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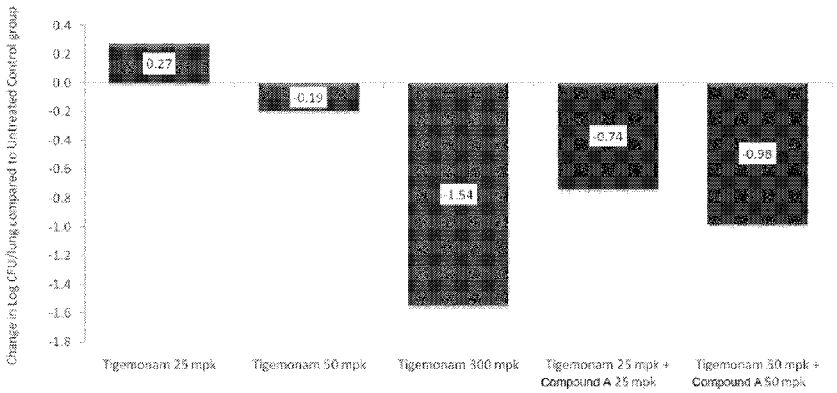

Figure 1

(57) Abstract: The present invention relates to compounds, compositions and methods for treating bacterial infections. Embodiments of the present invention include antibiotics and β-lactamase inhibitors to treat resistant infections.

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METHODS OF TREATING BACTERIAL INFECTIONS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/599148 entitled "METHODS OF TREATING BACTERIAL INFECTIONS" filed on February 15, 2012, the contents of which is incoproated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to compounds, compositions and methods for treating bacterial infections. Embodiments of the present invention include antibiotics and β-lactamase inhibitors to treat infections.

BACKGROUND

[0003] 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

[0004] 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 to render 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.

[0005] 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 or multiple amino acid substitutions in TEM-1 and SHV-1 resulted in the emergence of the extended-spectrum β-lactamase (ESBL) phenotype.

[0006] 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 are 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 and Europe. Treatment of resistant strains with carbapenems can be associated with poor outcomes. β-lactamases of the Class B are metallobeta-lactamases and are characterized by use of a metal ion such as zinc for activity. Examples of Class B enzymes include VIM, IMP, and the recently described NDM-1 enzyme. These enzymes may be located in a variety of Gram-negative pathogens, including *Enterobacteriaceae* and *Pseudomonas aeruginosa* Older β-lactamase inhibitors such as tazobactam and clavulanic acid are ineffective against Class B enzymes, and have little or no inhibitory activity against Class C and Class D ezymes. While clavulanate and tazobactam have activity against some Class A beta-lactamases like TEM-1, they have lower activity against Class A carbapenemases (e.g., KPC) as well as low activity 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

[0007] The present invention relates to compounds, compositions and methods for treating bacterial infections. Embodiments of the present invention include antibiotics and β-lactamase inhibitors to treat infections. Some embodiments include a method of increasing sensitivity of a bacterial infection to treatment with an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase, said method comprising: identifying a bacterial infection as including bacteria that comprises a serine β-lactamase and a metallo β-lactamase; and contacting said bacteria with an effective amount of a β-lactamase inhibitor. In some embodiments, contacting said bacteria with an effective amount of a β-lactamase inhibitor comprises administering the β-lactamase inhibitor to a subject having said bacterial infection.

[0008] Some embodiments include a method of treating a bacterial infection that includes bacteria comprising a serine β-lactamase and a metallo β-lactamase, said method comprising: contacting said bacteria with a β-lactamase inhibiting effective amount of a β-lactamase inhibitor and an antibacterially effective amount of an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase. Some embodiments also include identifying said bacterial infection as including bacteria that comprises a serine β-lactamase and a metallo β-lactamase. In some embodiments, contacting said bacteria with a β-lactamase inhibiting effective amount of a β-lactamase inhibitor and an antibacterially effective amount of an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase comprises administering the β-lactamase inhibitor and the antimicrobial compound resistant to degradation by a metallo β-lactamase to a subject having said bacterial infection. In some embodiments, said administering comprises administering a pharmaceutical composition comprising said β-lactamase inhibitor and said antimicrobial compound resistant to degradation by a metallo β-lactamase to said subject.

[0009] Some embodiments include use of an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase in the preparation of a medicament for use in combination with a β-lactamase inhibitor for treating a bacterial infection that includes bacteria comprising a serine β-lactamase and a metallo β-lactamase.

[0010] Some embodiments include use of a β-lactamase inhibitor in the preparation of a medicament for use in combination with an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase for treating a bacterial infection that includes bacteria comprising a serine β-lactamase and a metallo β-lactamase.

[0011] Some embodiments include use of a β-lactamase inhibitor in the preparation of a medicament for increasing the sensitivity of a bacterial infection to an antimicrobial β-

lactam compound resistant to degradation by a metallo β-lactamase, wherein the bacterial infection includes bacteria comprising a serine β-lactamase and a metallo β-lactamase.

[0012] In some embodiments, the antimicrobial compound resistant to degradation by a metallo β-lactamase has a K_m for the metallo β-lactamase greater than about 100 μM. In some embodiments, the antimicrobial compound resistant to degradation by a metallo β-lactamase has a K_m for the metallo β-lactamase greater than about 130 μM.

[0013] In some embodiments, the antimicrobial compound resistant to degradation by a metallo β-lactamase has a minimum inhibitory concentration for *E. coli* expressing the metallo β-lactamase less than about 250 μg/ml. In some embodiments, the antimicrobial compound resistant to degradation by a metallo β-lactamase has a minimum inhibitory concentration for *E. coli* expressing the metallo β-lactamase less than about 0.05 μg/ml.

[0014] In some embodiments, the antimicrobial compound resistant to degradation by a metallo β-lactamase comprises biapenem.

[0015] In some embodiments, the antimicrobial compound resistant to degradation by a metallo β-lactamase comprises a monobactam. In some embodiments, the antimicrobial compound resistant to degradation by a metallo β-lactamase is selected from the group consisting of Aztreonam, Tigemonam, Carumonam, SYN-2416, BAL30072, and Nocardicin A.

[0016] In some embodiments, the sensitivity to the antimicrobial compound resistant to degradation by a metallo β-lactamase of the bacteria contacted with the β-lactamase inhibitor increases at least about 8-fold compared to bacteria not contacted with the β-lactamase inhibitor. In some embodiments, the sensitivity to the antimicrobial compound resistant to degradation by a metallo β-lactamase of the bacteria contacted with the β-lactamase inhibitor increases at least about 4-fold compared to bacteria not contacted with the β-lactamase inhibitor. In some embodiments, erein the sensitivity to the antimicrobial compound resistant to degradation by a metallo β-lactamase of the bacteria contacted with the β-lactamase inhibitor increases at least about 2-fold compared to bacteria not contacted with the β-lactamase inhibitor.

[0017] In some embodiments, the serine β-lactamase is selected from the group consisting of NMC-A, SME, KPC-2, OXA-48, and KPC-3. In some embodiments, the serine β-lactamase comprises a KPC enzyme. In some embodiments, the serine β-lactamase comprises KPC-2.

