum β-lactam potentiation activity against the strains expressing β-lactamases.

Compound 1 was the most potent against the strains expressing KPCs and other class A enzymes (CTX-M-3), and some class C (MIR-1, CMY-2), and class D (OXA-2) enzymes.

TABLE 2

Strain	Organism	Description	PCR	Class	MPC8
KP1005	*Klebsiella pneumoniae*	ESBL	CTX-M-14	A	Z
KP1009	*Klebsiella pneumoniae*	ESBL	CTX-M-15	A	Y
EC1008	*Escherichia coli*	ESBL	CTX-M-3	A	X
KP1004	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	X
KP1008	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	X
EC1007	*Escherichia coli*	Serine carbapenemase	KPC-3	A	X
KP1010	*Klebsiella pneumoniae*	ESBL	SHV-12	A	Y
KP1012	*Klebsiella pneumoniae*	ESBL	SHV-18	A	Y
ec306	*Escherichia coli*	First ESBL described	SHV-2	A	Y
ec307	*Escherichia coli*	Common SHV ESBL	SHV-4	A	Y
ec308	*Escherichia coli*	Common SHV ESBL	SHV-5	A	Y
EC1009	*Escherichia coli*	ESBL	TEM-10	A	Z
ec302	*Escherichia coli*	Common ESBL in US	TEM-10	A	Z
EC1012	*Escherichia coli*	ESBL	TEM-12	A	Y
ec303	*Escherichia coli*	Common ESBL in US	TEM-12	A	Y
EC1011	*Escherichia coli*	ESBL	TEM-26	A	Z
ec304	*Escherichia coli*	Common ESBL in US	TEM-26	A	Z
ec300	*Escherichia coli*	Common ESBL in France	TEM-3	A	Y
ec301	*Escherichia coli*	ESBL	TEM-6	A	Z
CF1000	*Citrobacter freundii*	Hyper AmpC expression		C	Y
ECL1003	*Enterobacter cloacae*	Hyper AmpC expression		C	Z
ec310	*Escherichia coli*	E. cloacae -like Amp-C	ACT-1	C	X
EC1004	*Escherichia coli*	pAmpC	CMY-2	C	X
EC1010	*Escherichia coli*	pAmpC	CMY-6	C	Y

Strain	Organism	Description	PCR	Class	MPC8
EC1014	*Escherichia coli*	pAmpC	DHA-1	C	Z
EC1006	*Escherichia coli*	pAmpC	FOX-5	C	Y
EC1016	*Escherichia coli*	pAmpC	FOX-5	C	Z
ec309	*Escherichia coli*	E. cloacae -like Amp-C	MIR-1	C	X
KP1007	*Klebsiella pneumoniae*	ESBL	OXA-10, qnrB4	D	Y
KX1000	*Klebsiella oxytoca*	ESBL	OXA-2	D	X
X = MPC8 of 2.5 µg/mL or less. Y = MPC8 of greater than 2.5 µg/mL to 10 µg/mL. Z = MPC8 of greater than 10 µg/mL.					

[0273] Next, ceftazidime potentiation activity of several cyclic boronic acid ester derivatives was tested using a larger panel of strains expressing β-lactamase hydrolyzing enzymes. Ceftazidime MICs were determined alone and in the presence of fixed concentrations of various cyclic boronic acid ester derivatives. Most compounds were tested at 10 µg/mL. Cyclic boronic acid ester derivatives were capable of reducing ceftazidime MICs 4 to >64-fold depending on β-lactamase (Table 3).

TABLE 3

Strain	Organism	Description	PCR	Class	Ceftazidime MIC (µg/mL) with or without cyclic boronic acid ester derivative					
					Alone	3 at 10 µg/mL	4 at 10 µg/mL	5 at 10 µg/mL	6 at 10 µg/mL	7 at 10 µg/mL
KP1005	*Klebsiella pneumoniae*	ESBL	CTX-M-14	A	Z	Z	Z	Z	Z	Z
KP1009	*Klebsiella pneumoniae*	ESBL	CTX-M-15	A	Z	Z	Z	Z	Z	Z
KP1006	*Klebsiella pneumoniae*	ESBL	CTX-M2	A	Y	X	X	X	X	ND
EC1008	*Escherichia coli*	ESBL	CTX-M3	A	Z	Y	Y	Y	Y	Z
pa 1063	*Pseudomonas aeruginosa*	ESBL	GES-1	A	Z	Z	Z	Z	Z	Z
KP1004	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	Z	Y	Y	Y	Y	Z
KP1008	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	Y	X	X	X	X	Z

Strain	Organism	Description	PCR	Class	Ceftazidime MIC (μg/mL) with or without cyclic boronic acid ester derivative					
					Alone	3 at 10 μg/mL	4 at 10 μg/mL	5 at 10 μg/mL	6 at 10 μg/mL	7 at 10 μg/mL
EC1007	*Escherichia coli*	Serine carbapenemase	KPC-3	A	Z	X	X	X	X	Z
KP1010	*Klebsiella pneumoniae*	ESBL	SHV-12	A	Z	Z	Z	Y	Y	Z
KP1012	*Klebsiella pneumoniae*	ESBL	SHV-18	A	Z	Z	Z	Y	Y	Z
ec306	*Escherichia coli*	First ESBL described	SHV-2	A	Z	Z	Z	Z	Z	Z
ec307	*Escherichia coli*	Common SHV ESBL	SHV-4	A	Z	Z	Z	Y	Z	Z
ec308	*Escherichia coli*	Common SHV ESBL	SHV-5	A	Z	Z	Z	Z	Z	Z
KP1011	*Klebsiella pneumoniae*	ESBL	SHV-5	A	Y	X	X	X	X	ND
EC1009	*Escherichia coli*	ESBL	TEM-10	A	Z	Z	Z	Z	Z	Z
ec302	*Escherichia coli*	Common ESBL in US	TEM-10	A	Z	Z	Z	Z	Z	Z
EC1012	*Escherichia coli*	ESBL	TEM-12	A	Z	Z	Z	Y	Y	Z
ec303	*Escherichia coli*	Common ESBL in US	TEM-12	A	Z	Z	Z	Y	Y	Z
EC1011	*Escherichia coli*	ESBL	TEM-26	A	Z	Z	Z	Z	Z	Z
ec300	*Escherichia coli*	Common ESBL in France	TEM-3	A	Z	Z	Z	Y	Z	Z
ec301	*Escherichia coli*	ESBL	TEM-6	A	Z	Z	Z	Z	Z	Z
KP1014	*Klebsiella pneumoniae*	Metallo β-lactamase	Vim-1	B	Z	Z	Z	Z	Z	ND
CF1000	*Citrobacter freundii*	Hyper AmpC expression		C	Z	Z	Z	Y	Y	Z
CF1001	*Citrobacter freundii*	Hyper AmpC expression		C	Z	Z	Z	Y	Y	ND
ECL1002	*Enterobacter cloacae*	Hyper AmpC expression		C	Z	Z	Y	Y	Y	Z

Strain	Organism	Description	PCR	Class	Ceftazidime MIC (µg/mL) with or without cyclic boronic acid ester derivative					
					Alone	3 at 10 µg/mL	4 at 10 µg/mL	5 at 10 µg/mL	6 at 10 µg/mL	7 at 10 µg/mL
ECL1003	*Enterobacter cloacae*	Hyper AmpC expression		C	Z	Z	Z	Z	Z	ND
ec310	*Escherichia coli*	E. cloacae - like Amp-C	ACT-1	C	Z	Y	Y	X	X	Z
EC1004	*Escherichia coli*	pAmpC	CMY-2	C	Z	Y	Y	Y	Y	Z
SA1000	*Salmonella*	pAmpC	CMY-2	C	Z	Z	Y	Y	X	ND
KP1013	*Klebsiella pneumoniae*	pAmpC	CMY-2	C	Z	Z	Y	Y	Y	ND
EC1010	*Escherichia coli*	pAmpC	CMY-6	C	Z	Z	Y	Y	Y	Z
EC1014	*Escherichia coli*	pAmpC	DHA-1	C	Z	Y	Y	X	X	Z
EC1006	*Escherichia coli*	pAmpC	FOX-5	C	Z	Y	Z	Y	Y	Z
EC1016	*Escherichia coli*	pAmpC	FOX-5	C	Z	Z	Z	Z	Z	ND
ec309	*Escherichia coli*	E. cloacae - like Amp-C	MIR-1	C	Z	Y	Y	X	X	Z
PAM2005	*Pseudomonas aeruginosa*	ampC		C	Z	Z	Z	Z	Z	Z
PAM2035	*Pseudomonas aeruginosa*	ampC mexA:tet		C	Z	Z	Z	Y	Y	Z
KP1007	*Klebsiella pneumoniae*	ESBL	OXA-10	D	Z	Z	Z	Y	Y	Z
KX1000	*Klebsiella oxytoca*	ESBL	OXA-2	D	Z	Z	Y	Y	Y	Y
AB1054	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-23	D	Z	Z	Z	Z	Z	Z
AB1052	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-24	D	Z	Z	Z	Z	Z	ND
AB1057	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-58	D	Z	Z	Z	Z	Z	Z

X = MIC of 1 µg/mL or less.
Y = MIC of greater than 1 µg/mL to 8 µg/mL.
Z = MIC of greater than 8 µg/mL.
ND = Not Determined.

[0274] Biapenem is a carbapenem β-lactam; only selected β-lactamases confer resistance to this class of antibiotics. Among them are serine carbapemenases that belong to class A and class D. Biapenem potentiation is studied in strains expressing various carbapenemases from these classes using CB assays. Various cyclic boronic acid ester derivatives showed significant potentiation of biapenem against the strains expressing class A carbapenemases: MPC8 (minimal potentiation concentration of cyclic boronic acid ester derivative(μg/mL) to reduce the MIC of Biapenem 8-fold) varied from 0.02 μg/mL to 0.16 μg/mL (Table 4). Cyclic boronic acid ester derivatives were capable of reducing biapenem MICs up to 1000-fold (Table 4).

TABLE 4

Strain	Organism	Description	PCR	Class	Compound	MPC8
ECL1004	*Enterobacter cloacae*	Serine carbapenemase	NMC-A	A	**1**	Y
EC1007	*Escherichia coli*	Serine carbapenemase	KPC-3	A	**1**	X
KP1004	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	**1**	Y
SM1000	*Serratia marcescens*	Serine carbapenemase	SME-2	A	**1**	Y
ECL1004	*Enterobacter cloacae*	Serine carbapenemase	NMC-A	A	**2**	Y
EC1007	*Escherichia coli*	Serine carbapenemase	KPC-3	A	**2**	X
KP1004	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	**2**	X
SM1000	*Serratia marcescens*	Serine carbapenemase	SME-2	A	**2**	Y
ECL1004	*Enterobacter cloacae*	Serine carbapenemase	NMC-A	A	**3**	X
EC1007	*Escherichia coli*	Serine carbapenemase	KPC-3	A	**3**	X
KP1004	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	**3**	X
KP1008	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	**3**	X
SM1000	*Serratia marcescens*	Serine carbapenemase	SME-2	A	**3**	Y
AB1052	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-24	D	**3**	Z
AB1054	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-23	D	**3**	Z
AB1057	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-58	D	**3**	Z
ECL1004	*Enterobacter cloacae*	Serine carbapenemase	NMC-A	A	**4**	X
EC1007	*Escherichia coli*	Serine carbapenemase	KPC-3	A	**4**	X

Strain	Organism	Description	PCR	Class	Compound	MPC8
KP1004	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	**4**	X
KP1008	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	**4**	X
SM1000	*Serratia marcescens*	Serine carbapenemase	SME-2	A	**4**	X
AB1052	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-24	D	**4**	Z
AB1054	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-23	D	**4**	Z
AB1057	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-58	D	**4**	Z
ECL1004	*Enterobacter cloacae*	Serine carbapenemase	NMC-A	A	**5**	Y
EC1007	*Escherichia coli*	Serine carbapenemase	KPC-3	A	**5**	X
KP1004	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	**5**	X
SM1000	*Serratia marcescens*	Serine carbapenemase	SME-2	A	**5**	Y
AB1052	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-24	D	**5**	Z
AB1054	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-23	D	**5**	Z
AB1057	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-58	D	**5**	Z
ECL1004	*Enterobacter cloacae*	Serine carbapenemase	NMC-A	A	**6**	Y
EC1007	*Escherichia coli*	Serine carbapenemase	KPC-3	A	**6**	X
KP1004	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	**6**	X
SM1000	*Serratia marcescens*	Serine carbapenemase	SME-2	A	**6**	Y
AB1052	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-24	D	**6**	Z
AB1054	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-23	D	**6**	X
AB1057	*Acinetobacter baumannii*	OXA-carbapenemase	OXA-58	D	**6**	Z

X = MPC8 of less than 0.16 μg/mL.
Y = MPC8 of 0.16 μg/mL to 1 μg/mL.
Z = MPC8 of greater than 1 μg/mL.

Example 12

[0275] The ability of β-lactamase inhibitors to inhibit hydrolysis of ceftazidime and biapenem was studied. Lysates were prepared from bacteria expressing various β-lactamases as a source of enzymes. Bacterial lysates were prepared as follows. A single colony from the fresh over-night plate was transferred to 5 mL of LB broth and grown to OD_{600} = 0.6-0.8. Next, this culture was transferred to 500 mL of LB and grown

to OD_{600} = 0.7-0.9. Cells were pelleted by centrifugation at 5000 RPM (JA-14 rotor) for 15 minutes at room temperature. The pellet was resuspended in 10 mL of PBS. Five freeze-thaw cycles by putting cells at -20°C and thawing them at the room temperature were next applied. After the last thaw step cells were spun down at 18K for 30 minutes and the supernatant was collected. This lysate was stored at -20°C.

[0276] Next, the activity of bacterial lysates was optimized for ceftazidime and biapenem cleavage as follows. 50 µl of buffer A (50 mM Sodium Phosphate pH=7; 0.5% glucose, 1 mM $MgCl_2$) was added to each well of 96-well UV-transparent plate. 50 µl of lysate was titrated vertically in 96-well plate column to generate 2-fold lysate dilutions. 100 µl of buffer A was added to each well, placed in plate reader at 37°C and incubated for 15 minutes. 50 µl of 50 µg/mL solutions of ceftazidime or biapenem in buffer A (pre-incubated at 37°C for 15 minutes) were added to each well. Hydrolysis of ceftazidime and biapenem was measured at 250 nm and 296 nm, respectively. This experiment was used to determine the optimal lysate dilution which produced a linear curve of relative UV signal that decreased to approximately OD=0.3-0.5 over 1 hour.

[0277] Finally, the potency of cyclic boronic acid ester derivative to inhibit the cleavage of ceftazidime and biapenem cleavage by bacterial lysates was determined. 100 µl of buffer A (50 mM Sodium Phosphate pH=7; 0.5% glucose, 1 mM $MgCl_2$) was added to each well of 96-well UV-transparent plate. 50 µl of 6 x cyclic boronic acid ester derivative solution in buffer A was titrated vertically in 96-well plate column to generate 3-fold dilutions. 50 µl of diluted lysate in buffer A (optimal dilution is determined in experiment above) was added, and the plate was incubated in the plate reader at 37°C for 15 minutes. 50 µl of 50 µg/mL solutions of ceftazidime or biapenem in buffer A (pre-incubated at 37°C for 15 minutes) were next added to each well and hydrolysis of ceftazidime or biapenem was recorded at 250 nm and 296 nm, respectively. EC_{50} of inhibition was determined by plotting the rate of ceftazidime or biapenem cleavage vs. cyclic boronic acid ester derivative concentration.

[0278] The results of these experiments are presented in Table 5 and Table 6. These experiments demonstrate that the described compounds are inhibitors with a broad-spectrum activity towards various β-lactamases.

TABLE 5

Strain	Organism	Description	PCR	Class	IC_{50} (μg/mL) of inhibition of Ceftazidime hydrolysis					
					Tazobactam	3	4	5	6	7
KP1005	*Klebsiella pneumoniae*	ESBL	CTX-M-14	A	X	Z	Z	X	Y	Z
KP1009	*Klebsiella pneumoniae*	ESBL	CTX-M-15	A	X	Z	Z	X	Y	Y
pa 1063	*Pseudomonas aeruginosa*	ESBL	GES-1	A	Y	Z	Y	X	Y	Y
KP1004	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	Z	X	X	X	X	Z
KP1008	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	Z	Y	X	X	X	Z
EC1007	*Escherichia coli*	Serine carbapenemase	KPC-3	A	Z	Y	X	X	X	Z
KP1010	*Klebsiella pneumoniae*	ESBL	SHV-12	A	X	Z	Z	Y	Z	Z
KP1012	*Klebsiella pneumoniae*	ESBL	SHV-18	A	X	Z	Z	Y	Y	Z
ec306	*Escherichia coli*	First ESBL described	SHV-2	A	Y	Z	Z	Y	Y	Z
ec308	*Escherichia coli*	Common SHV ESBL	SHV-5	A	X	Z	Z	Z	Z	Z
ec302	*Escherichia coli*	Common ESBL in US	TEM-10	A	X	Y	Z	X	Y	Y
ec303	*Escherichia coli*	Common ESBL in US	TEM-12	A	X	Z	Z	Y	Z	Y
ec304	*Escherichia coli*	Common ESBL in US	TEM-26	A	X	Z	Z	Y	Y	Y
ec300	*Escherichia coli*	Common ESBL in France	TEM-3	A	X	Z	Z	Y	Z	Z
ec301	*Escherichia coli*	ESBL	TEM-6	A	X	Z	Z	Y	Y	Y
ECL1003	*Enterobacter cloacae*	Hyper AmpC expression		C	ND	Z	Z	Y	Z	Z
EC1014	*Escherichia coli*	pAmpC	DHA-1	C	ND	Z	Z	Y	Z	Z
KP1007	*Klebsiella pneumoniae*	ESBL	OXA-10	D	Y	Z	Z	Y	Z	Z
KX1000	*Klebsiella oxytoca*	ESBL	OXA-2	D	X	Z	Z	X	Y	Z

Strain	Organism	Description	PCR	Class	IC_{50} (μg/mL) of inhibition of Ceftazidime hydrolysis					
					Tazobactam	3	4	5	6	7
X = IC_{50} of less than 0.1 μg/mL. Y = IC_{50} of 0.1 μg/mL to 1 μg/mL. Z = IC_{50} of greater than 1 μg/mL. ND = Not Determined.										

TABLE 6

Strain	*Organism*	Description	PCR	Class	IC_{50} (μg/mL) of inhibition of biapenem hydrolysis					
					Tazobactam	3	4	5	6	7
EC1007	*Escherichia coli*	Serine carbapenemase	KPC-3	A	Z	Y	Y	X	X	Z
KP1004	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	Z	Z	Y	X	Y	ND
KP1008	*Klebsiella pneumoniae*	Serine carbapenemase	KPC-2	A	Z	Z	Z	Y	Y	ND
SM1000	*Serratia marcescens*	Serine carbapenemase	SME-2	A	Y	Z	Y	X	Y	Z
X = IC_{50} of less than 0.1 μg/mL. Y = IC_{50} of 0.1 μg/mL to 1 μg/mL. Z = IC_{50} of greater than 1 μg/mL. ND = Not Determined.										

[0279] The potency and spectrum of β-lactamase inhibitors is also determined by assessing their aztreonam potentiation activity in a dose titration potentiation assay using strains of various bacteria that are resistant to aztreonam due to expression of various β-lactamases. Aztreonam is a monobactam antibiotic and, similar to ceftazidime, is hydrolyzed by the majority of beta-lactamases that belong to class A, C or D (but not class B). The potentiation effect is observed as the ability of BLI compounds to inhibit growth in the presence of sub-inhibitory concentration of aztreonam. MIC of test strains vary from 32 μg/mL to > 128 μg/mL. Aztreonam is present in the test medium at 4 μg/mL. Compounds were tested at the highest concentration of 40 μg/mL. In this assay potency of compounds is determined as a concentration of BLIs to inhibit growth of bacteria in the presence of 4 μg/mL of aztreonam ($MPC_{@4}$). Tables 7, 8 and 9 summarize BLI potency of aztreonam potentiation ($MPC_{@4}$) for various strains overexpressing class A (ESBLs), class A (KPCs), and class C and class D beta-lactamases, respectively. Aztreonam MIC for each strain is also shown. Table 7 summarizes activity of BLIs to

potentiate aztreonam against strains expressing class A ESBLs. Table 8 summarizes activity of BLIs to potentiate aztreonam against strains expressing class A KPCs. Table 9 summarizes activity of BLIs to potentiate aztreonam against strains expressing class C and D enzymes.

TABLE 7

Aztreonam MIC (μg/mL)	>128	>128	64	>128	32	128	>128	64
	AZT MPC_4 CTX-M-14 KP1005	AZT MPC_4 CTX-M-15 KP1009	AZT MPC_4 SHV-5 ec308	AZT MPC_4 SHV-12 KP1010	AZT MPC_4 SHV-18 KP1012	AZT MPC_4 TEM-10 EC1009	AZT MPC_4 TEM-10 ec302	AZT MPC_4 TEM-26 ec304
Clavulanic Acid	1.25	1.25	0.08	0.04	0.04	0.16	0.3	0.04
Tazobactam	10	20	10	1.25	1.15	2.5	5	0.6
3	Z	Z	Z	Z	Z	Z	Z	Z
4	Z	Z	Z	Z	Z	Z	Z	Z
5	Z	Y	Y	Y	X	Y	Z	Y
6	Z	Z	Z	Y	Y	Y	Z	Y
7	Z	Z	Z	Z	Y	X	Y	Y
33	Z	Z	Z	Z	Z	Z	Z	Z
34	Z	Z	Z	Z	Z	Z	Z	Z
35	Z	Z	Z	Z	Z	Z	Z	Z
36	Z	Z	Z	Y	Y	Z	Z	Y
37	Z	Z	Z	Y	X	Y	Z	Y
38	Z	Z	Z	Y	Z	Z	Z	Z
39	Z	Z	Z	Z	Y	Z	Z	Y
40	Z	Z	Z	Y	Z	Z	Z	Z
41	Z	Z	Z	Z	Z	Z	Z	Z
42	Z	Z	Z	Z	Z	Z	Z	Z
43	Z	Z	Z	Y	Y	Y	Z	Y
45	Z	Z	Z	Z	Z	Z	Z	Z
46	Z	Z	Z	Z	Z	Z	Z	Z
47	Z	Z	Z	Z	Z	Z	Z	Z
48	Z	Z	Z	Z	Z	Z	Z	Z
49	Z	Z	Z	Z	Y	Z	Z	Z
50	Z	Z	Z	Z	Z	Z	Z	Z
51	Z	Z	Z	Z	Y	Y	Z	Z
52	Z	Z	Z	Z	Z	Z	Z	Z
53	Z	Z	Z	Z	Z	Z	Z	Z
54	Z	Z	Z	Z	Z	Z	Z	Z
55	Z	Z	Z	Z	Z	Z	Z	Y
56	Z	Z	Z	Z	Z	Z	Z	Z

57	Z	Z	Z	Z	Y	Z	Z	Z
58	Z	Z	Z	Z	Z	Z	Z	Z
59	Z	Z	Z	Z	Z	Z	Z	Z
60	Z	Z	Z	Z	Z	Z	Z	Z
61	Z	Z	Z	Y	Y	Z	Z	Z
62	X	X	X	X	X	X	Y	X
63	Y	Y	Y	X	X	Y	Z	Y
64	Y	Y	X	X	X	Y	Y	X
65	Z	Z	Z	Z	Z	Z	Z	Z
66	Z	Z	Z	Z	Z	Z	Z	Z

X = $MPC_{@4}$ of less than 5 µg/mL.
Y = $MPC_{@4}$ of 5 µg/mL to 20 µg/mL.
Z = $MPC_{@4}$ of greater than 20 µg/mL.
ND = Not Determined.

TABLE 8

Aztreonam MIC	>128	64	>128	Aztreonam MIC	>128	64	>128
	AZT MPC_4 KPC-2 KP1004	AZT MPC_4 KPC-2 KP1008	AZT MPC_4 KPC-3 EC1007		AZT MPC_4 KPC-2 KP1004	AZT MPC_4 KPC-2 KP1008	AZT MPC_4 KPC-3 EC1007
Clavulanic Acid	>40	20	40	Clavulanic Acid	>40	20	40
Tazobactam	>40	>40	>40	Tazobactam	>40	>40	>40
3	X	X	X	**48**	X	X	X
4	X	X	X	**49**	X	X	X
5	X	X	X	**50**	X	X	X
6	X	X	X	**51**	X	X	X
33	X	X	X	**52**	Y	X	X
34	X	X	X	**53**	Y	X	X
35	Y	X	X	**54**	Z	X	Y
36	Z	Z	Z	**55**	Y	X	X
37	X	X	X	**56**	Y	X	X
38	Z	X	X	**57**	X	X	X
39	Y	X	X	**58**	Z	Z	Z
40	Z	Y	Z	**59**	Z	Z	Z
41	Y	X	X	**60**	Z	Y	Y
42	Y	X	X	**61**	X	X	X
43	X	X	X	**62**	Y	X	Y
				63	Z	Y	Y
45	Z	Y	X	**64**	Z	X	Y
46	X	X	X	**65**	Z	Z	Z
47	Z	Y	Y	**66**	Y	X	X

X = $MPC_{@4}$ of less than 5 µg/mL.
Y = $MPC_{@4}$ of 5 µg/mL to 20 µg/mL.
Z = $MPC_{@4}$ of greater than 20 µg/mL.
ND = Not Determined.

TABLE 9

Class	C	C	C	D	D
Aztreonam MIC	64	>128	32	128	128
	AZT $MPC_{@4}$ ECL1002	AZT $MPC_{@4}$ CMY-6 EC1010	AZT $MPC_{@4}$ PAM2035	AZT $MPC_{@4}$ OXA-10, qnrB4 KP1007	AZT $MPC_{@4}$ OXA-2, KPX1001
Clavulanic Acid	>40	40	>40	0.08	5
Tazobactam	>40	20	20	5	>40
3	Z	Z	Z	Z	Z
4	Y	Y	Z	Z	Z
5	Y	Y	X	X	Y
6	Y	Z	Y	Y	Z
33	Z	Z	Z	Z	Z
34	Z	Z	Z	Z	Z
35	Z	Z	Z	Z	Z
36	Z	Z	Z	Y	Z
37	Z	Z	Z	Z	X
38	Z	Z	Z	Z	Z
39	Z	Z	Z	Z	Z
40	Z	Z	Z	Z	Z
41	Z	Z	Z	Z	Z
42	Z	Z	Z	Z	Z
43	Y	Y	Y	Z	Y
45	Z	Z	Z	Z	Z
46	Z	Z	Z	Z	Z
47	Z	Z	Z	Z	Z
48	Z	Z	Z	Z	Z
49	Z	Z	Y	Z	Y
50	Z	Z	Z	Z	Y
51	Z	Z	Z	Z	Y
52	Z	Z	Z	Z	Z
53	Z	Z	Z	Z	Y
54	Z	Z	Z	Z	Z
55	Z	Z	Z	Z	Z
56	Z	Z	Z	Z	Y
57	Z	Z	Z	Z	Z

58	Z	Z	Z	Z	Z
59	Z	Z	Z	Z	Z
60	Z	Z	Z	Z	Z
61	Y	Y	Y	Y	Y
62	Z	X	X	X	Y
63	Y	Y	Y	Y	Y
64	Y	Z	Y	X	Y
65	Z	Z	Z	Z	Z
66	Z	Z	Z	Z	Z

X = $MPC_{@4}$ of less than 5 μg/mL.
Y = $MPC_{@4}$ of 5 μg/mL to 20 μg/mL.
Z = $MPC_{@4}$ of greater than 20 μg/mL.
ND = Not Determined.

[0280] The potency and spectrum of β-lactamase inhibitors is also determined by assessing their biapenem potentiation activity in a dose titration potentiation assay using strains expressing serine carbapemenases (such as KPC). The potentiation effect is observed as the ability of BLI compounds to inhibit growth in the presence of sub-inhibitory concentration of biapenem. MIC of test strains vary from 4 μg/mL to > 1 μg/mL. Biapenem is present in the test medium at 1 μg/mL. Compounds tested at the highest concentration of 40 μg/mL. In this assay potency of compounds is determined as a concentration of BLIs to inhibit growth of bacteria in the presence of 1 μg/mL of biapenem ($MPC_{@1}$). Table 10 summarizes BLI potency of biapenem potentiation ($MPC_{@1}$). Biapenem MIC for each strain is also shown.

TABLE 10

Biapenem MIC	>8	8	4	8	Biapenem MIC	>8	8	4	8
	BPM $MPC_{@1}$ KP100 4 KPC-2	BPM $MPC_{@1}$ KP100 8 KPC-2	BPM $MPC_{@1}$ EC100 7 KPC-3	BPM $MPC_{@1}$ ECL100 4 NMC-A		BPM $MPC_{@1}$ KP100 4 KPC-2	BPM $MPC_{@1}$ KP100 8 KPC-2	BPM $MPC_{@1}$ EC100 7 KPC-3	BPM $MPC_{@1}$ ECL100 4 NMC-A
Tazobactam	40	0.3	5	0.6	Tazobactam	40	0.3	5	0.6
3	X	X	X	Y	**48**	X	X	X	X
4	X	X	X	X	**49**	X	X	X	X
5	X	X	X	X	**50**	X	X	X	X
6	X	X	X	X	**51**	X	X	X	Y
33	X	X	X	X	**52**	X	X	X	Y
34	X	X	X	Y	**53**	X	X	X	Y
35	X	X	X	Y	**54**	X	X	X	X
36	Z	X	Y	X	**55**	X	X	X	X

37	X	X	X	X	**56**	X	X	X	X
38	X	X	X	X	**57**	X	X	X	X
39	X	X	X	X	**58**	Z	Z	Z	Z
40	Y	X	Y	Y	**59**	Y	X	X	X
41	X	X	X	Y	**60**	X	X	X	X
42	X	X	X	Y	**61**	X	X	X	X
43	X	X	X	X	**62**	X	X	X	X
					63	Y	X	Y	Y
45	Y	X	X	Z	**64**	Y	X	X	X
46	X	X	X	X	**65**	Y	X	Y	Z
47	Y	X	X	Z	**66**	X	X	X	X

X = $MPC_{@1}$ of less than 1 μg/mL.
Y = $MPC_{@1}$ of 1 μg/mL to 5 μg/mL.
Z = $MPC_{@1}$ of greater than 5 μg/mL.
ND = Not Determined.

[0281] Some bacterial lysates were also optimized for the cleavage of aztreonam and nitrocefin. EC_{50} of inhibition was determined by plotting the rate of aztreonam or nitrocefin cleavage vs. BLI concentration. The results of these experiments are presented in Table 11. These experiments confirmed that the described compounds are inhibitors with a broad-spectrum activity towards various β-lactamases.

TABLE 11

	AZT IC_{50} KP1005 CTX-M-14	AZT IC_{50} KP1009 CTX-M-15	AZT IC_{50} ec302 TEM-10	AZT IC_{50} ec304 TEM-26	AZT IC_{50} KP1004 KPC-2	AZT IC_{50} KP1008 KPC-2	AZT IC_{50} EC1007 KPC-3	AZT IC_{50} KP1007 OXA-10	AZT IC_{50} KPX1001 OXA-2	NCF IC_{50} EC1010 pAmpC (CMY-6)
Clavulanic Acid	0.0548	0.247	0.027	0.027	0.74	2.22	1.48	1.48	0.08	ND
Tazobactam	<0.0274	0.027	0.055	0.027	0.74	2.22	0.74	4.44	0.0274	ND
3	X	Z	Z	Z	X	Y	X	Z	Z	Z
4	X	Y	Z	Z	X	X	X	Z	Z	Z
5	X	Y	Z	Z	X	X	X	Z	X	Z
6	X	X	Z	Z	X	X	X	Z	Y	Z
33	X	Z	Z	Z	Y	Y	X	Z	Y	Z
34	Z	Z	Z	Z	Y	Y	X	Z	Z	Z
35	Z	Z	Z	Z	Z	Z	X	Z	Z	Z
36	X	X	X	X	Y	Y	X	Z	Z	Z
37	X	X	Z	Z	X	X	X	Y	Y	X
38	X	Y	Z	Y	X	X	X	Z	Y	Y
39	Y	Y	Z	Y	X	Y	X	Z	Y	Z
40	X	X	Z	Y	Y	Z	Y	Y	X	Y
41	Z	Z	Z	Z	X	X	X	Z	Z	Z
42	Z	Z	Z	Z	X	X	X	Z	Z	Z
43	Y	Z	Z	Z	X	X	X	Z	Y	Z

45	Z	Z	Z	Z	Y	Y	X	Z	Z	Z
46	Z	Z	Z	Z	X	X	X	Z	Z	Z
47	Z	Z	Z	Z	Y	Y	X	Z	Z	Z
48	Y	Z	Z	Z	X	Y	X	Z	Y	Z
49	Y	Z	Z	Z	X	X	X	Z	Y	Z
50	Y	Z	Z	Z	X	X	X	Z	Z	Z
51	Z	Z	Z	Z	X	X	X	Z	Y	Y
52	Z	Z	Z	Z	X	Y	Y	Z	Z	Z
53	Z	Z	Z	Z	X	Y	Y	Z	Y	Z
54	X	Z	Z	Z	X	X	X	Z	Y	Y
55	Y	Z	Z	Y	X	X	X	Z	Y	Z
56	X	Y	Z	Z	X	X	X	Z	Y	Y
57	X	Z	Z	Z	X	X	X	Z	Z	Z
58	Y	Z	Z	Z	X	X	X	Z	Z	Z
59	Z	Z	Z	Z	Y	X	Y	Z	Y	Z
60	Y	Y	Z	Z	X	X	X	Z	Y	Y
61	Y	Z	Z	Z	X	X	X	Z	Y	Z
62	Y	Y	Z	Y	Y	X	X	Z	Z	Z
63	Y	Y	Z	Z	Y	Y	Y	Z	Y	Y
65	Y	Z	Z	Z	Y	Y	Z	Z	Y	Z
66	Y	Z	Z	Z	X	X	X	Z	X	Z

X = IC_{50} of less than 0.5 µg/mL.
Y = IC_{50} of 0.5 µg/mL to 2 µg/mL.
Z = IC_{50} of greater than 2 µg/mL.
ND = Not Determined.