[0018] In some embodiments, the metallo β-lactamase comprises NDM-1.

[0019] In some embodiments, the metallo β-lactamase comprises IMP, VIM, SPM, and GIM.

[0020] In some embodiments, the bacterial infection comprises a bacterium selected from the group consisting of *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*, and *Staphylococcus saccharolyticus*.

[0021] In some embodiments, a mammal has said bacterial infection. In some embodiments, a human has said bacterial infection.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] FIG. 1 shows a graph of change in Log CFU/lung in a neutopenic mouse thigh infection model treated with Tigemonam alone or with the BLI, Compound A (also known as Compound 68).

DETAILED DESCRIPTION

[0023] The present invention relates to compounds, compositions and methods for treating bacterial infections. Embodiments of the present invention include antibiotics and β-lactamase inhibitors to treat or prevent bacterial infections. Some embodiments include methods of treating or preventing a bacterial infection comprising administering a β-lactamase. Some such embodiments include contacting the bacteria causing the bacterial infection with a β-lactamase inhibitor and an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase, such as a monobactam or biapenem. Some embodiments include identifying the bacterial infection as including a bacteria comprises a β-lactamase.

[0024] Some embodiments include methods of increasing the sensitivity of a bacterial infection to treatment with an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase, such as a monobactam or biapenem. Some such embodiments include contacting the bacteria causing the infection with an effective amount of a β-lactamase inhibitor. Some such embodiments include indentifying a bacterial infection as including a bacteria that comprises a β-lactamase, and contacting the bacterial infection with an effective amount of a β-lactamase inhibitor. In some embodiments, the β-lactamase inhibitor increases the sensitivity of the bacteria *in vitro* and *in vivo* to an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase, such as a monobactam or biapenem, compared to a bacterial infection not contacted with the β-lactamase inhibitor by at least about 2-fold, at least about 4-fold, at least about 8-fold, at least about 16-fold, and at least about 32-fold.

[0025] In some embodiments, the β-lactamase comprises a serine β-lactamase. In some embodiments, the β-lactamase comprises a metallo β-lactamase. In some embodiments, the bacteria comprises both a serine β-lactamase and a metallo β-lactamase. In preferred embodiments, the β-lactamase comprises a carbapenemase.

[0026] Examples of serine β-lactamases include KPC enzymes that are considered carbapenemases since they hydrolyze carbapenems as well as other beta-lactam antibiotics. Examples of KPC enzymes include KPC-2, KPC-3, KPC-3, KPC-4, KPC-5, KPC-6, KPC-7, KPC-8, KPC-9, KPC-10, and KPC-11 (*see e.g.*, Bush, K. *et al.*, (2010) Antimicro. Agents & Chemo. 54:969-976, incorporated by reference in its entirety). In some embodiments, the serine β-lactamases is NMC-A, SME, KPC-2, OXA-48, and KPC-3. In some embodiments, the serine β-lactamases is KPC-2. Examples of metallo β-lactamases include NDM-1, IMP, VIM, SPM, and GIM (*see e.g.*, Walsh T.R., *et al.*, (2005) Am. Soc. Micro. 18:306-325, incorporated herein by reference in its entrirety). In some embodiments, the metallo β-lactamase comprises NDM-1.

[0027] Methods of identifying a bacterial infection as including bacteria that comprise a β-lactamase, including one or more particular β-lactamases, are well known in the art. Examples of identifying a bacterial infection as including bacteria that comprise a β-lactamase include PCR and phenotypic tests, including screens based on media such as ChromID ESBL culture medium (*see e.g.*, Nordmann P. *et al.*, (2011) J. Clin. Micro. 49:718-721, incorporated herein by reference in its entirety).

Definitions

[0028] 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.

[0029] 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.

[0030] 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.

[0031] 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.**[0130]** 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.

[0032] As used herein, "cycloalkyl" means a fully saturated carbocyclyl ring system. Examples include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0033] As used herein, "cycloalkenyl" means a carbocyclyl ring system having at least one double bond. An example is cyclohexenyl.

[0034] 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.

[0035] 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.

[0036] 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.

[0037] 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.

[0038] 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.

[0039] 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-).

[0040] 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.

[0041] 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".

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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.

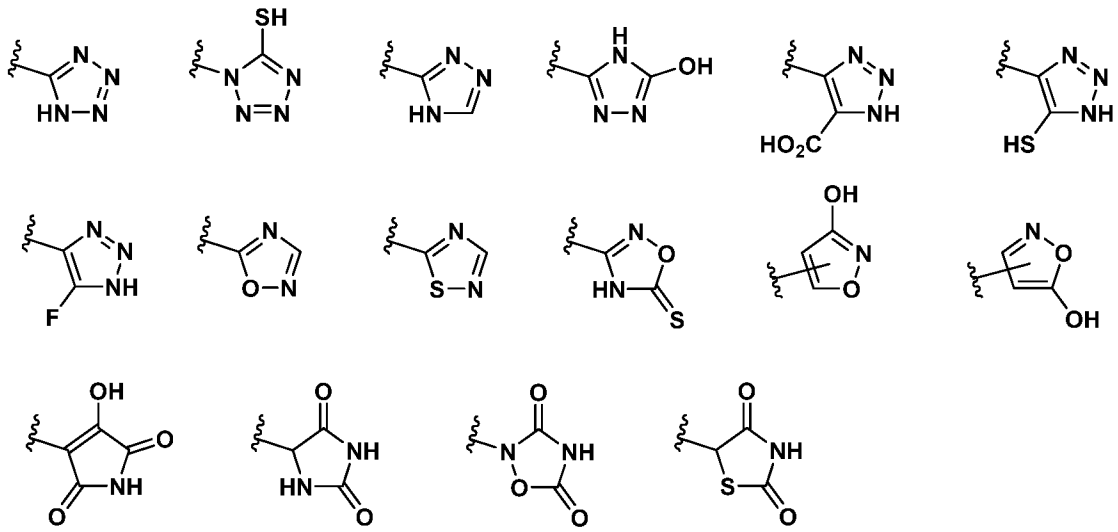
[0052] In some embodiments, substituted group(s) is (are) substituted with one or more substituent(s) individually and independently selected from C_1-C_6 alkyl, C_3-C_7 carbocycle, amino ($-NH_2$), amino(C_1-C_6)alkoxy, carboxyl, oxo (=O), C_1-C_6 alkylthio, amino(C_1-C_6)alkylthio, guanidinyl, aryl, 5-7 membered heterocyclyl, heteroarylalkyl, hydroxy, halo, amino(C_1-C_6)alkoxy, and amino(C_1-C_6)alkoxyalkyl.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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 herein. 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 herein.