Example 13

[0282] Selected β-lactamase inhibitors were also tested for their ability to potentiate the monobactam tigemonam. The potentiation effect is observed as the ability of BLI compounds to inhibit growth in the presence of sub-inhibitory concentration of tigemonam. MIC of test strains vary from 8 µg/mL to > 128 µg/mL. Tigemonam is present in the test medium at 4 µg/mL. Compounds tested at the highest concentration of 40 µg/mL. In this assay potency of compounds is determined as a concentration of BLIs to inhibit growth of bacteria in the presence of 4 µg/mL of aztreonam ($MPC_{@4}$). Tables 12 and 13 summarize BLI potency of tigemonam potentiation ($MPC_{@4}$) for various strains overexpressing class A (ESBLs), class C and class D beta-lactamases, respectively. Tigemonam MIC for each strain is also shown. Table 12 summarizes activity of BLIs to potentiate tigemonam against strains expressing class A ESBLs. Table 13 summarizes activity of BLIs to potentiate aztreonam against strains expressing class C and D enzymes.

TABLE 12

Tigemonam MIC (µg/mL)	512	256	>512	256	64	256	>512	512
	MPC_4 CTX-M-14 KP1005	MPC_4 CTX-M-15 KP1009	MPC_4 SHV-5 ec308	MPC_4 SHV-12 KP1010	MPC_4 SHV-18 KP1012	MPC_4 TEM-10 EC1009	MPC_4 TEM-10 ec302	MPC_4 TEM-26 ec304
Tazobactam	10	10	5	1.25	1.25	2.5	5	1.25
Clavulanic Acid	2.5	1.25	<=0.6	<=0.6	<=0.6	<=0.6	2.5	<=0.6
5	Z	Z	Z	Z	Z	Z	Z	Z
9	Z	Z	Z	Z	Z	Z	Z	Z
18	X	X	Y	X	X	X	Y	Y
37	Z	Z	Z	Z	Z	Z	Z	Z
48	Z	Z	Z	Z	Z	Z	Z	Z
63	Z	Y	Z	Y	Y	Z	Z	Z
64	Z	Y	Y	X	Y	Y	Z	Z
67	Z	Y	Z	Y	Y	Z	Z	Z
68	Y	Y	Y	X	X	Y	Y	Y

X = $MPC_{@4}$ of less than 2 µg/mL.
Y = $MPC_{@4}$ of 2 µg/mL to 10 µg/mL.
Z = $MPC_{@4}$ of greater than 10 µg/mL.
ND = Not Determined.

TABLE 13

Class	C	C	C	D	S
Tigemonam MIC (µg/mL)	32	16	8	256	8
	MPC_4 ECL1002	MPC_4 CMY-6, EC1010	MPC_4 PAM2035	MPC_4 OXA-10, KP1007	MPC_4 OXA-2, KPX1001
Tazobactam	10	2.5	5	5	40
Clavulanic Acid	>40	40	>40	<=0.6	1.25
5	Y	X	X	Z	X
9	Y	Y	Y	Z	X
18	Y	X	X	Y	Y
37	X	X	X	Z	X
48	Y	X	Y	Z	X
63	Y	X	Y	Y	X
64	X	X	Y	X	Y
67	Y	X	X	Z	X
68	Y	X	Y	X	X

X = $MPC_{@4}$ of less than 2 µg/mL.
Y = $MPC_{@4}$ of 2 µg/mL to 10 µg/mL.
Z = $MPC_{@4}$ of greater than 10 µg/mL.
ND = Not Determined.

Example 14

[0283] Checkerboard assays were used to evaluate the ability of Compound **5** to potentiate various carbapenems (biapenem, doripenem, ertapenem, imipenem, and meropenem) against the strains expressing KPC alone or in combination with additional beta-lactamases. The highest concentration of Compound **5** was 10 mg/L. The results are present in the Table 14. Compound **5** was capable to significantly potentiate multiple carbapenems.

TABLE 14

		Concentration of Compound 5 (mg/L) to Potentiate Carbapenem (mg/L)									
Organism	**Strain**	**Enzymes**	**Antibiotic**	***0***	***0.16***	***0.31***	***0.625***	***1.25***	***2.5***	***5***	**10**
Klebsiella pneumoniae	KP1004	KPC-2	Biapenem	Z	X	X	X	X	X	X	X
Klebsiella pneumoniae	KP1004	KPC-2	Doripenem	Y	Y	X	X	X	X	X	X
Klebsiella pneumoniae	KP1004	KPC-2	Ertapenem	Z	Z	Y	Y	X	X	X	X
Klebsiella pneumoniae	KP1004	KPC-2	Imipenem	Z	X	X	X	X	X	X	X
Klebsiella pneumoniae	KP1004	KPC-2	Meropenem	Z	Y	Y	X	X	X	X	X
Klebsiella pneumoniae	KP1008	KPC-2	Biapenem	Z	X	X	X	X	X	NG	NG
Klebsiella pneumoniae	KP1008	KPC-2	Doripenem	Y	X	X	X	X	X	NG	NG
Klebsiella pneumoniae	KP1008	KPC-2	Ertapenem	Z	X	X	X	X	X	NG	NG
Klebsiella pneumoniae	KP1008	KPC-2	Imipenem	Y	X	X	X	X	X	NG	NG
Klebsiella pneumoniae	KP1008	KPC-2	Meropenem	Y	X	X	X	X	X	NG	NG
Klebsiella pneumoniae	KP1082	KPC-2, SHV-1	Biapenem	Y	X	X	X	X	X	X	X
Klebsiella pneumoniae	KP1082	KPC-2, SHV-1	Doripenem	Y	X	X	X	X	X	X	X
Klebsiella pneumoniae	KP1082	KPC-2, SHV-1	Ertapenem	Y	X	X	X	X	X	X	X
Klebsiella pneumoniae	KP1082	KPC-2, SHV-1	Imipenem	Y	X	X	X	X	X	X	X
Klebsiella pneumoniae	KP1082	KPC-2, SHV-1	Meropenem	Y	X	X	X	X	X	X	X
Klebsiella pneumoniae	KP1087	KPC-2, CTX-M-15, SHV-11, TEM-1	Biapenem	Z	Z	Z	Z	Y	Y	X	X
Klebsiella pneumoniae	KP1087	KPC-2, CTX-M-15, SHV-11, TEM-1	Doripenem	Z	Z	Z	Z	Z	Y	Y	X
Klebsiella pneumoniae	KP1087	KPC-2, CTX-M-15, SHV-11, TEM-1	Ertapenem	Z	Z	Z	Z	Z	Z	Y	Y

Klebsiella pneumoniae	KP1087	KPC-2, CTX-M-15, SHV-11, TEM-1	Imipenem	Z	Y	Y	Y	Y	Y	X	X
Klebsiella pneumoniae	KP1087	KPC-2, CTX-M-15, SHV-11, TEM-1	Meropenem	Z	Z	Z	Z	Z	Y	Y	X
Klebsiella oxytoca	KX1019	KPC-2, OXA-2	Biapenem	Z	Y	Y	Y	Y	Y	X	X
Klebsiella oxytoca	KX1019	KPC-2, OXA-2	Doripenem	Y	Y	Y	Y	X	X	X	X
Klebsiella oxytoca	KX1019	KPC-2, OXA-2	Ertapenem	Z	Y	Y	Y	Y	Y	X	X
Klebsiella oxytoca	KX1019	KPC-2, OXA-2	Imipenem	Y	Y	Y	Y	X	X	X	X
Klebsiella oxytoca	KX1019	KPC-2, OXA-2	Meropenem	Y	Y	Y	X	X	X	X	X
Klebsiella oxytoca	KX1017	KPC-2, OXA-2, SHV-30	Biapenem	Y	Y	Y	X	X	X	X	X
Klebsiella oxytoca	KX1017	KPC-2, OXA-2, SHV-30	Doripenem	Y	Y	Y	Y	X	X	X	X
Klebsiella oxytoca	KX1017	KPC-2, OXA-2, SHV-30	Ertapenem	Z	Y	Y	Y	Y	X	X	X
Klebsiella oxytoca	KX1017	KPC-2, OXA-2, SHV-30	Imipenem	Z	Y	X	X	X	X	X	X
Klebsiella oxytoca	KX1017	KPC-2, OXA-2, SHV-30	Meropenem	Y	Y	Y	X	X	X	X	X
Klebsiella oxytoca	KX1018	KPC-2, SHV-40, OXY-1	Biapenem	Z	X	X	X	X	X	NG	NG
Klebsiella oxytoca	KX1018	KPC-2, SHV-40, OXY-1	Doripenem	Y	X	X	X	X	X	NG	NG
Klebsiella oxytoca	KX1018	KPC-2, SHV-40, OXY-1	Ertapenem	Z	X	X	X	X	X	NG	NG
Klebsiella oxytoca	KX1018	KPC-2, SHV-40, OXY-1	Imipenem	Y	X	X	X	X	X	NG	NG
Klebsiella oxytoca	KX1018	KPC-2, SHV-40, OXY-1	Meropenem	Y	X	X	X	X	X	NG	NG
Escherichia coli	EC1007	KPC-3	Biapenem	Z	X	X	X	X	X	X	X
Escherichia coli	EC1007	KPC-3	Doripenem	Y	X	X	X	X	X	X	X
Escherichia coli	EC1007	KPC-3	Ertapenem	Z	X	X	X	X	X	X	X
Escherichia coli	EC1007	KPC-3	Imipenem	Z	X	X	X	X	X	X	X
Escherichia coli	EC1007	KPC-3	Meropenem	Y	X	X	X	X	X	X	X
Enterobacter cloacae	ECL1058	KPC-3, SHV-11, TEM-1	Biapenem	Z	Y	Y	Y	X	X	X	X
Enterobacter cloacae	ECL1058	KPC-3, SHV-11, TEM-1	Doripenem	Z	Y	Y	Y	Y	X	X	X

Enterobacter cloacae	ECL10 58	KPC-3, SHV-11, TEM-1	Ertapenem	Z	Z	Z	Z	Y	Y	X	X
Enterobacter cloacae	ECL10 58	KPC-3, SHV-11, TEM-1	Imipenem	Z	Y	Y	Y	X	X	X	X
Enterobacter cloacae	ECL10 58	KPC-3, SHV-11, TEM-1	Meropenem	Z	Y	Y	Y	Y	X	X	X
Enterobacter cloacae	ECL10 59	KPC-3, SHV-12, TEM-1	Biapenem	Y	X	X	X	X	X	X	X
Enterobacter cloacae	ECL10 59	KPC-3, SHV-12, TEM-1	Doripenem	Y	X	X	X	X	X	X	X
Enterobacter cloacae	ECL10 59	KPC-3, SHV-12, TEM-1	Ertapenem	Y	X	X	X	X	X	X	X
Enterobacter cloacae	ECL10 59	KPC-3, SHV-12, TEM-1	Imipenem	Y	X	X	X	X	X	X	X
Enterobacter cloacae	ECL10 59	KPC-3, SHV-12, TEM-1	Meropenem	Y	X	X	X	X	X	X	X
Klebsiella pneumoniae	KP1083	KPC-3, SHV-1, TEM-1	Biapenem	Z	Y	X	X	X	X	X	X
Klebsiella pneumoniae	KP1083	KPC-3, SHV-1, TEM-1	Doripenem	Z	Y	X	X	X	X	X	X
Klebsiella pneumoniae	KP1083	KPC-3, SHV-1, TEM-1	Ertapenem	Z	Y	X	X	X	X	X	X
Klebsiella pneumoniae	KP1083	KPC-3, SHV-1, TEM-1	Imipenem	Z	Y	X	X	X	X	X	X
Klebsiella pneumoniae	KP1083	KPC-3, SHV-1, TEM-1	Meropenem	Z	Y	X	X	X	X	X	X
Klebsiella pneumoniae	KP1084	KPC-3, SHV-11, TEM-1	Biapenem	Z	Z	Z	Z	Z	Y	X	X
Klebsiella pneumoniae	KP1084	KPC-3, SHV-11, TEM-1	Doripenem	Z	Z	Z	Z	Y	Y	Y	X
Klebsiella pneumoniae	KP1084	KPC-3, SHV-11, TEM-1	Ertapenem	Z	Z	Z	Z	Z	Z	Y	Y
Klebsiella pneumoniae	KP1084	KPC-3, SHV-11, TEM-1	Imipenem	Z	Z	Z	Y	Y	Y	X	X
Klebsiella pneumoniae	KP1084	KPC-3, SHV-11, TEM-1	Meropenem	Z	Z	Z	Z	Z	Y	Y	X
Klebsiella pneumoniae	KP1088	KPC-3, SHV-11, TEM-1	Biapenem	Z	Y	X	X	X	X	X	X
Klebsiella pneumoniae	KP1088	KPC-3, SHV-11, TEM-1	Doripenem	Y	Y	Y	X	X	X	X	X
Klebsiella pneumoniae	KP1088	KPC-3, SHV-11, TEM-1	Ertapenem	Z	Z	Y	X	X	X	X	X
Klebsiella pneumoniae	KP1088	KPC-3, SHV-11, TEM-1	Imipenem	Z	Y	X	X	X	X	X	X

Klebsiella pneumoniae	KP1088	KPC-3, SHV-11, TEM-1	Meropenem	Z	Y	Y	X	X	X	X	X

X = MIC of less than 0.5 mg/L.
Y = MIC of 0.5 mg/L to 4 mg/L.
Z = MIC of greater than 4 mg/L.
NG = No Growth.

Example 15

[0284] An *in vivo* model can be used to evaluate the single dose pharmacokinetic properties and absolute oral bioavailability of a test compound. As described more specifically below, a test compound is administered to Sprague-Dawley (SD) rats either intravenously or orally in a crossover study design and the resulting pharmacokinetic properties and oral bioavailability are measured.

[0285] For intravenous administration, male rats were given a 30 minutes intravenous infusion dose of 20 or 50 mg/kg of Compound **5** via femoral vein cannula. Plasma samples (0.3ml) were collected from jugular vein cannula at 0.17, 0.33, 0.47, 0.58, 0.68, 0.75, 1, 2, 3, 4, and 6 hrs after the dosing. For oral administration, male rats were given 50 mg/kg of Compound **5** (in saline) or Compound **62** (in 100% ethanol) orally using an oral gavage tip. Plasma samples were collected from each rat at 0.08, 0.17, 0.25, .33, .50, .75, 1, 2, 3, 4, and 6 hrs after the dosing.

[0286] Plasma concentrations of the compounds were tested using LC/MS/MS method with a lower limit of quantification of 10ng/mL for Compound **5** and 100ng/mL for Compound **62**. Extraction: 50µL volumes of plasma from samples and standards were extracted using 200µL of methanol with 100mM ammonium acetate, 2µg/mL gatifloxacin (internal standard for Compound **62**) and 2ug/mL Compound **38** (internal standard for Compound **5**). The samples were mixed and centrifuged for 30min at 3000xg. 150µL of supernatant was removed and added to 450µL of water.

[0287] HPLC – mass spectrometry: An Agilent 1100HPLC pump, HTC PAL autosampler and a Sciex 3200Q mass spectrometer were used for separation and quantification. Compound **62** and its internal standard were detected using +ESI. Compound **5** and its internal standard were detected using –ESI. LC/MS/MS: 1) Column: Chromolith FastGradient RP-18e, 50 x 2mm; 2) Mobile phase A: Aqueous Water with 0.1% TFA, Orgainic phase B: Acetonitrile with 0.1% TFA; Flow Rate: 600µL/min; Injection volume: 10µL; HPLC gradient: 5% B→60%B, 0.01→1.5 min; 60% B, 1.5→1.6 min; 60%B→5%B, 1.6→1.7 min; 5%B, 1.7→2.7 min.

[0288] Plasma concentrations were modeled using WinNonlin® (Pharsight Corp, Mountain View, CA).

[0289] In this experiment, three male Sprague Dawley rats were given Compound **5** by intravenous or oral route. At designated time points, bloods were collected and analyzed. As shown in the above Table 15 and Figure 1, Compound **5** has a linear PK in rats. However, Compound **5** it is not orally absorbed.

[0290] **TABLE 15**

Route of Adm	Dose/ (mg/kg)	$T_{1/2}$ (hr)	Cmax (mg/L)	CL/F (L/h/kg)	AUC (mg*h/L)
IV	20	1.56	19.82	1.65	12.15
IV	50	4.53	45.93	1.77	28.19
PO	50	1.55	0.29	60.38	0.81

[0291] In this experiment, three male Sprague dawley rats were given Compound **5** by intravenous or Compound **62** orally (pro-drug for Compound **5**). Plasma samples were collected at designated time points and analyzed for the presence of Compound **5**. This study was designed to determine the oral bioavailability of Compound **62** a pro-drug of Compound **5**. Male rats (non-fasted) were orally administered 50 mg/kg of the prodrug Compound **62**. As shown in Figure 2, the pro-drug of Compound **5** has oral bioavailability of greater than 80%.

[0292] Polymorphs can be detected, identified, classified and characterized using well-known techniques such as, but not limited to, differential scanning calorimetry (DSC), thermogravimetry (TGA) and powder X-ray diffractometry (PXRD).

Example 16

[0293] The crystal structure of Compound **5** was analyzed using X-ray powder diffraction ("PXRD"). The X-ray diffraction data were collected at room temperature using a PANalytical X'Pert Pro diffractometer (Cu Kα radiation) fitted with an automatic sample changer, a theta-theta goniometer, automatic beam divergence slits, a secondary monochromator and a scintillation counter. Samples were prepared for analysis by packing the powder into a 12mm diameter, 0.25mm deep cavity that had been cut into a Si zero-background wafer specimen mount. The sample was rotated while being irradiated with copper K-alpha 1 X-rays (wavelength = 1.5406 Ångstroms) with the X-ray tube operated at 45kV/40mA. The analyses were performed with the goniometer running

in continuous mode set for a 5 second count per 0.02° step over a two theta range of 2° to 55°. The illustrative PXRD pattern for Compound **5** is shown in Figure 3.

[0294] As will be appreciated by the skilled crystallographer, the relative intensities of the various peaks reported in Figure 3 may vary due to a number of factors such as orientation effects of crystals in the X-ray beam or the purity of the material being analyzed or the degree of crystallinity of the sample. The peak positions may also shift for variations in sample height but the peak positions will remain substantially as defined in Figure 3. The skilled crystallographer also will appreciate that measurements using a different wavelength will result in different shifts according to the Bragg equation - $n\lambda = 2d \sin \theta$. Such further PXRD patterns generated by use of alternative wavelengths are considered to be alternative representations of the PXRD patterns of the crystalline materials of the present invention and as such are within the scope of the present invention.

[0295] Table 16 lists peak positions and relative intensities for the PXRD pattern of Figure 3. Accordingly, some embodiments include a crystalline form of Compound **5** having three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more characterstic PXRD (wavelength = 1.5406 Å) peaks selected from 9.0°, 15.7°, 17.3°, 17.6°, 18.1°, 21.3°, 22.4°, 23.5°, 24.9°, 27.2°, 27.4°, 28.1°, 29.1°, 31.2°, and 35.7° 2θ. Some embodiments include a crystalline form of Compound **5** having three or more, four or more, five or more, or six characterstic PXRD (wavelength = 1.5406 Å) peaks selected from 9.0°, 17.3°, 17.6°, 18.1°, 22.4°, and 27.2° 2θ. Some embodiments include a crystalline form of Compound **5** having characteristic PXRD (wavelength = 1.5406 Å) peaks at 9.1°, 17.3°, 17.6°, and 18.1° 2θ.

TABLE 16

°2θ	Area [cts°2θ]	d-spacing [Å]
9.0088	870.8	9.80831
12.0132	29.19	7.36118
13.2369	19.12	6.68332
15.4527	55.73	5.72961
16.6911	41.97	5.30719
17.3464	285.76	5.10815
17.59	171.25	5.03794
18.1212	475.59	4.89145
19.9585	23.95	4.4451
20.1214	18.12	4.40949

21.3328	84.5	4.16175
22.4035	147.38	3.96521
22.9212	39.45	3.87681
23.48	60.99	3.78579
24.8881	77.52	3.5747
26.1352	20.92	3.40689
26.3458	20.23	3.38013
27.2278	162.9	3.27261
27.357	50.29	3.25744
28.0871	54.62	3.17441
29.0644	51.29	3.06985
29.63	30.23	3.01253
30.1989	19.34	2.95706
31.2457	65.66	2.86033
32.1641	32.04	2.78073
33.7983	19.84	2.64992
35.1614	21.23	2.55025
35.6871	57.8	2.51388
36.5979	22	2.45338
37.7599	33.73	2.3805
39.8439	31.99	2.26066

[0296] As is well understood in the art, because of the experimental variability when X-ray diffraction patterns are measured on different instruments, the peak positions are assumed to be equal if the two theta (2θ) values agree to within 0.2° (i.e., ± 0.2°). For example, the United States Pharmacopeia states that if the angular setting of the 10 strongest diffraction peaks agree to within ± 0.2° with that of a reference material, and the relative intensities of the peaks do not vary by more than 20%, the identity is confirmed. Accordingly, peak positions within 0.2° of the positions recited herein are assumed to be identical.

Example 17

[0297] DSC measure thermal transition temperatures at which a crystalline form absorbs or releases heat when its crystal structure changes or it melts. TGA is used to measure thermal stability and the fraction of volatile components of a sample by monitoring the weight change as the sample is heated. If infrared spectroscopy is conducted on the volatile components outgassed during TGA analysis of a pseudopolymorph (TGA-IR), then the molecular composition of the pseudopolymorph can be determined. These techniques are thus useful for characterizing solid state forms existing as solvates and/or hydrates.

[0298] Compound **5** was analyzed using differential scanning calorimetry (DSC). A TA Instruments Q100 differential scanning calorimeter equipped with an

autosampler and a refrigerated cooling system under 40 mL/min N_2 purge was used to perform the analysis. Each sample was heated from 25 to 300°C at 15°C per minute in an aluminium pan with the lid laid on top, with a nitrogen purge gas. The data from DSC analyses are dependent on several factors, including the rate of heating, the purity of the sample, crystal size, and sample size. The DSC thermogram obtained for the sample of Compound **5** is shown in Figure 4 overlayed with the TGA thermogram. These data reveal a single endothermic transition at 155°C.

[0299] Thermogravimetric-infrared (TG-IR) Analysis was preformed on a TA Instruments Q5000 thermogravimetric analyzer interfaced to a Nicolet 6700 FT-IR spectrometer (Thermo Electron) equipped with an external TGA-IR module with a gas flow cell and DTGS detector. The FT-IR wavelength verification was performed using polystyrene, and the TG calibration standards were nickel and Alumel™. The sample was placed in a platinum or aluminium sample pan, and the pan was inserted into the TG furnace. The TG instrument was started first, immediately followed by the FT-IR instrument. The TG instrument was operated under a flow of helium at 90 and 10 cc/min for the purge and balance, respectively. The furnace was heated under nitrogen at a rate of 15°C./minute to a final temperature of 230°C. IR spectra were collected approximately every 32 seconds for approximately 13 minutes. Each IR spectrum used 32 co-added scans collected at a spectral resolution of 4 cm^{-1}. The TGA thermogram obtained for the sample of Compound **5** is shown in Figure 4 overlayed with the DSC thermogram. These TGA data with IR analysis of the evolved gas indicate that the input material is non-solvated but loses one mole-equivalent of water between 135 and 181°C.

[0300] **[0338]** All references cited herein, including but not limited to published and unpublished applications, patents, and literature references, are incorporated herein by reference in their entirety and are hereby made a part of this specification. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

[0301] The term "comprising" as used herein is synonymous with "including," "containing," or "characterized by," and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

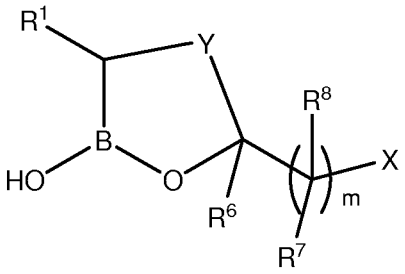
[0302] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the

numerical parameters set forth herein are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of any claims in any application claiming priority to the present application, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[0303] The above description discloses several methods and materials that are susceptible to modifications, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this disclosure or practice of the methods disclosed herein. Consequently, it is not intended that this invention be limited to the specific embodiments disclosed herein, but that it cover all modifications and alternatives coming within the true scope and spirit of the invention.

WHAT IS CLAIMED IS:

1. A compound having the structure of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

Y is a 1-4 atom alkylene or 2-4 atom alkenylene linker, optionally substituted by one or more substituents selected from the group consisting of Cl, F, CN, CF_3, $-R^9$, $-OR^9$, $-C(=O)NR^9R^{10}$, and $-C(=O)OR^9$, wherein said alkylene or alkenylene linker is optionally fused to an optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^1 is selected from a group consisting of $-C_{1-9}$alkyl, $-C_{2-9}$alkenyl, $-C_{2-9}$alkynyl, $-NR^9R^{10}$, $-C_{1-9}$alkylR^{11}, $-C_{2-9}$alkenylR^{11}, $-C_{2-9}$alkynylR^{11}, -carbocyclyl-R^{11}, $-CH(OH)C_{1-9}$alkylR^9, $-CH(OH)C_{2-9}$alkenylR^9, $-CH(OH)C_{2-9}$alkynylR^9, -CH(OH)carbocyclyl-R^9, $-C(=O)R^9$, $-C(=O)C_{1-9}$alkylR^9, $-C(=O)C_{2-9}$alkenylR^9, $-C(=O)C_{2-9}$alkynylR^9, $-C(=O)C_{2-9}$carbocyclyl-R^9, $-C(=O)NR^9R^{10}$, $-N(R^9)C(=O)R^9$, $-N(R^9)C(=O)NR^9R^{10}$, $-N(R^9)C(=O)OR^9$, $-N(R^9)C(=O)C(=NR^{10})R^9$, $-N(R^9)C(=O)C(=CR^9R^{10})R^9$, $-N(R^9)C(=O)C_{1-4}$alkyl$N(R^9)C(=O)R^9$, $-N(R^9)C(=NR^{10})R^9$, $-C(=NR^{10})NR^9R^{10}$, $-N=C(R^9)NR^9R^{10}$, $-N(R^9)SO_2R^9$, $-N(R^9)SO_2NR^9R^{10}$, $-N=CHR^9$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

R^6 is selected from a group consisting of H, $-C_{1-9}$alkyl, C_{2-9}alkenyl, $-C_{2-9}$alkynyl, carbocyclyl, $-C_{1-9}$alkylR^{11}, $-C_{2-9}$alkenylR^{11}, $-C_{2-9}$alkynylR^{11}, carbocyclyl-R^{11}, $-C(=O)OR^9$, $-C_{1-9}$alkylCO_2R^9, $-C_{2-9}$alkenylCO_2R^9, $-C_{2-9}$alkynylCO_2R^9, and -carbocyclyl-CO_2R^9, or alternatively:

(iv) R^6 and an R^7 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl,

(v) R^6 and a carbon atom in Y are taken together with intervening atoms to form a substituted or unsubstituted carbocyclyl or substituted or unsubstitued heterocyclyl, or

(vi) R^6 is absent when the carbon to which it is attached is a ring atom in an aryl or heteroaryl ring;

each R^7 is independently selected from a group consisting of H, halo , $-C_{1-9}$alkyl, $-C_{2-9}$alkenyl, $-C_{2-9}$alkynyl, $-NR^9R^{10}$, $-OR^9$, $-C_{1-9}$alkylCO_2R^9, $-C_{2-9}$alkenylCO_2R^9, $-C_{2-9}$alkynylCO_2R^9, and -carbocyclyl-CO_2R^9, or independently:

(i) R^6 and an R^7 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl,

(ii) R^7 and an R^8 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl,

(iii) an R^7 and a carbon atom in Y are taken together with intervening atoms to form a substituted or unsubstituted carbocyclyl or substituted or unsubstitued heterocyclyl,

(iv) each of the following conditions are met:

(a) Y is a 3-4 atom alkylene or 3-4 atom alkenylene linker,

(e) R^6 is absent,

(f) R^7 and a carbon atom in Y are taken together with intervening atoms to form a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl, and

(g) each R^8 attached to a ring atom forming part of the substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl formed by R^7 and Y is absent;

each R^8 is independently selected from a group consisting of H, halo , -C_{1-9}alkyl, -C_{2-9}alkenyl, -C_{2-9}alkynyl, –NR^9R^{10}, -OR^9, -C_{1-9}alkylCO_2R^9, -C_{2-9}alkenylCO_2R^9,–C_{2-9}alkynylCO_2R^9, -carbocyclyl-CO_2R^9, or independently:

(i) an R^7 and an R^8 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl,

(ii) a geminal R^7 and R^8 together form–C_{2-9} alkenylenylCO_2R^9, or

(iii) each R^8 attached to a ring atom forming part of a substituted or unsubstituted aryl is absent;

each R^9 is independently selected from a group consisting of H, -C_{1-9}alkyl, C_{2-9}alkenyl, -C_{2-9}alkynyl, carbocyclyl, -C_{1-9}alkylR^{11}, -C_{2-9}alkenylR^{11}, -C_{2-9}alkynylR^{11}, -carbocyclyl-R^{11}, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

each R^{10} is independently selected from a group consisting of H, -C_{1-9}alkyl, -OR^9, -CH(=NH), -C(=O)OR^9, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

each R^{11} is independently selected from a group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

X is selected from a group consisting of H, -CO_2R^{12}, and carboxylic acid isosteres;

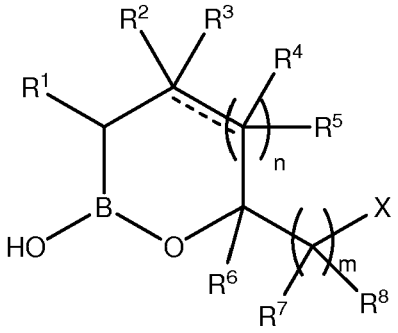
R^{12} is selected from a group consisting of H, C_{1-9}alkyl, -$(CH_2)_{0-3}$-R_{11}, -$C(R^{13})_2OC(O)C_{1-9}$alkyl, -$C(R^{13})_2OC(O)R^{11}$, -$C(R^{13})_2OC(O)OC_{1-9}$alkyl and -$C(R^{13})_2OC(O)OR^{11}$;

each R^{13} is independently selected from a group consisting of H and C_{1-4}alkyl; and

m is independently zero or an integer from 1 to 2,

wherein each C_{1-9}alkyl, C_{2-9}alkenyl, and C_{2-9}alkynyl is independently optionally substituted.

2. The compound of claim 1, having the structure of formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

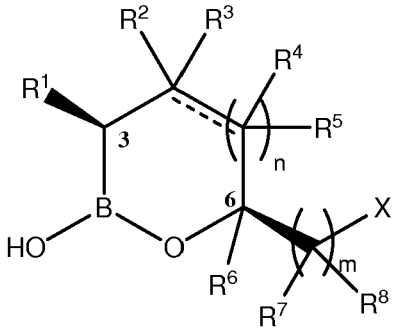
the bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond with the proviso that the dashed and solid line can only be a double bond when n is 1;

R^2 and R^4 are independently selected from a group consisting of Cl, F, CN, CF_3, $-R^9$, $-OR^9$, $-C(=O)NR^9R^{10}$, and $-C(=O)OR^9$; or alternatively, R^2 and R^4 are taken together with the atoms to which they are attached to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

R^3 and R^5 are independently selected from a group consisting of Cl, F, CN, CF_3, $-R^9$, $-OR^9$, $-C(=O)NR^9R^{10}$, and $-C(=O)OR^9$, with the proviso that if the bond represented by a dashed and solid line is a double bond then R^3 and R^5 are absent; and

n is independently zero or an integer from 1 to 2.