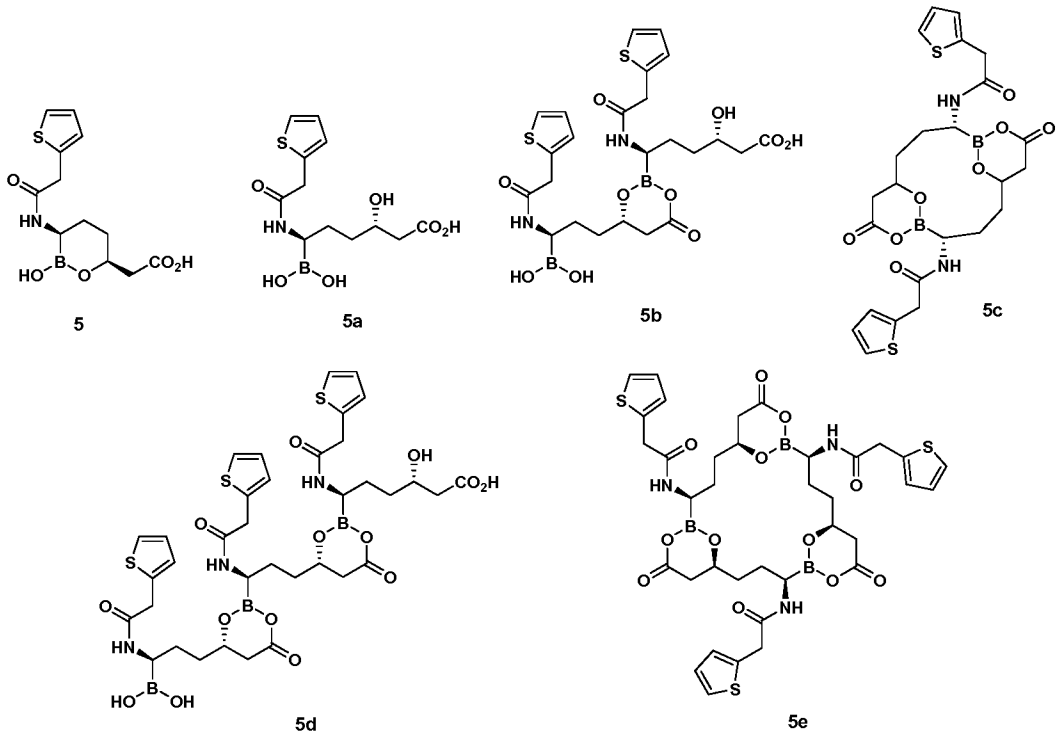


[0057] It is also contemplated that when chemical substituents are added to a carboxylic isostere, the compound retains the properties of a carboxylic isostere. It is contemplated that when a carboxylic isostere is optionally substituted with one or more moieties selected from R^9 as defined herein, 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.

[0058] Other carboxylic acid isosteres not specifically exemplified in this specification are also contemplated.

[0059] 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.

[0060] In some embodiments, due to the facile exchange of boron esters, some of 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.



[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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).

[0068] "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.

[0069] "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.

[0070] 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).

[0071] "Treat," "treatment," or "treating," as used herein refers to administering a pharmaceutical composition for prophylactic and/or therapeutic purposes. The term "prophylactic treatment," "prevent," "prevention," or "preventing" 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

[0072] Some embodiments include pharmaceutical compositions comprising: (a) a safe and therapeutically effective amount of a beta lactamase inhibitor provided herein; and (b) a

pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition additionally comprises an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase, such as a monobactam or biapenem.

[0073] The β-lactamase inhibitors are administered at a therapeutically effective dosage, e.g., a dosage sufficient to inihibit the β-lactamase to a level sufficient to provide treatment or prevention of a bacterial infection when used in combination with an antibiotic such as an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase, such as a monobactam or biapenem biapenem. While human dosage levels have yet to be optimized for the compounds of the preferred embodiments, generally, a daily dose for most of the β-lactamase inhibitors 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.

[0074] 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.

[0075] 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.

[0076] In addition to the active ingredients 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.

[0077] 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.

[0078] 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.

[0079] 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 or compounds that are 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, or 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.

[0080] 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).

[0081] 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 active ingredients. 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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.

[0090] 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.

[0091] In a similar vein, an ophthalmically acceptable antioxidant includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[0092] 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.

[0093] 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.

[0094] 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. In various embodiments, the pH of the final composition ranges from 2 to 8, or preferably from 4 to 7. 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.

[0095] The compositions for intravenous administration may be provided to caregivers in the form of one more solids that are reconstituted shortly prior to administration. In other embodiments, the compositions are provided in solution ready to administer. In still

other embodiments, the compositions are provided in a solution that is further diluted prior to administration. In embodiments that include administering a β-lactamase inhibitor in combination with an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase, such as a monobactam or biapenem, 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.

[0096] 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.

Methods of Treatment

[0097] Some embodiments of the present invention include methods of treating bacterial infections with the compounds and compositions comprising β-lactamase inhibitors 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.

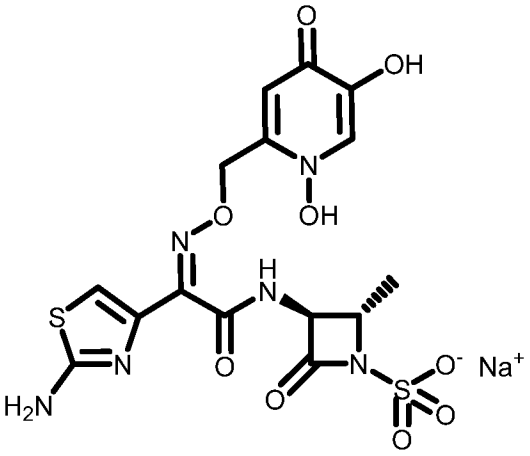
[0098] Some embodiments include co-administering a β-lactamase inhibitor with an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase, such as a monobactam or biapenem. As used herein "an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase" includes an antimicrobial compound that is relatively resistant to hydolysis by a metallo β-lactamase compared to an antimicrobial compound that is hydrolyzed by a metallo β-lactamase. For example, in some embodiments, the K_m of an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase with a metallo β-lactamase, such as NDM-1, can be at least about 10 μM, at least about 20 μM, at least about 30 μM, at least about 40 μM, at least about 50 μM, at least about 60 μM, at least about 70 μM, at least about 80 μM, at least about 90 μM, at least about 100 μM, at least about 110 μM, at least about 120 μM, at least about 130 μM, at least about 140 μM, at least about 150 μM, at least about 160 μM, at least about 170 μM, at least about 180 μM, at least about 190 μM, and at least about 100 μM. In some embodiments, the K_m of an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase with a metallo β-lactamase, such as NDM-1,

can be at least about 150 μM, at least about 200 μM, at least about 250 μM, at least about 300 μM, at least about 350 μM, at least about 400 μM, at least about 450 μM, at least about 500 μM.