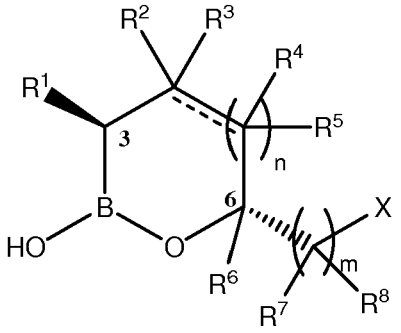
3. The compound of claim 2 having the defined 3,6-cis-stereochemistry shown in formula IIa:



IIa

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 2 having the defined 3,6-trans-stereochemistry shown in formula IIb:



IIb

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 2 to 4, wherein:

R^1 is selected from a group consisting of -C_{1-9}alkyl, -C_{2-9}alkenyl, -C_{2-9}alkynyl, –NR^9R^{10}, -C_{1-9}alkylR^{11}, -C_{2-9}alkenylR^{11}, -C_{2-9}alkynylR^{11}, -CH(OH)C_{1-9}alkylR^9, -CH(OH)C_{2-9}alkenylR^9, -CH(OH)C_{2-9}alkynylR^9, -C(=O)R^9, -C(=O)C_{1-9}alkylR^9, -C(=O)C_{2-9}alkenylR^9, -C(=O)C_{2-9}alkynylR^9, -C(=O)NR^9R^{10}, -N(R^9)C(=O)R^9, -N(R^9)C(=O)NR^9R^{10}, –N(R^9)C(=O)OR^9, -N(R^9)C(=O)C(=NR^{10})R^9, -N(R^9)C(=O)C_{1-4}alkylN(R^9)C(=O)R^9, –N(R^9)C(=NR^{10})R^9, -C(=NR^{10})NR^9R^{10}, -N=C(R^9)NR^9R^{10}, -N(R^9)SO_2R^9, –N(R^9)$SO_2NR^9R^{10}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

R^6 is selected from a group consisting of H, -C_{1-9}alkyl, C_{2-9}alkenyl, -C_{2-9}alkynyl, -C_{1-9}alkylR^{11}, -C_{2-9}alkenylR^{11}, -C_{2-9}alkynylR^{11}, -C(=O)OR^9, and -C_{1-9}alkylCO_2R^9, -C_{2-9}alkenylCO_2R^9, and –C_{2-9}alkynylCO_2R^9, or alternatively R^6 and an R^7 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

each R^7 is independently selected from a group consisting of H, –NR^9R^{10}, -OR^9, and -C_{1-9}alkylCO_2R^9, -C_{2-9}alkenylCO_2R^9, and –C_{2-9}alkynylCO_2R^9, or independently, R^6 and an R^7 or independently an R^7 and an R^8 are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

each R^8 is independently selected from a group consisting of H, –NR^9R^{10}, -OR^9, and -C_{1-9}alkylCO_2R^9, -C_{2-9}alkenylCO_2R^9, and –C_{2-9}alkynylCO_2R^9, or independently, an R^7 and an R^8 are taken together with the atoms to which they

are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

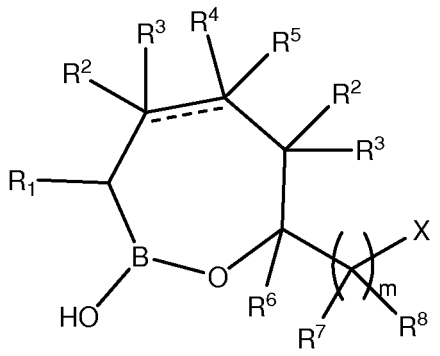
each R^9 is independently selected from a group consisting of H, -C_{1-9}alkyl, C_{2-9}alkenyl, -C_{2-9}alkynyl, -C_{1-9}alkylR^{11}, -C_{2-9}alkenylR^{11}, -C_{2-9}alkynylR^{11}, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -$(CH_2)_{0-3}$carbocyclyl, and substituted or unsubstituted heterocyclyl;

each R^{10} is independently selected from a group consisting of H, -C_{1-9}alkyl, -OR^9, -CH(=NH), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl; and

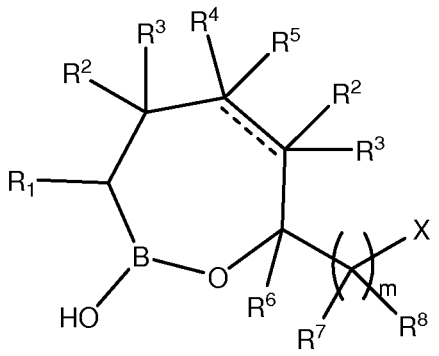
X is selected from a group consisting of H, -CO_2H and carboxylic acid isosteres.

6. The compound of any one of claims 2 to 4, wherein n is 1.

7. The compound of claim 1, having the structure of formula IIIa or IIIb:



IIIa



IIIb

or a pharmaceutically acceptable salt thereof, wherein:

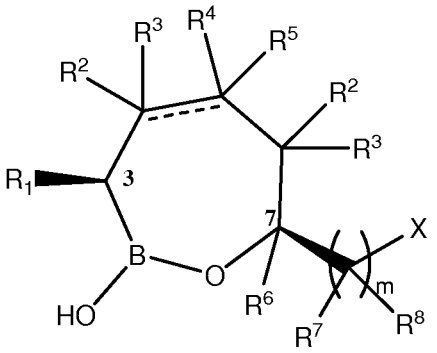
the bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond;

each R^2 and R^4 are independently selected from a group consisting of Cl, F, CN, CF_3, -R^9, -OR^9, -C(=O)NR^9R^{10}, and -C(=O)OR^9; or alternatively, an R^2 and R^4 are taken together with the atoms to which they are attached to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

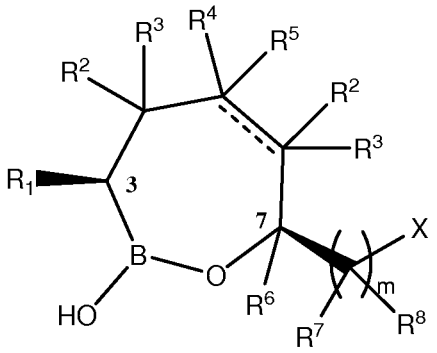
each R^3 and R^5 are independently selected from a group consisting of Cl, F, CN, CF_3, -R^9, -OR^9, -C(=O)NR^9R^{10}, and -C(=O)OR^9, with the proviso that if

the bond represented by a dashed and solid line is a double bond then R^3 and R^5 are absent.

8. The compound of claim 7, having the 3,7-cis-stereochemistry shown in formula IIIc and IIId:



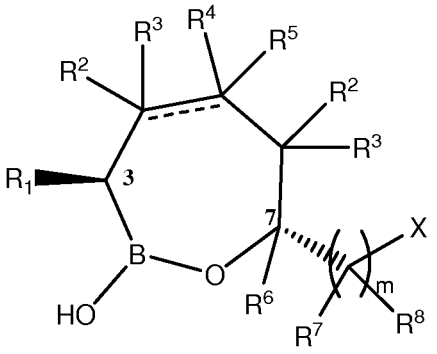
IIIc



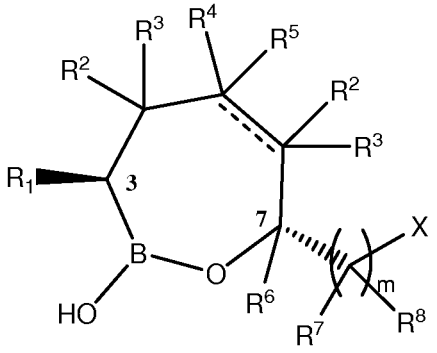
IIId

or a pharmaceutically acceptable salt thereof.

9. The compound of claim 7, having the 3,7-trans-stereochemistry shown in formula IIIe and IIIf:



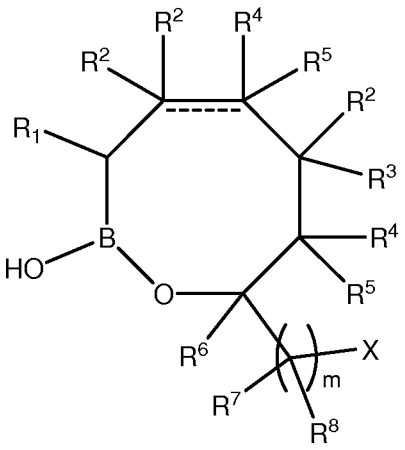
IIIe



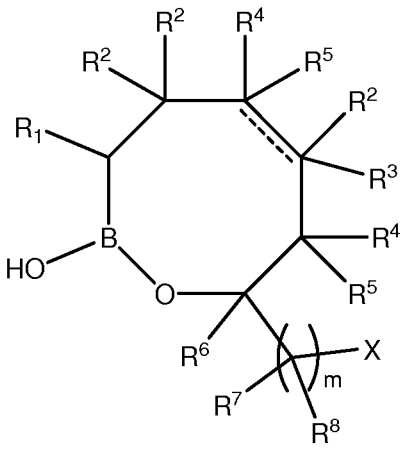
IIIf

or a pharmaceutically acceptable salt thereof.

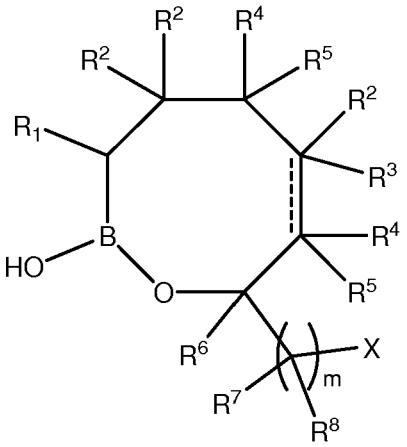
10. The compound of claim 1, having the structure of formula IVa, IVb, or IVc:



IVa



IVb



IVc

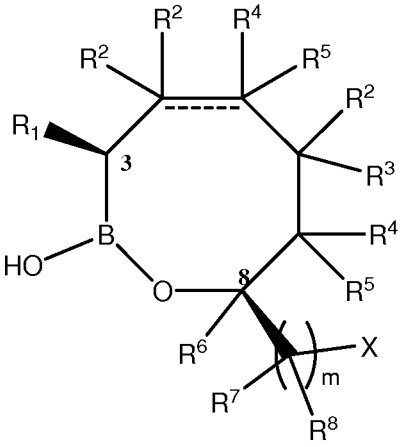
or a pharmaceutically acceptable salt thereof, wherein:

the bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond;

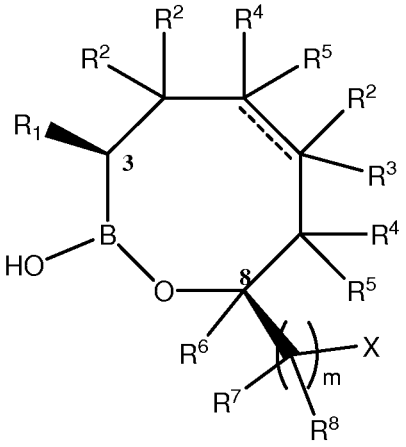
each R^2 and each R^4 are independently selected from a group consisting of Cl, F, CN, CF_3, $-R^9$, $-OR^9$, $-C(=O)NR^9R^{10}$, and $-C(=O)OR^9$; or alternatively, an R^2 and an R^4 are taken together with the atoms to which they are attached to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

each R^3 and each R^5 are independently selected from a group consisting of Cl, F, CN, CF_3, $-R^9$, $-OR^9$, $-C(=O)NR^9R^{10}$, and $-C(=O)OR^9$, with the proviso that if the bond represented by a dashed and solid line is a double bond then the R^3 and R^5 attached to the carbon atoms bonded that bond are absent.

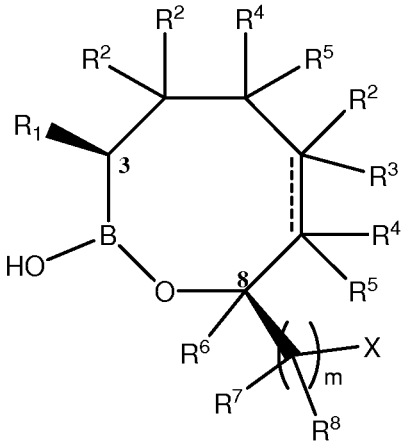
11. The compound of claim 10, having the 3,8-cis-stereochemistry shown in formula IVd, IVe, and IVf:



IVd



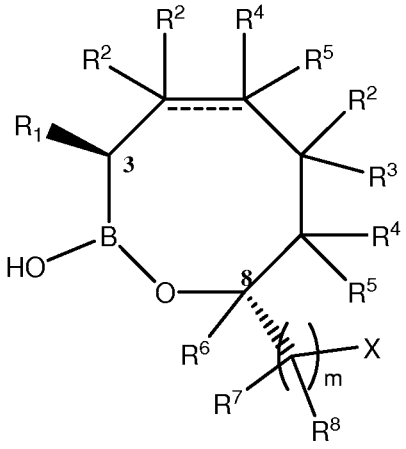
IVe



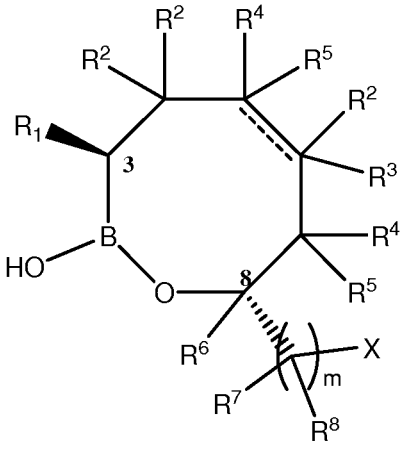
IVf

or a pharmaceutically acceptable salt thereof.

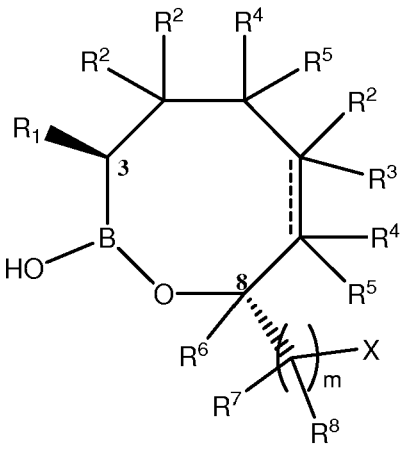
12. The compound of claim 10, having the 3,8-trans-stereochemistry shown in formula IVg, IVh, and IVi:



IVg



IVh



IVi

or a pharmaceutically acceptable salt thereof.

13. The compound of any one of claims 2-12, wherein each R^2, R^3, R^4, and R^5 are hydrogen.

14. The compound of any one of claims 2-13, wherein the bond represented by a dashed and solid line is a single bond.

15. The compound of any one of claims 2-13, wherein the bond represented by a dashed and solid line is a double bond.

16. The compound of any one of claims 1-15, wherein R^6 and each R^7 and R^8 is hydrogen.

17. The compound of any one of claims 1-16, wherein R^1 is $-NHC(=O)C_{1-9}alkylR^{11}$.

18. The compound of claim 17, wherein R^{11} is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

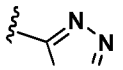
19. The compound of claim 18, wherein R^{11} is thien-2-yl.

20. The compound of any one of claims 1-19, wherein R^1 is $-NHC(=O)C(=NOR^9)R^{9'}$, wherein $R^{9'}$ is selected from the group consisting of C_{1-9}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl and substituted or unsubstituted heterocyclyl.