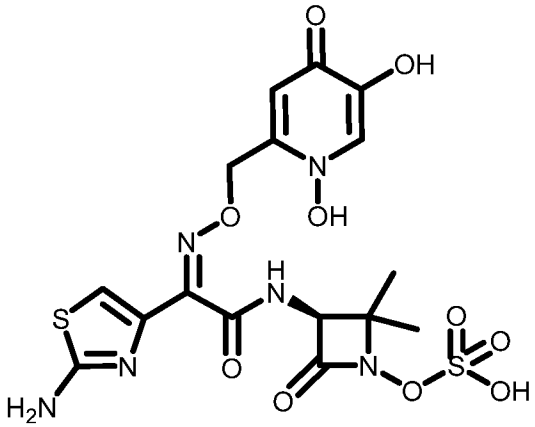
[0099] In some embodiments, an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase includes an antimicrobial compound with a metallo β-lactamase having a k_{cat} of at least about 50 s^{-1}, 100 s^{-1}, 150 s^{-1}, 200 s^{-1}, 250 s^{-1}, 300 s^{-1}, 350 s^{-1}, 400 s^{-1}, 450 s^{-1}, and 500 s^{-1}.

[0100] In some embodiments, an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase includes an antimicrobial compound with a minimum inhibitory concentration (MIC) against a pathogenic microorganism expressing a metallo β-lactamase, such as NMD-1, such as *Klebsiella* spp. and *E. coli*, or *Pseudomonas aeruginosa*, less than about 300 μg/ml, less than about 250 μg/ml, less than about 200 μg/ml, less than about 150 μg/ml, less than about 100 μg/ml, less than about 50 μg/ml. In some embodiments, an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase includes an antimicrobial compound with a MIC against a pathogenic microorganism expressing a metallo β-lactamase, such as NMD-1, less than about 50 μg/ml, less than about 40 μg/ml, less than about 30 μg/ml, less than about 20 μg/ml, less than about 10 μg/ml, and less than about 1 μg/ml. In some embodiments, an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase includes an antimicrobial compound with a MIC against a pathogenic microorganism expressing a metallo β-lactamase, such as NMD-1, less than about 1.00 μg/ml, less than about 0.90 μg/ml, less than about 0.80 μg/ml, less than about 0.70 μg/ml, less than about 0.60 μg/ml, less than about 0.50 μg/ml, less than about 0.40 μg/ml, less than about 0.30 μg/ml, less than about 0.20 μg/ml, and less than about 0.10 μg/ml. In some embodiments, an antimicrobial compound resistant to degradation by a metallo β-lactamase, such as NDM-1, includes an antimicrobial compound with a MIC against a pathogenic microorganism expressing a metallo β-lactamase, such as NMD-1, less than about 0.10 μg/ml, less than about 0.09 μg/ml, less than about 0.08 μg/ml, less than about 0.07 μg/ml, less than about 0.06 μg/ml, less than about 0.05 μg/ml, less than about 0.04 μg/ml, less than about 0.03 μg/ml, less than about 0.02 μg/ml, and less than about 0.01 μg/ml. In some of the foregoing embodiments, the pathogenic microorganism comprises a single metallo β-lactamase. In some of the foregoing embodiments, the pathogenic microorganism comprises more than one metallo β-lactamase.

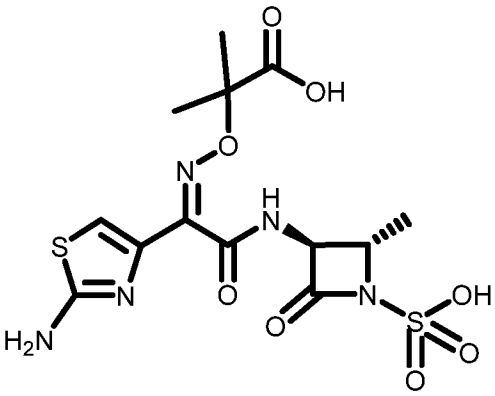
[0101] Examples of monobactams include SYN-2416 (also known as PTX2416), BAL30072, Aztreonam, Tigemonam, and Carumonam, the structures of which are:



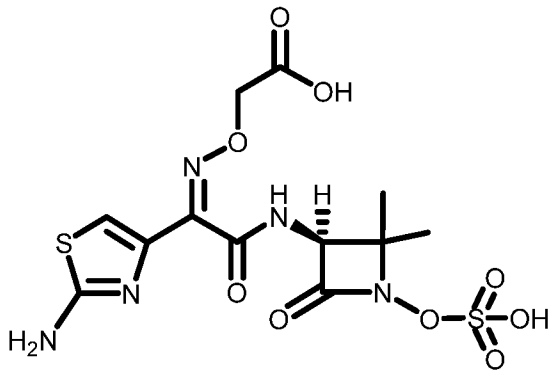
SYN-2416
PTX-2416



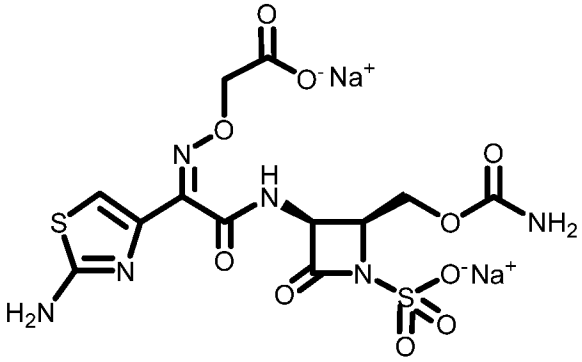
BAL-30072



aztreonam



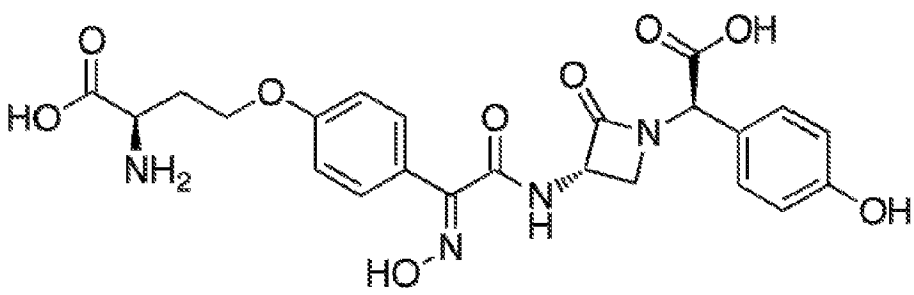
tigemonam



carumonam

and .

[0102] Some embodiments include an antimicrobial compound useful with the methods, compositions and compounds provided herein includes Nocardicin A, having the following formula:



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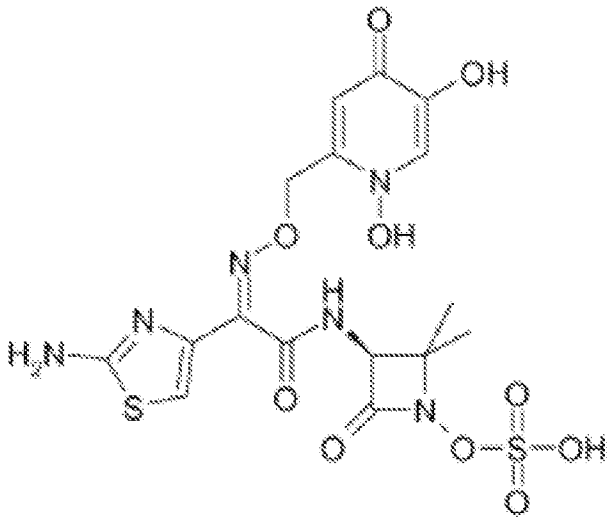
[0103] Some embodiments include an antimicrobial compound useful with the methods, compositions and compounds provided herein are described in Int. Pub. WO2008116813, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



wherein, the oxyimino group i.e. >C=N-O- has Z-orientation, or a pharmaceutically acceptable salt thereof.

[0104] Some embodiments may also include co-administering additional medicinal agents. 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.

Indications

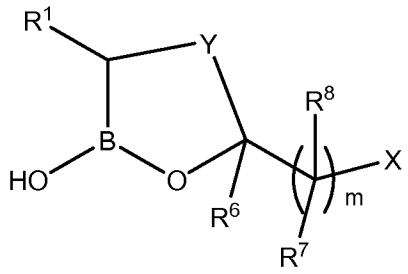
[0105] The compounds and compositions comprising β-lactamase inhibitors described herein and their combinations with an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase, such as a monobactam or biapenem, can be used to treat bacterial infections. Bacterial infections 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.

[0106] 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*.

β-lactamase inhibitors

[0107] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in PCT/US2011/046957, incorporated herein by reference in its entirety. Some embodiments include 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 $-C_{1\text{-}9}$alkyl, $-C_{2\text{-}9}$alkenyl, $-C_{2\text{-}9}$alkynyl, $-NR^9R^{10}$, $-C_{1\text{-}9}$alkylR^{11}, $-C_{2\text{-}9}$alkenylR^{11}, $-C_{2\text{-}9}$alkynylR^{11}, -carbocyclyl-R^{11}, $-CH(OH)C_{1\text{-}9}$alkylR^9, $-CH(OH)C_{2\text{-}9}$alkenylR^9, $-CH(OH)C_{2\text{-}9}$alkynylR^9, -CH(OH)carbocyclyl-R^9, $-C(=O)R^9$, $-C(=O)C_{1\text{-}9}$alkylR^9, $-C(=O)C_{2\text{-}9}$alkenylR^9, $-C(=O)C_{2\text{-}9}$alkynylR^9, $-C(=O)C_{2\text{-}9}$carbocyclyl-R^9, $-C(=O)NR^9R^{10}$, $-N(R^9)C(=O)R^9$, $-N(R^9)C(=O)NR^9R^{10}$, $-N(R^9)C(=O)OR^9$, $-N(R^9)C(=O)C(=NR^{10})R^9$, $-N(R^9)C(=O)C(=NOR^{10})R^9$, $-N(R^9)C(=O)C(=CR^9R^{10})R^9$, $-N(R^9)C(=O)C_{1\text{-}4}$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, $-C_{1\text{-}9}$alkyl, $C_{2\text{-}9}$alkenyl, $-C_{2\text{-}9}$alkynyl, carbocyclyl, $-C_{1\text{-}9}$alkylR^{11}, $-C_{2\text{-}9}$alkenylR^{11}, $-C_{2\text{-}9}$alkynylR^{11}, carbocyclyl-R^{11}, $-C(=O)OR^9$, $-C_{1\text{-}9}$alkylCO_2R^9, $-C_{2\text{-}9}$alkenylCO_2R^9, $-C_{2\text{-}9}$alkynylCO_2R^9, and -carbocyclyl-CO_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, or alternatively 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;

each R^7 is independently selected from a group consisting of H, $-NR^9R^{10}$, $-OR^9$, $-C_{1-9}alkylCO_2R^9$, $-C_{2-9}alkenylCO_2R^9$, $-C_{2-9}alkynylCO_2R^9$, and -carbocyclyl-CO_2R^9, or independently, 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, or independently, 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, or independently a geminal R^7 and R^8 together form a $-C_{2-9}$ alkenylenylCO$_2R^9$;

each R^8 is independently selected from a group consisting of H, $-NR^9R^{10}$, $-OR^9$, $-C_{1-9}alkylCO_2R^9$, $-C_{2-9}alkenylCO_2R^9$,$-C_{2-9}alkynylCO_2R^9$, -carbocyclyl-CO_2R^9, or independently, 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, or independently a geminal R^7 and R^8 together form a $-C_{2-9}$ alkenylenylCO$_2R^9$;

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 $-C(R^{13})_2OC(O)OR^{11}$;

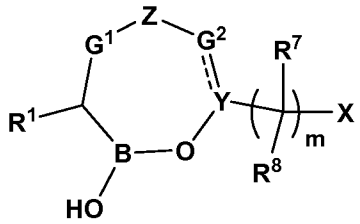
each R^{13} is independently selected from a group consisting of H and $C_{1-4}alkyl$; and

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

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

[0108] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in U.S. Provisional Application No. 61/529,859,

incorporated herein by reference in its entirety. Some embodiments include a compound having the structure of formula II:



II

or pharmaceutically acceptable salt thereof, wherein:

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

$G^{1\alpha}$ is selected from a divalent group consisting of -C($R^{a\alpha}R^{b\alpha}$)-, -C(=$R^{a\alpha}$)-, -C($R^{a\alpha}R^{b\alpha}$)C($R^{c\alpha}R^{d\alpha}$)-, -C($R^{a\alpha}$)=C($R^{c\alpha}$)-, -C(=O)C($R^{a\alpha}R^{b\alpha}$)-, -C($R^{a\alpha}R^{b\alpha}$)C(=O)-, and a bond;

$G^{2\alpha}$ is selected from a divalent group consisting of -C($R^{e\alpha}R^{f\alpha}$)-, -C(=$R^{e\alpha}$)-, =C($R^{e\alpha}$)-, -C($R^{e\alpha}R^{f\alpha}$)C($R^{g\alpha}R^{h\alpha}$)-, -C($R^{e\alpha}R^{f\alpha}$)C($R^{g\alpha}R^{h\alpha}$)C($R^{i\alpha}R^{j\alpha}$)-, -C(=O)-, -C(=O)C($R^{e\alpha}R^{f\alpha}$)-, -C($R^{e\alpha}R^{f\alpha}$)C(=O)-, -C(=O)C($R^{e\alpha}R^{f\alpha}$)C($R^{g\alpha}R^{h\alpha}$)-, -C($R^{e\alpha}R^{f\alpha}$)C($R^{g\alpha}R^{h\alpha}$)C(=O)-, -C(=O)C($R^{e\alpha}R^{f\alpha}$)C($R^{g\alpha}R^{h\alpha}$)C($R^{i\alpha}R^{j\alpha}$)-, -C($R^{e\alpha}R^{f\alpha}$)C($R^{g\alpha}R^{h\alpha}$)C($R^{i\alpha}R^{j\alpha}$)C(=O)-, -C($R^{e\alpha}$)=C($R^{g\alpha}$)-,-C($R^{e\alpha}$)=C($R^{g\alpha}$)C($R^{i\alpha}R^{j\alpha}$)- and -C($R^{e\alpha}R^{f\alpha}$)C($R^{g\alpha}$)=C($R^{j\alpha}$)-;