21. The compound as in any one of claims 1-20, wherein X is $-CO_2H$.

22. The compound as in any one of claims 1-20, wherein X is a carboxylic acid isostere.

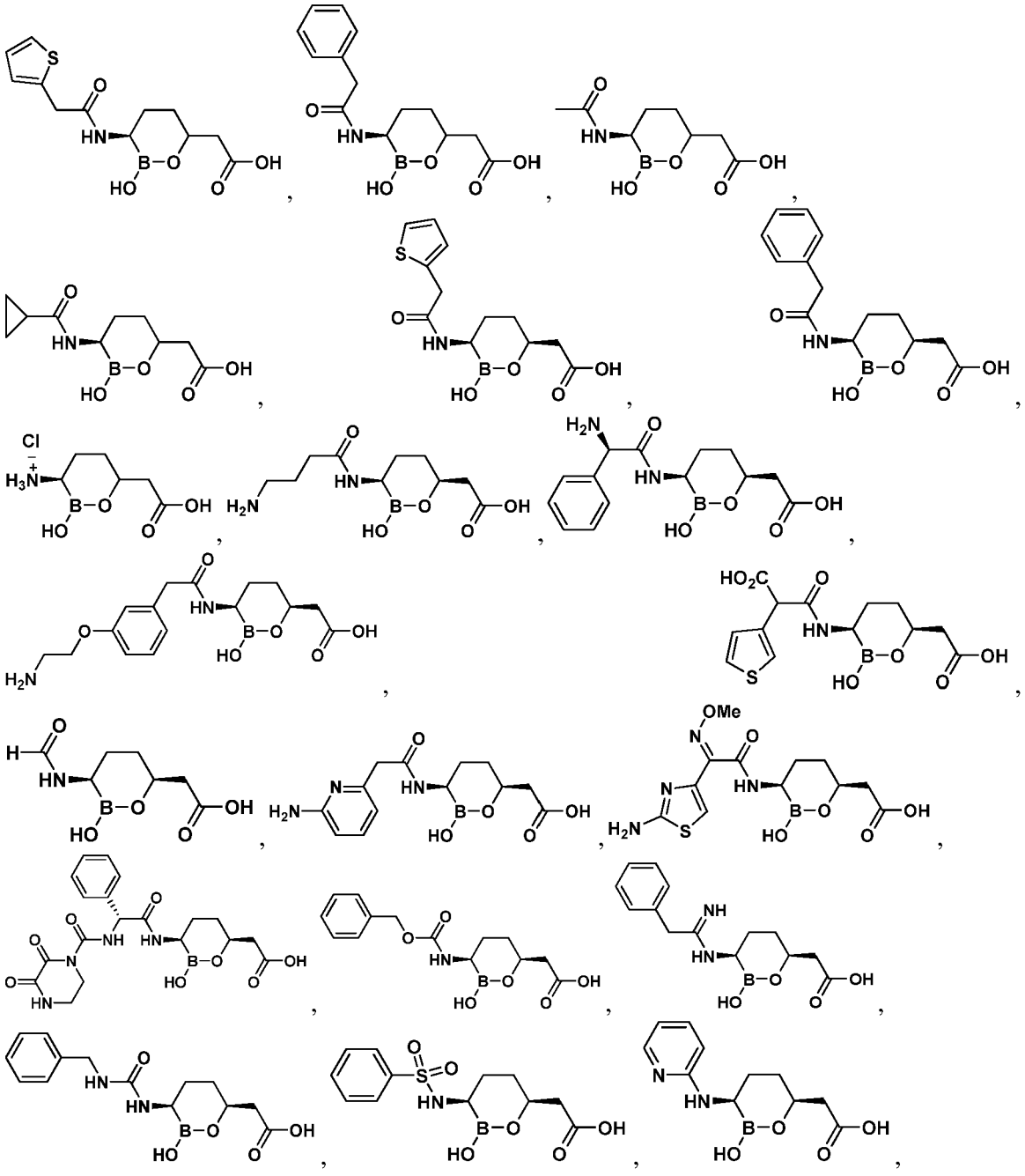
23. The compound of claim 22, wherein the carboxylic acid isostere is selected from the group consisting of $-P(O)(OR^9)_2$, $-P(O)(R^9)(OR^9)$,$-P(O)(OR^{12'})_2$, -

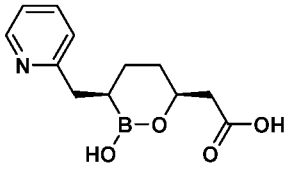
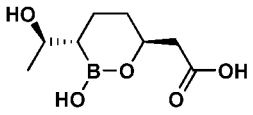
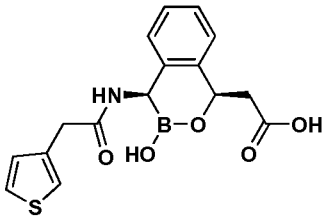
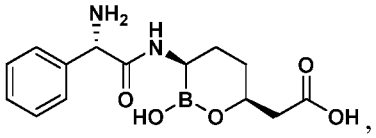
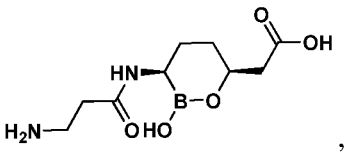
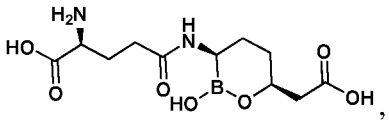
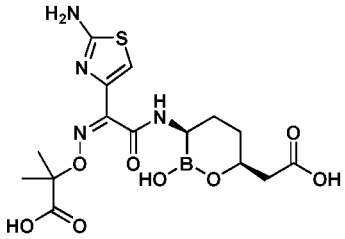
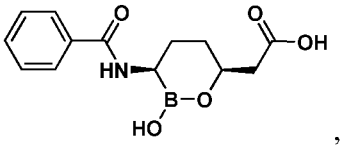
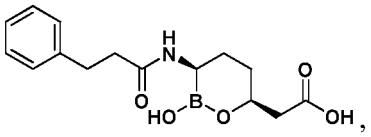
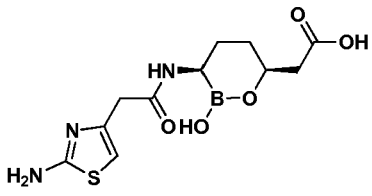
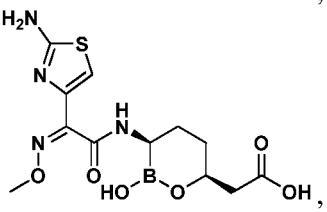
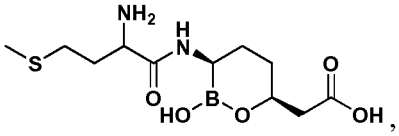
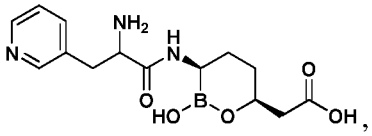
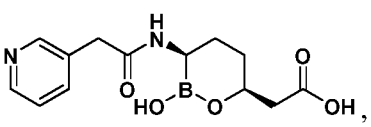
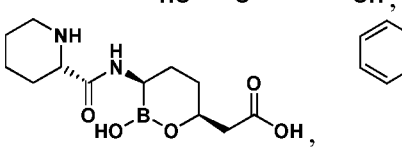
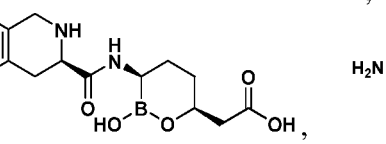
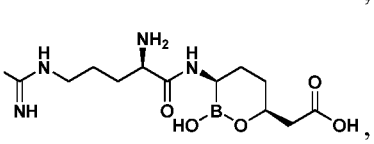
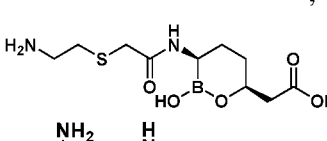
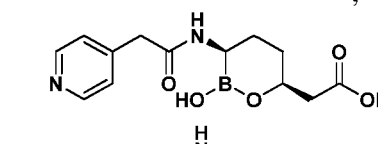
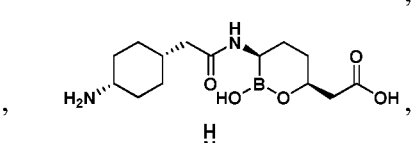
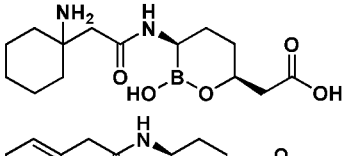
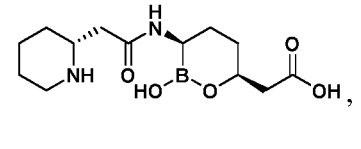
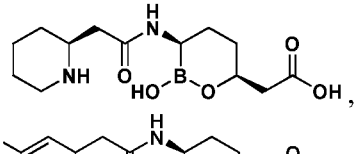
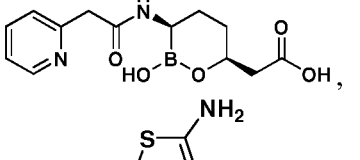
P(O)(R^9)($OR^{12'}$), -CON(R^9)OH, -SO_3H, -SO_2N(R^9)OH, and , wherein $R^{12'}$ is selected from the group consisting of H, R_{11}, -C(R^{13})$_2$OC(O)C$_{1-9}$alkyl, -C(R^{13})$_2$OC(O)R^{11}, -C(R^{13})$_2$OC(O)OC$_{1-9}$alkyl and -C(R^{13})$_2$OC(O)OR^{11}.

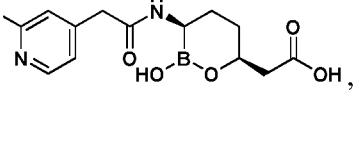
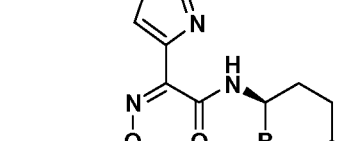
24. The compound as in any one of claims 1-23, wherein m is 1.

25. The compound as in any one of claims 1-24, wherein R^6, R^7 and R^8 are H.

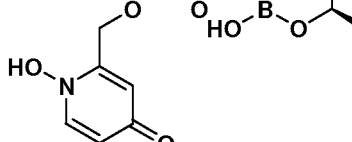
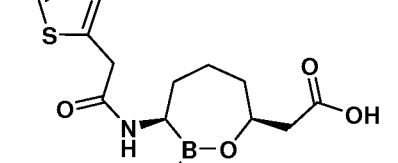
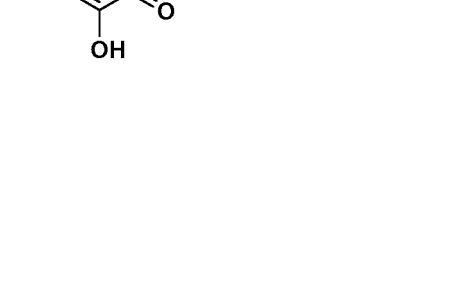
26. The compound of claim 1, having a structure selected from the group consisting of:



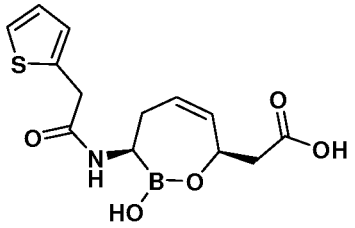
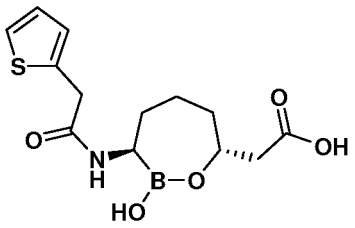
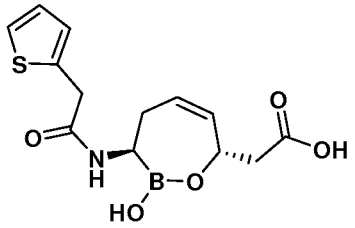
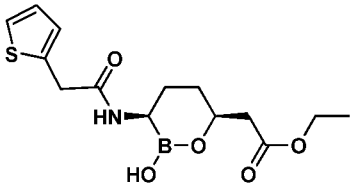
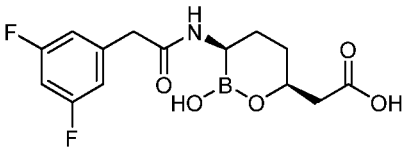
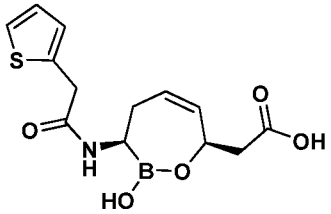
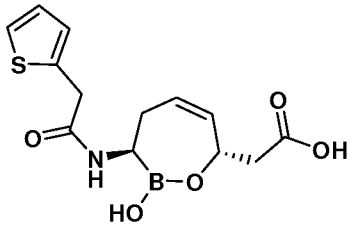
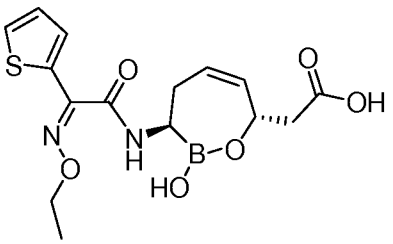
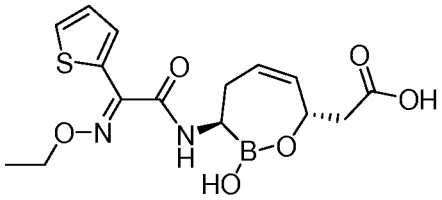
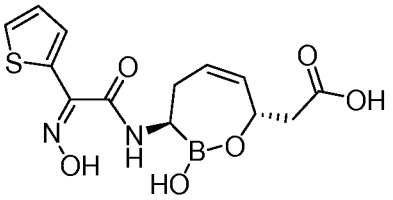
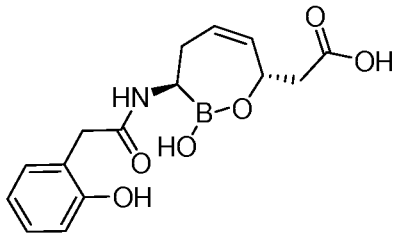
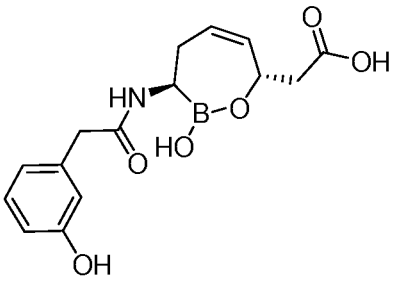
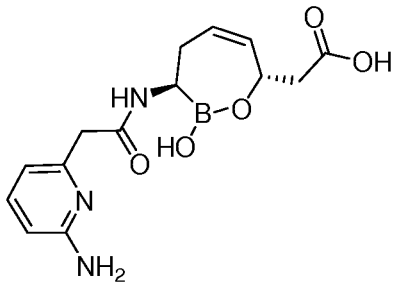
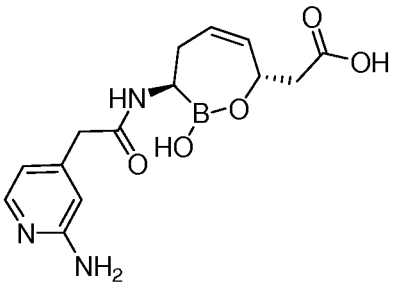
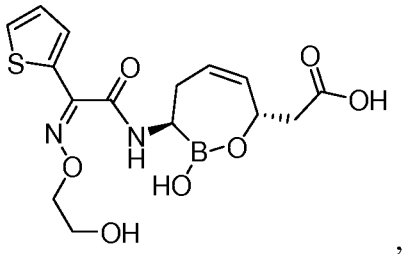
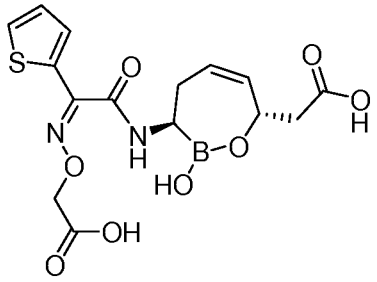