$R^{a\alpha}$, $R^{b\alpha}$, $R^{c\alpha}$, $R^{d\alpha}$, $R^{e\alpha}$, $R^{f\alpha}$, $R^{g\alpha}$, $R^{h\alpha}$, $R^{i\alpha}$, and $R^{j\alpha}$ are independently selected from a group consisting of H, Cl, F, CN, CF_3, -$R^{9\alpha}$, -$OR^{9\alpha}$, $NR^{9\alpha}R^{10\alpha}$, -C(=O)$NR^{9\alpha}R^{10\alpha}$, and -C(=O)$OR^{9\alpha}$, or independently: $R^{a\alpha}$ and $R^{c\alpha}$, $R^{e\alpha}$ and an $R^{7\alpha}$, $R^{k\alpha}$ and $R^{c\alpha}$, $R^{k\alpha}$ and $R^{e\alpha}$, $R^{e\alpha}$ and $R^{g\alpha}$, and $R^{g\alpha}$ and $R^{j\alpha}$ are taken together with the atoms to which they are attached and any intervening atoms to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl, or independently $R^{e\alpha}$ and $R^{f\alpha}$ are taken together with the atoms to which they are attached and any intervening atoms to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

$R^{a\alpha}$ and $R^{e\alpha}$ are $=CR^{9\alpha}R^{10\alpha}$ or independently $R^{a\alpha}$ and $R^{k\alpha}$, or $R^{e\alpha}$ and $R^{k\alpha}$, 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;

Z^{α} is selected from a divalent group consisting of $-C(R^{9\alpha}R^{10\alpha})-$, -O-, -S-, $-N(R^{9\alpha})-$, $-N[C(=O)R^{9\alpha}]-$, $-N[C(=O)NR^{9\alpha}R^{10\alpha}]-$, $-N[C(=O)OR^{9\alpha}]-$, $-N[C(=NR^{10\alpha})R^{9\alpha}]-$, $-N[SO_2R^{9\alpha}]-$, $-N[SO_2NR^{9\alpha}R^{10\alpha}]-$, $-N(R^{9\alpha})C(=O)-$, $-C(R^{9\alpha}R^{k\alpha})-$, $-C(=R^{k\alpha})-$, $-N(R^{k\alpha})-$, and a bond;

$R^{k\alpha}$ and $R^{c\alpha}$, $R^{k\alpha}$ and $R^{e\alpha}$, $R^{a\alpha}$ and $R^{k\alpha}$, or $R^{e\alpha}$ and $R^{k\alpha}$ are taken together with any intervening atoms to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

Y^{α} is selected from a group consisting of N, $CR^{6\alpha}$, and C, with the proviso that when Z^{α} is a bond, $-C(R^{9\alpha}R^{10\alpha})-$, $-C(R^{9\alpha}R^{k\alpha})-$, or $-C(=R^{k\alpha})-$, then Y^{α} is N;

$R^{6\alpha}$ is selected from a group consisting of H, $-C_{1\text{-}9}$alkyl, $-C_{2\text{-}9}$alkenyl, $-C_{2\text{-}9}$alkynyl, carbocyclyl, $-C_{1\text{-}9}$alkyl$R^{11\alpha}$, $-C_{2\text{-}9}$alkenyl$R^{11\alpha}$, $-C_{2\text{-}9}$alkynyl$R^{11\alpha}$, carbocyclyl-$R^{11\alpha}$, $-C(=O)OR^{9\alpha}$ and $-C_{1\text{-}9}$alkyl$CO_2R^{9\alpha}$, $-C_{2\text{-}9}$alkenyl$CO_2R^{9\alpha}$, $-C_{2\text{-}9}$alkynyl$CO_2R^{9\alpha}$, and -carbocyclyl-$CO_2R^{9\alpha}$, or alternatively $R^{6\alpha}$ and an $R^{7\alpha}$ or $R^{6\alpha}$ and $R^{e\alpha}$ are taken together with the atoms to which they are attached and any intervening atoms to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

each $R^{7\alpha}$ is independently selected from a group consisting of H, halo , $-C_{1\text{-}9}$alkyl, $-C_{2\text{-}9}$alkenyl, $-C_{2\text{-}9}$alkynyl, $-NR^{9\alpha}R^{10\alpha}$, $-OR^{9\alpha}$, $-C_{1\text{-}9}$alkyl$CO_2R^{9\alpha}$, $-C_{2\text{-}9}$alkenyl$CO_2R^{9\alpha}$, $-C_{2\text{-}9}$alkynyl$CO_2R^{9\alpha}$, and -carbocyclyl-$CO_2R^{9\alpha}$, or independently, $R^{6\alpha}$ and an $R^{7\alpha}$ or an $R^{7\alpha}$ and an $R^{8\alpha}$ are taken together with the atoms to which they are attached and any intervening atoms to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl, or independently an $R^{7\alpha}$ and $R^{e\alpha}$ are are taken together with intervening atoms to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl;

each $R^{8\alpha}$ is independently selected from a group consisting of H, halo , $-C_{1\text{-}9}$alkyl, $-C_{2\text{-}9}$alkenyl, $-C_{2\text{-}9}$alkynyl, $-NR^{9\alpha}R^{10\alpha}$, $-OR^{9\alpha}$, $-C_{1\text{-}9}$alkyl$CO_2R^{9\alpha}$, $-C_{1\text{-}9}$alkyl$CO_2R^{9\alpha}$, $-C_{2\text{-}9}$alkenyl$CO_2R^{9\alpha}$, $-C_{2\text{-}9}$alkynyl$CO_2R^{9\alpha}$, and -carbocyclyl-$CO_2R^{9\alpha}$, or independently, and $R^{7\alpha}$ and an $R^{8\alpha}$ are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl, or independently, each $R^{8\alpha}$ attached to a ring atom forming part of the substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl is absent;

each $R^{9\alpha}$ 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}alkyl$R^{11\alpha}$, C_{2-9}alkenyl$R^{11\alpha}$, -C_{2-9}alkynyl$R^{11\alpha}$, -carbocyclyl-$R^{11\alpha}$, -C_{1-9}alkyl$CO_2R^{12\alpha}$, C_{2-9}alkenyl$CO_2R^{12\alpha}$, -C_{2-9}alkynyl$CO_2R^{12\alpha}$, -carbocyclyl-$CO_2R^{12\alpha}$, -C_{1-9}alkyl-$N(R^{12\alpha})OR^{12\alpha}$, C_{2-9}alkenyl-$N(R^{12\alpha})OR^{12\alpha}$, -$C_{2-9}$alkynyl-$N(R^{12\alpha})OR^{12\alpha}$, -carbocyclyl-$N(R^{12\alpha})OR^{12\alpha}$, -$C_{1-9}$alkyl-$OR^{12\alpha}$, C_{2-9}alkenyl-$OR^{12\alpha}$, -C_{2-9}alkynyl-$OR^{12\alpha}$, -carbocyclyl-$OR^{12\alpha}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

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

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

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

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

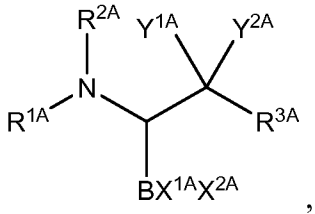
each X^{α} is independently selected from a group consisting of H, -$CO_2R^{12\alpha}$, and carboxylic acid isosteres;

m^{α} is independently zero or an integer from 1 to 2;

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; and

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

[0109] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in U.S. Pub. No. 2010/0120715, incorporated herein by reference in its entirety. Some embodiments include a compound having the following structure:



,

wherein, R^{1A} is -$C(O)R^{4A}$; -$C(O)NR^{4A}R^{5A}$; -$C(O)OR^{4A}$; -$S(O)_2R^{4A}$, -$C(=NR^{4A}R^{5A})R^{4A}$, -$C(=NR^{4A}R^{5A})NR^{4A}R^{5A}$, hydrogen, or is selected from the group consisting of: (a) aryl group

substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (b) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (c) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido;

R^{2A} is hydrogen, or is selected from the group consisting of: (a) C_1-C_6 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_6 carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_7 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy,

heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

R^{3A} is an aryl or heteroaryl group substituted with from 1 to 4 substituents wherein one of the substituents is a hydroxyl or amino group located at the 2 position relative to the group containing Y^{1A} and Y^{2A}, and wherein the remaining substituents are selected from the group consisting of hydroxyl, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, amino, aminocarbonyl, carbonyl, aminosulfonyl, alkylaryl, aryl, aryloxy, carboxyl, cyano, guanidino, halogen, heteroaryl, heterocyclyl, sulfido, sulfonyl, sulfoxido, sulfonic acid, sulfate, and thiol;

R^{4A} is selected from the group consisting of: (a) C_1-C_{10} alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_{10} carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_{10} cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino

group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

R^{5A} is hydrogen or is selected from the group consisting of: (a) C_1-C_6 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_{10} carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_7 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally

substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

X^{1A} and X^{2A} are independently hydroxyl, halogen, $NR^{4A}R^{5A}$, C_1-C_6 alkoxy, or when taken together X^{1A} and X^{2A} form a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or when taken together X^{1A} and X^{2A} form a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or when taken together X^{1A} and X^{2A} form a cyclic boron amide-ester where said chain contains from 2-20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or X^{1A} and R^{1A} together form a cyclic ring where said ring contains 2 to 10 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, and X^{2A} is hydroxyl, halogen, $NR^{4A}R^{5A}$, C_1-C_6 alkoxy, or X^{1A} and R^{3A} together form a cyclic ring where said ring contains 3 to 10 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, and X^{2A} is hydroxyl, halogen, $NR^{4A}R^{5A}$, or C_1-C_6 alkoxy;

Y^{1A} and Y^{2A} are independently hydrogen, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, amino, aminosulfonyl, aminocarbonyl, carbonyl, alkylaryl, aryl, aryloxy, carboxyl, cyano, halogen, heteroaryl, heteroaryloxy, heterocyclyl, sulfido, sulfonyl, or sulfoxido, or taken together Y^{1A} and Y^{2A} form a cyclic structure containing from 3-12 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S;

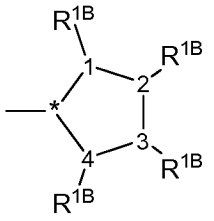
or a salt thereof;

provided that, when R^{1A} is -C(O)R^{4A}, R^{2A} is hydrogen, R^{3A} is a phenyl group having two substituents consisting of a hydroxyl at the 2-position and a carboxylic acid at the 3-position relative to the group containing Y^{1A} and Y^{2A}, X^{1A} and X^{2A} are hydroxyl or X^{1A} is hydroxyl and X^{2A} is replaced by the ortho-hydroxyl oxygen of R^{3A} such that a 6-membered ring is formed, and Y^{1A} and Y^{2A} are hydrogen, R^{4A} is not unsubstituted C_1 alkyl.

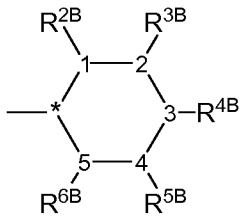
[0110] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in U.S. 6,184,363, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:

$$(OH)_2—B—R^B$$

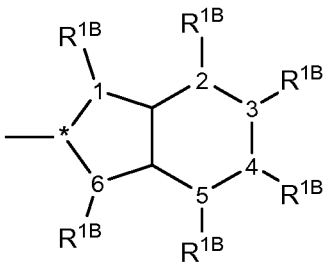
wherein, R^B is naphthalene, phenanthrene, or has one of the following formulas:



(2^B)



(3^B)



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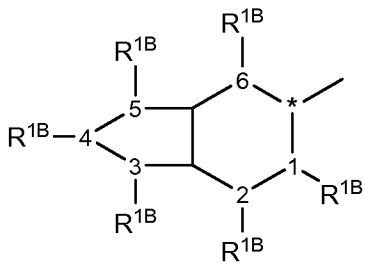

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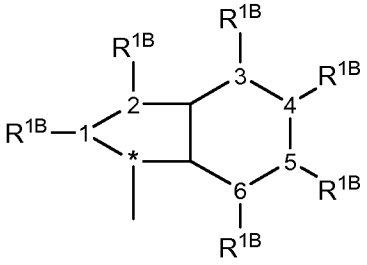
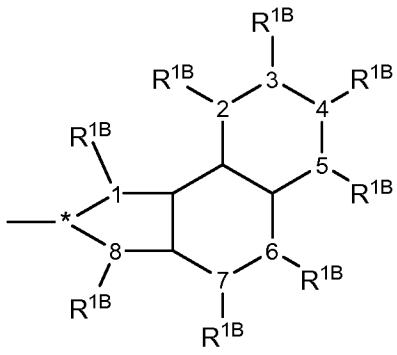


(6^B)



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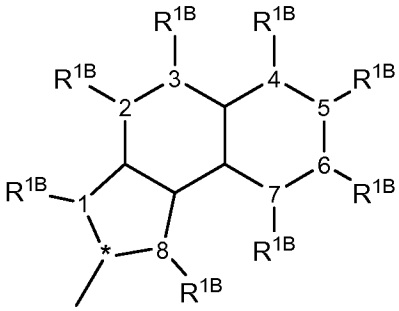

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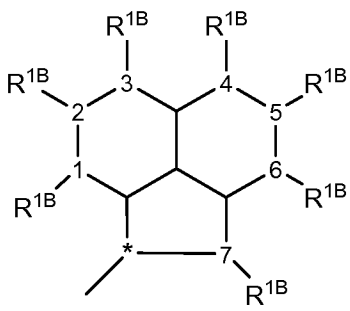
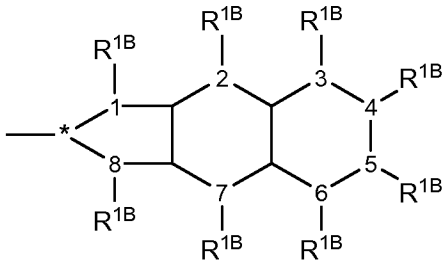