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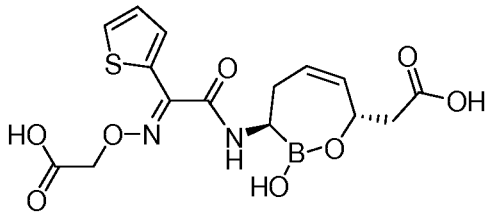
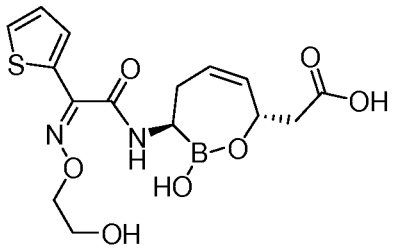
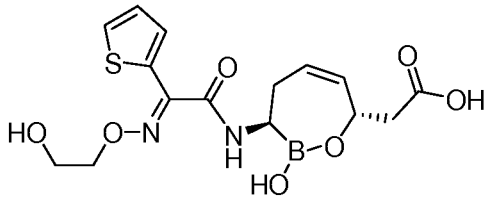
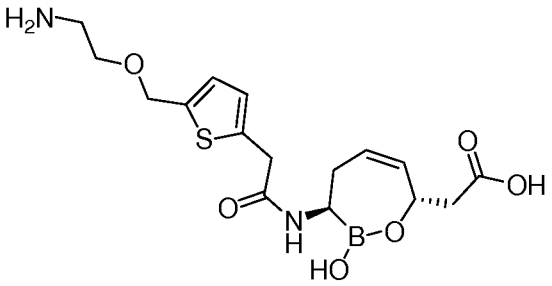
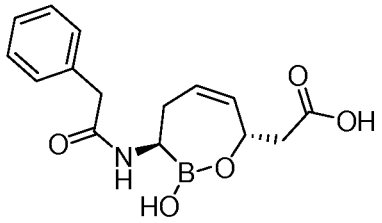
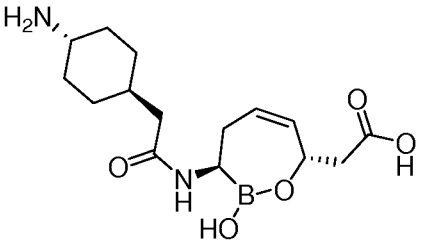
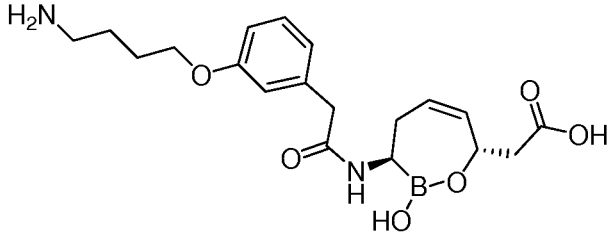
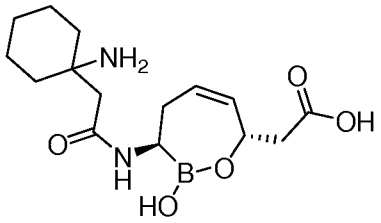
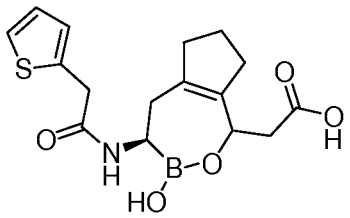
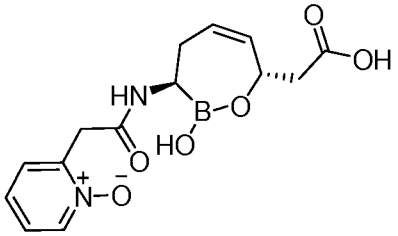
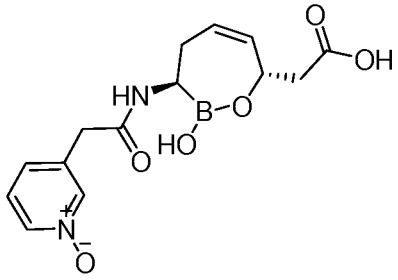
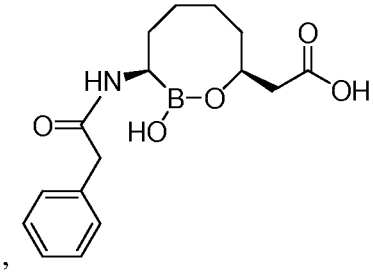
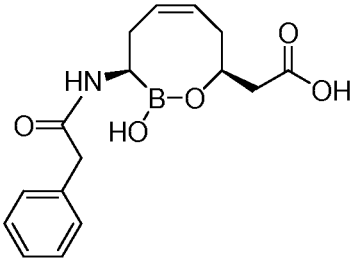
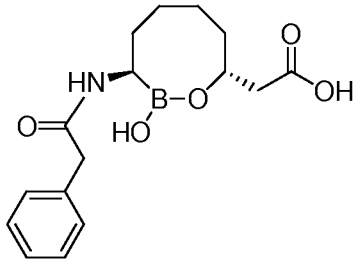
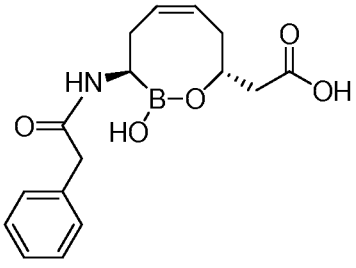
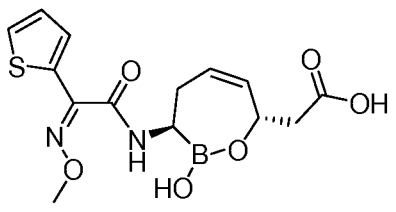
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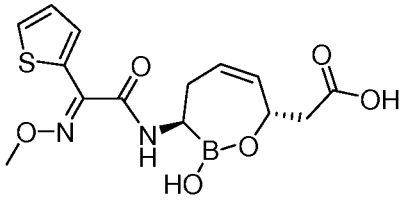
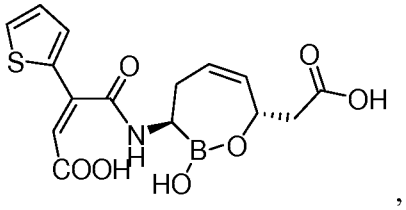
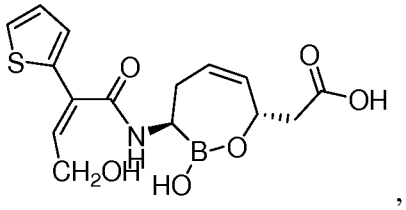
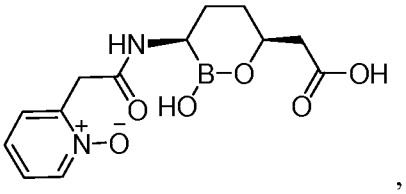
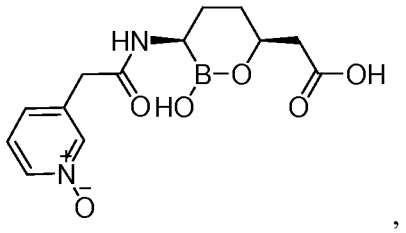
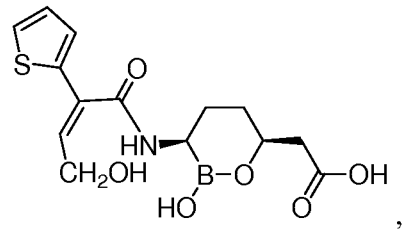
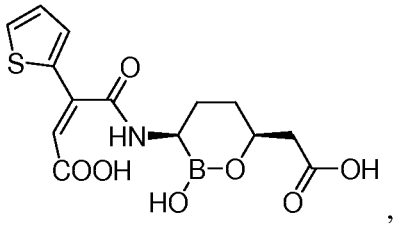
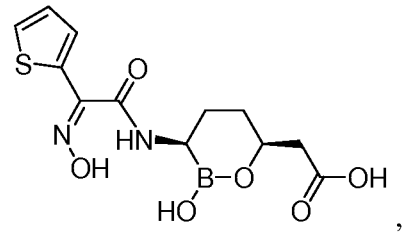
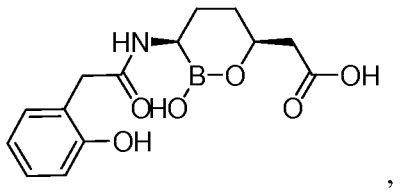
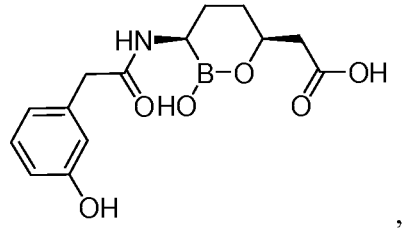
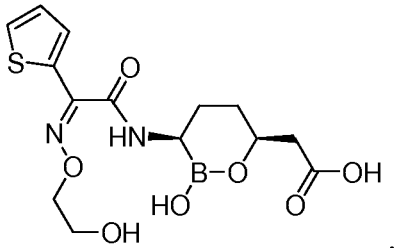
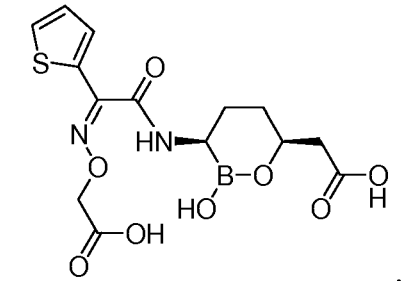
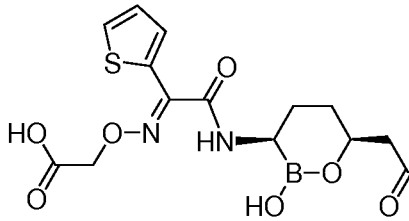
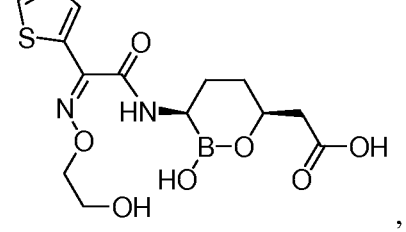
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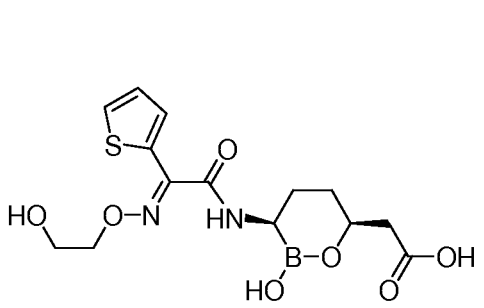
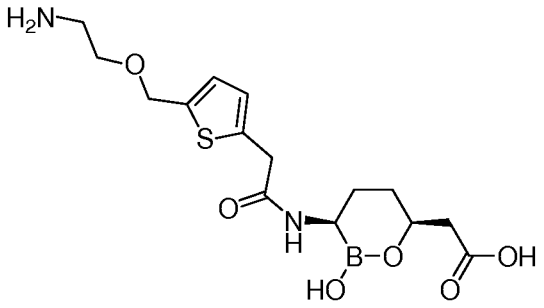
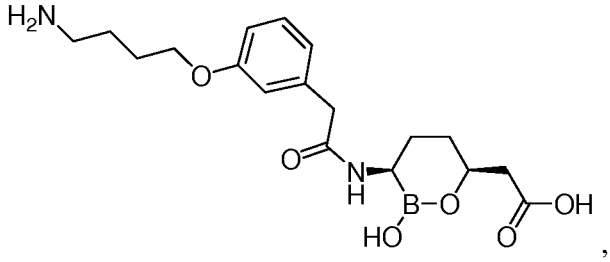
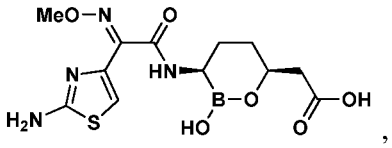
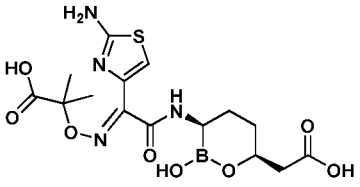
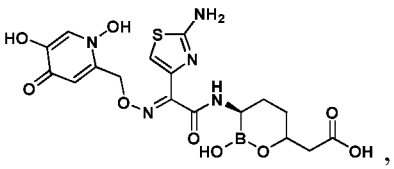
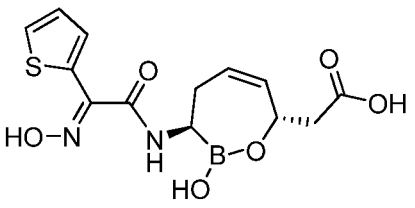
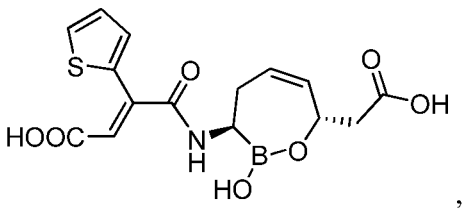
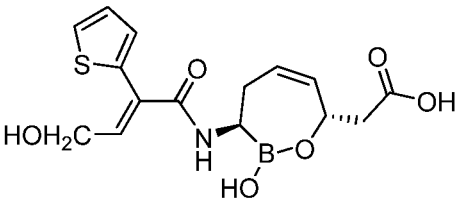
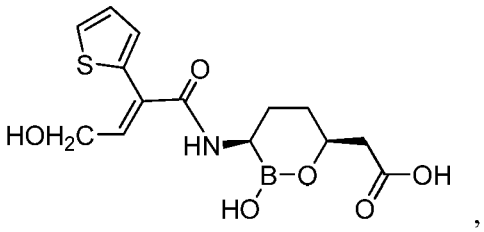
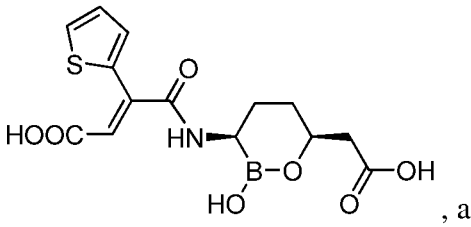
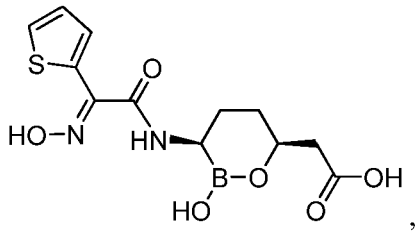

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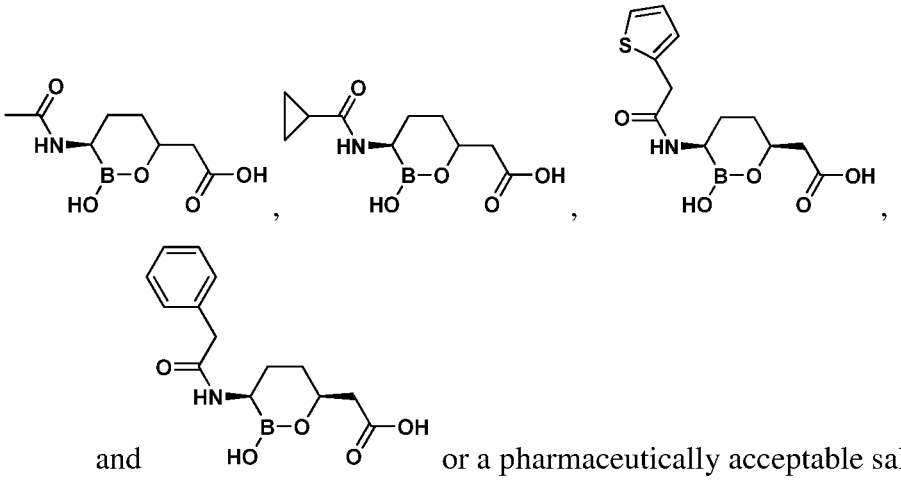
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[0304] or a pharmaceutically acceptable salt thereof.

27. The compound of claim 1, having a structure selected from the group consisting of:



and or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1-27 and a pharmaceutically acceptable excipient.

29. The pharmaceutical composition of claim 28, further comprising an additional medicament.

30. The composition of claim 29, wherein the additional medicament is selected from an antibacterial agent, antifungal agent, an antiviral agent, an anti-inflammatory agent, or an anti-allergic agent.

31. The composition of claim 30, wherein the additional medicament is a β-lactam antibacterial agent.

32. The composition of claim 31, wherein the β-lactam is selected from Amoxicillin, Ampicillin (Pivampicillin, Hetacillin, Bacampicillin, Metampicillin, Talampicillin), Epicillin, Carbenicillin (Carindacillin), Ticarcillin, Temocillin, Azlocillin, Piperacillin, Mezlocillin, Mecillinam (Pivmecillinam), Sulbenicillin, Benzylpenicillin (G), Clometocillin, Benzathine benzylpenicillin, Procaine benzylpenicillin, Azidocillin, Penamecillin, Phenoxymethylpenicillin (V), Propicillin, Benzathine phenoxymethylpenicillin, Pheneticillin, Cloxacillin (Dicloxacillin, Flucloxacillin), Oxacillin, Meticillin, Nafcillin, Faropenem, Biapenem, Doripenem, Ertapenem, Imipenem, Meropenem, Panipenem, Tomopenem, Razupenem, Cefazolin, Cefacetrile, Cefadroxil, Cefalexin, Cefaloglycin, Cefalonium, Cefaloridine, Cefalotin, Cefapirin, Cefatrizine, Cefazedone, Cefazaflur, Cefradine, Cefroxadine, Ceftezole, Cefaclor, Cefamandole, Cefminox, Cefonicid, Ceforanide, Cefotiam, Cefprozil, Cefbuperazone, Cefuroxime, Cefuzonam, Cefoxitin, Cefotetan, Cefmetazole, Loracarbef, Cefixime, Ceftazidime, Ceftriaxone, Cefcapene, Cefdaloxime, Cefdinir, Cefditoren, Cefetamet,

Cefmenoxime, Cefodizime, Cefoperazone, Cefotaxime, Cefpimizole, Cefpiramide, Cefpodoxime, Cefsulodin, Cefteram, Ceftibuten, Ceftiolene, Ceftizoxime, Flomoxef, Latamoxef, Cefepime, Cefozopran, Cefpirome, Cefquinome, Ceftobiprole, Ceftaroline, CXA-101, RWJ-54428, MC-04,546, ME1036, BAL30072, SYN 2416, Ceftiofur, Cefquinome, Cefovecin, Aztreonam, Tigemonam, Carumonam, RWJ-442831, RWJ-333441, or RWJ-333442.

33. The composition of claim 31, wherein the β-lactam is selected from Ceftazidime, Biapenem, Doripenem, Ertapenem, Imipenem, Meropenem, or Panipenem.

34. The composition of claim 31, wherein the β-lactam is selected from Aztreonam, Tigemonam, BAL30072, SYN 2416, or Carumonam.

35. The composition of claim 34, wherein:

the β-lactam is Tigemonam;

the composition is suitable for oral administration;

X is $-CO_2R^{12}$; and

R^{12} is selected from a group consisting of C_{1-9}alkyl, $-(CH_2)_{0-3}-R_{11}$, $-C(R^{13})_2OC(O)C_{1-9}$alkyl, $-C(R^{13})_2OC(O)R^{11}$, $-C(R^{13})_2OC(O)OC_{1-9}$alkyl and $-C(R^{13})_2OC(O)OR^{11}$.

36. A compound according to any one of claims 1-27 for use in the treatment or prevention of a bacterial infection.

37. A method of treating or preventing a bacterial infection, comprising administering to a subject in need thereof, a compound according to any one of claims 1-27.

38. The method of claim 37, further comprising administering an additional medicament.

39. The method of claim 38, wherein the additional medicament is selected from an antibacterial agent, antifungal agent, an antiviral agent, an anti-inflammatory agent, or an anti-allergic agent.

40. The method of claim 39, wherein the additional medicament is a β-lactam antibacterial agent.

41. The method of claim 40, wherein the β-lactam is selected from Amoxicillin, Ampicillin (Pivampicillin, Hetacillin, Bacampicillin, Metampicillin, Talampicillin), Epicillin, Carbenicillin (Carindacillin), Ticarcillin, Temocillin, Azlocillin, Piperacillin, Mezlocillin, Mecillinam (Pivmecillinam), Sulbenicillin, Benzylpenicillin (G), Clometocillin, Benzathine benzylpenicillin, Procaine benzylpenicillin, Azidocillin,

Penamecillin, Phenoxymethylpenicillin (V), Propicillin, Benzathine phenoxymethylpenicillin, Pheneticillin, Cloxacillin (Dicloxacillin, Flucloxacillin), Oxacillin, Meticillin, Nafcillin, Faropenem, Biapenem, Doripenem, Ertapenem, Imipenem, Meropenem, Panipenem, Tomopenem, Razupenem, Cefazolin, Cefacetrile, Cefadroxil, Cefalexin, Cefaloglycin, Cefalonium, Cefaloridine, Cefalotin, Cefapirin, Cefatrizine, Cefazedone, Cefazaflur, Cefradine, Cefroxadine, Ceftezole, Cefaclor, Cefamandole, Cefminox, Cefonicid, Ceforanide, Cefotiam, Cefprozil, Cefbuperazone, Cefuroxime, Cefuzonam, Cefoxitin, Cefotetan, Cefmetazole, Loracarbef, Cefixime, Ceftazidime, Ceftriaxone, Cefcapene, Cefdaloxime, Cefdinir, Cefditoren, Cefetamet, Cefmenoxime, Cefodizime, Cefoperazone, Cefotaxime, Cefpimizole, Cefpiramide, Cefpodoxime, Cefsulodin, Cefteram, Ceftibuten, Ceftiolene, Ceftizoxime, Flomoxef, Latamoxef, Cefepime, Cefozopran, Cefpirome, Cefquinome, Ceftobiprole, Ceftaroline, CXA-101, RWJ-54428, MC-04,546, ME1036, BAL30072, SYN 2416, Ceftiofur, Cefquinome, Cefovecin, Aztreonam, Tigemonam, Carumonam, RWJ-442831, RWJ-333441, or RWJ-333442.

42. The method of claim 40, wherein the β-lactam is selected from Ceftazidime, Biapenem, Doripenem, Ertapenem, Imipenem, Meropenem, or Panipenem.

43. The method of claim 40, wherein the β-lactam is selected from Aztreonam, Tigemonam, BAL30072, SYN 2416, or Carumonam.

44. The method of any one of claims 37-43, wherein the subject is a mammal.

45. The method of claim 44, wherein the mammal is a human.

46. The method of any one of claims 37-45, wherein the infection comprises a bacteria selected from *Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas acidovorans, Pseudomonas alcaligenes, Pseudomonas putida, Stenotrophomonas maltophilia, Burkholderia cepacia, Aeromonas hydrophilia, Escherichia coli, Citrobacter freundii, Salmonella typhimurium, Salmonella typhi, Salmonella paratyphi, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Francisella tularensis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia alcalifaciens, Providencia rettgeri, Providencia stuartii, Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Yersinia intermedia, Bordetella pertussis, Bordetella parapertussis, Bordetella bronchiseptica, Haemophilus influenzae, Haemophilus parainfluenzae,*

Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus ducreyi, Pasteurella multocida, Pasteurella haemolytica, Branhamella catarrhalis, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Borrelia burgdorferi, Vibrio cholerae, Vibrio parahaemolyticus, Legionella pneumophila, Listeria monocytogenes, Neisseria gonorrhoeae, Neisseria meningitidis, Kingella, Moraxella, Gardnerella vaginalis, Bacteroides fragilis, Bacteroides distasonis, Bacteroides 3452A homology group, Bacteroides vulgatus, Bacteroides ovalus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides eggerthii, Bacteroides splanchnicus, Clostridium difficile, Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium leprae, Corynebacterium diphtheriae, Corynebacterium ulcerans, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus intermedius, Staphylococcus hyicus subsp. hyicus, Staphylococcus haemolyticus, Staphylococcus hominis, or *Staphylococcus saccharolyticus*.

47. The method of any one of claims 37-45 wherein the infection comprises a bacteria selected from *Pseudomonas aeruginosa, Pseudomonas fluorescens, Stenotrophomonas maltophilia, Escherichia coli, Citrobacter freundii, Salmonella typhimurium, Salmonella typhi, Salmonella paratyphi, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Yersinia intermedia, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Vibrio cholerae, Vibrio parahaemolyticus, Legionella pneumophila, Listeria monocytogenes, Neisseria gonorrhoeae, Neisseria meningitidis, Moraxella, Bacteroides fragilis, Bacteroides vulgatus, Bacteroides ovalus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides eggerthii,* or *Bacteroides splanchnicus*.

48. Use of a compound according to any one of claims 1-27 in the preparation of a medicament for the treatment or prevention of a bacterial infection.

49. The use of claim 48, further comprising the use of an additional medicament for treating or preventing a bacterial infection.

50. The use of claim 49, wherein the additional medicament is selected from an antibacterial agent, antifungal agent, an antiviral agent, an anti-inflammatory agent or an anti-allergic agent.

51. The use of claim 50, wherein the additional medicament comprises is a β-lactam antibacterial agent.

52. The use of claim 51, wherein the β-lactam is selected from Amoxicillin, Ampicillin (Pivampicillin, Hetacillin, Bacampicillin, Metampicillin, Talampicillin), Epicillin, Carbenicillin (Carindacillin), Ticarcillin, Temocillin, Azlocillin, Piperacillin, Mezlocillin, Mecillinam (Pivmecillinam), Sulbenicillin, Benzylpenicillin (G), Clometocillin, Benzathine benzylpenicillin, Procaine benzylpenicillin, Azidocillin, Penamecillin, Phenoxymethylpenicillin (V), Propicillin, Benzathine phenoxymethylpenicillin, Pheneticillin, Cloxacillin (Dicloxacillin, Flucloxacillin), Oxacillin, Meticillin, Nafcillin, Faropenem, Biapenem, Doripenem, Ertapenem, Imipenem, Meropenem, Panipenem, Tomopenem, Razupenem, Cefazolin, Cefacetrile, Cefadroxil, Cefalexin, Cefaloglycin, Cefalonium, Cefaloridine, Cefalotin, Cefapirin, Cefatrizine, Cefazedone, Cefazaflur, Cefradine, Cefroxadine, Ceftezole, Cefaclor, Cefamandole, Cefminox, Cefonicid, Ceforanide, Cefotiam, Cefprozil, Cefbuperazone, Cefuroxime, Cefuzonam, Cefoxitin, Cefotetan, Cefmetazole, Loracarbef, Cefixime, Ceftazidime, Ceftriaxone, Cefcapene, Cefdaloxime, Cefdinir, Cefditoren, Cefetamet, Cefmenoxime, Cefodizime, Cefoperazone, Cefotaxime, Cefpimizole, Cefpiramide, Cefpodoxime, Cefsulodin, Cefteram, Ceftibuten, Ceftiolene, Ceftizoxime, Flomoxef, Latamoxef, Cefepime, Cefozopran, Cefpirome, Cefquinome, Ceftobiprole, Ceftaroline, CXA-101, RWJ-54428, MC-04,546, ME1036, BAL30072, SYN 2416, Ceftiofur, Cefquinome, Cefovecin, Aztreonam, Tigemonam, Carumonam, RWJ-442831, RWJ-333441, or RWJ-333442.

53. The use of claim 51, wherein the β-lactam is selected from Ceftazidime, Biapenem, Doripenem, Ertapenem, Imipenem, Meropenem or Panipenem.

54. The use of claim 51, wherein the β-lactam is selected from Aztreonam, Tigemonam, BAL30072, SYN 2416, or Carumonam.

55. The use of any one of claims 48-54, wherein the subject is a mammal.

56. The use of claim 55, wherein the mammal is a human.

57. The use of any one of claims 48-56, wherein the infection comprises a bacteria selected from *Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas acidovorans, Pseudomonas alcaligenes, Pseudomonas putida,*

Stenotrophomonas maltophilia, Burkholderia cepacia, Aeromonas hydrophilia, Escherichia coli, Citrobacter freundii, Salmonella typhimurium, Salmonella typhi, Salmonella paratyphi, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Francisella tularensis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia alcalifaciens, Providencia rettgeri, Providencia stuartii, Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Yersinia intermedia, Bordetella pertussis, Bordetella parapertussis, Bordetella bronchiseptica, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus ducreyi, Pasteurella multocida, Pasteurella haemolytica, Branhamella catarrhalis, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Borrelia burgdorferi, Vibrio cholerae, Vibrio parahaemolyticus, Legionella pneumophila, Listeria monocytogenes, Neisseria gonorrhoeae, Neisseria meningitidis, Kingella, Moraxella, Gardnerella vaginalis, Bacteroides fragilis, Bacteroides distasonis, Bacteroides 3452A homology group, Bacteroides vulgatus, Bacteroides ovalus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides eggerthii, Bacteroides splanchnicus, Clostridium difficile, Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium leprae, Corynebacterium diphtheriae, Corynebacterium ulcerans, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus intermedius, Staphylococcus hyicus subsp. hyicus, Staphylococcus haemolyticus, Staphylococcus hominis, or *Staphylococcus saccharolyticus*.

58. The use of any one of claims 48-56, wherein the infection comprises a bacteria selected from *Pseudomonas aeruginosa, Pseudomonas fluorescens, Stenotrophomonas maltophilia, Escherichia coli, Citrobacter freundii, Salmonella typhimurium, Salmonella typhi, Salmonella paratyphi, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Yersinia intermedia, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus haemolyticus, Haemophilus*

parahaemolyticus, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Vibrio cholerae, Vibrio parahaemolyticus, Legionella pneumophila, Listeria monocytogenes, Neisseria gonorrhoeae, Neisseria meningitidis, Moraxella, Bacteroides fragilis, Bacteroides vulgatus, Bacteroides ovalus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides eggerthii, or *Bacteroides splanchnicus*.

59. A sterile container, comprising:

a compound of any one of claims 1-27 in solid form; and

an antibacterial agent in solid form.

60. The container of claim 59, wherein the antibacterial agent is a β-lactam.

61. The container of claim 60, wherein the β-lactam is selected from Amoxicillin, Ampicillin (Pivampicillin, Hetacillin, Bacampicillin, Metampicillin, Talampicillin), Epicillin, Carbenicillin (Carindacillin), Ticarcillin, Temocillin, Azlocillin, Piperacillin, Mezlocillin, Mecillinam (Pivmecillinam), Sulbenicillin, Benzylpenicillin (G), Clometocillin, Benzathine benzylpenicillin, Procaine benzylpenicillin, Azidocillin, Penamecillin, Phenoxymethylpenicillin (V), Propicillin, Benzathine phenoxymethylpenicillin, Pheneticillin, Cloxacillin (Dicloxacillin, Flucloxacillin), Oxacillin, Meticillin, Nafcillin, Faropenem, Biapenem, Doripenem, Ertapenem, Imipenem, Meropenem, Panipenem, Tomopenem, Razupenem, Cefazolin, Cefacetrile, Cefadroxil, Cefalexin, Cefaloglycin, Cefalonium, Cefaloridine, Cefalotin, Cefapirin, Cefatrizine, Cefazedone, Cefazaflur, Cefradine, Cefroxadine, Ceftezole, Cefaclor, Cefamandole, Cefminox, Cefonicid, Ceforanide, Cefotiam, Cefprozil, Cefbuperazone, Cefuroxime, Cefuzonam, Cefoxitin, Cefotetan, Cefmetazole, Loracarbef, Cefixime, Ceftazidime, Ceftriaxone, Cefcapene, Cefdaloxime, Cefdinir, Cefditoren, Cefetamet, Cefmenoxime, Cefodizime, Cefoperazone, Cefotaxime, Cefpimizole, Cefpiramide, Cefpodoxime, Cefsulodin, Cefteram, Ceftibuten, Ceftiolene, Ceftizoxime, Flomoxef, Latamoxef, Cefepime, Cefozopran, Cefpirome, Cefquinome, Ceftobiprole, Ceftaroline, CXA-101, RWJ-54428, MC-04,546, ME1036, BAL30072, SYN 2416, Ceftiofur, Cefquinome, Cefovecin, Aztreonam, Tigemonam, Carumonam, RWJ-442831, RWJ-333441, or RWJ-333442.

62. The container of claim 60, wherein the β-lactam is selected from Ceftazidime, Biapenem, Tomopenem, Doripenem, Ertapenem, Imipenem, Meropenem or Panipenem.

63. The container of claim 60, wherein the β-lactam is selected from Aztreonam, Tigemonam, BAL30072, SYN 2416, or Carumonam.

64. The container of any one of claims 59-63, wherein the compound and the antibacterial agent are blended.

65. The container of any one of claims 59-63, wherein the compound and the antibacterial agent are not blended.

66. The container of any one of claims 59-65, wherein the compound is in crystalline form.

67. The container of any one of claims 59-66, wherein the antibacterial agent is in crystalline form.

68. The container of any one of claims 59-65, wherein the compound and the antimicrobial agent are lyophiles.

69. The container of any one of claims 59-68, wherein the molar ratio of compound to antibacterial agent is from 1:8 to 8:1.

70. The container of any one of claims 59-68, wherein the molar ratio of compound to antibacterial agent is from 1:2 to 2:1.

71. The container of any one of claims 59-68, wherein the molar ratio of compound to antibacterial agent is 1:1.

72. The container of any one of claims 59-71, further comprising a pH adjuster.

73. The container of claim 72, wherein the pH adjuster comprises NaOH.

74. The container of claim 72, wherein the pH adjuster comprises citric acid.

75. A method of preparing a pharmaceutical composition for administration, comprising reconstituting the contents of the sterile container of claim 59 using a pharmaceutically acceptable diluent.

76. The method of claim 75, wherein the diluent comprises a saline solution.

77. The method of claim 75, wherein the diluent comprises a dextrose solution.

78. A method of administration, comprising administering the reconstituted solution of claim 75 intravenously to a patient.