(9^B)



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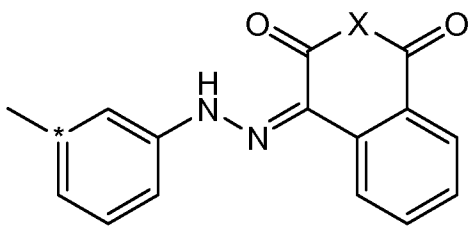

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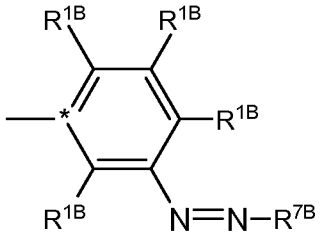
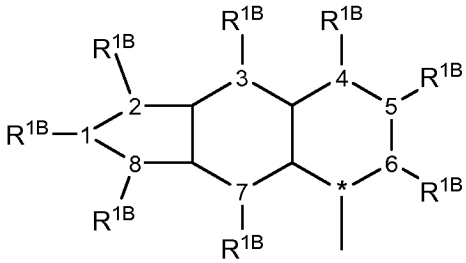
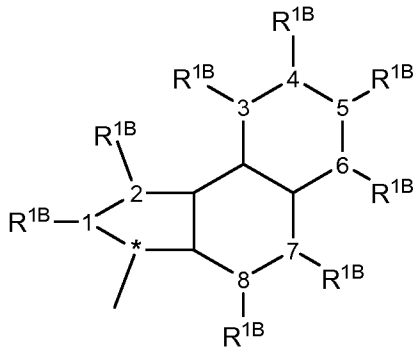


(12B)



(13B)



(14B)

wherein, ring system (2^B), (3^B), (4^B), (5^B), (6^B), (7^B), (8^B), (9^B), (10^B), (13^B) or (14^B) is aromatic or nonaromatic;

the atom center * is (R) or (S) in the case of chiral compounds;

positions 1, 2, 3, 4, 5, 6, 7 and 8 each independently is C, N, O or S;

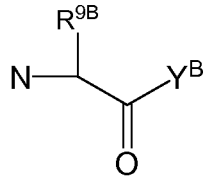
R^{1B} through R^{6B} each independently is a lone pair, H, $B(OH)_2$, a halogen atom, CF_3, CH_2 CF_3, CCl_3, CH_2 CCl_3, CBR^{3B}, CH_2 CBR^{3B}, NO_2, lower alkyl, CO_2H, CHCHCOOH, $CH_2CH_2CH_2$ COOH, SO_3H, PO_3H, OSO_3H, OPO_3H, OH, NH_2, $CONH_2$, $COCH_3$, OCH_3, or phenyl boronic acid, except that R^{2B}, R^{3B}, R^{4B}, R^{5B} and R^{6B} cannot all simultaneously be H, R^{2B} cannot be lower alkyl when R^{3B}, R^{4B}, R^{5B} and R^{6B} are H, R^{3B} cannot be NH_2, OH or lower alkyl when R^{2B}, R^{4B}, R^{5B} and R^{6B} are H, and R^{4B} cannot be lower alkyl when R^{2B}, R^{3B}, R^{5B} and R^{6B} are H;

R^{7B} is H, CF_3, CCl_3, CBR^{3B}, CH_2CF_3, CH_2CCl_3, CH_2CBR^{3B}, NO_2, $COCH_3$, OCH_3, lower alkyl, cyclic alkene, cyclic alkene substituted with one or more substituents R^{8B}, heterocyclic alkene, or heterocyclic alkene substituted with one or more substituents R^{8B};

each R^{8B} is independently H, $B(OH)_2$, a halogen atom, CF_3, CCl_3, CBR^{3B}, CH_2CF_3, CH_2CCl_3, CH_2CBR^{3B}, NO_2, lower alkyl, OH, NH_2, $N(CH_3)_2$, $N(CH_3)CH_2CH_3$, $NHCOCH_3$,

COOH, CHCHCOOH, $CH_2CH_2CH_2COOH$, $COCH_3$, OCH_3, phenyl boronic acid, $CONH_2$, $CONHCH_2COOH$, $CONHCH_2CONH_2$, $CONHCH_2CONHCH_2R^{10B}$, SO_2NH_2, SO_2NHCH_2COOH, $SO_2NHCH_2CONH_2$, or $SO_2NHCH_2CONHCH_2R^{10B}$;

X is O, NH, NCH_3 or



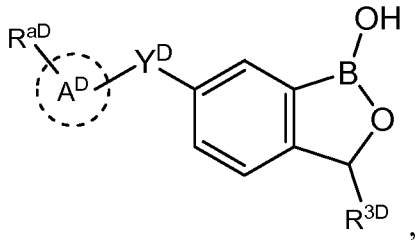
;

Y^B is OH, NH_2, NCH_3, $N(CH_3)_2$, $NHCOCH_3$ or $NHCOCH_2COOH$;

R^{9B} is H, a halogen atom, CF_3, CCl_3, CBR^{3B}, CH_2 CF_3, CH_2 CCl_3, CH_2CBR^{3B}, NO_2, CO_2H, CHCHCOOH, $CH_2CH_2CH_2COOH$, SO_3H, PO_3H, OSO_3 H, OPO_3H, OH, NH_2, $CONH_2$, $COCH_3$, OCH_3, phenyl boronic acid, lower alkyl, or a side chain of a standard amino acid; and

R^{10B} is a side chain of a standard amino acid.

[0111] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in U.S. Pub. No. 2010/0256092, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



,

wherein, A^D is a member selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

Y^D is a member selected from O and $-S(O)_2NH-$ wherein the sulfur in $-S(O)_2NH-$ is covalently attached to A^D;

R^{3D} is a member selected from H, cyano and substituted alkyl;

R^{aD} is a member selected from H, $-OR^{10D}$, $-NR^{10D}R^{11D}$, $-SR^{10D}$, $-S(O)R^{10D}$, $-S(O)_2R^{10D}$, $-S(O)_2NR^{10D}R^{11D}$, $-C(O)R^{10D}$, $--C(O)OR^{10D}$, $-C(O)NR^{10D}R^{11D}$, nitro, cyano, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

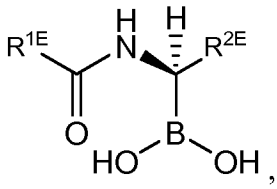
wherein, each R^{10D} and each R^{11D} is a member independently selected from H, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

with the proviso that R^{10D} and R^{11D}, together with the nitrogen to which they are attached, are optionally combined to form a 5- to 7-membered substituted or unsubstituted heterocycloalkyl ring;

with the proviso that when Y^D is O, R^{3D} is a member selected from cyano and substituted alkyl; with the proviso that when Y^D is $-S(O)_2NH-$, R^{3D} is H, and R^{aD} is not H or unsubstituted alkyl or halosubstituted alkyl,

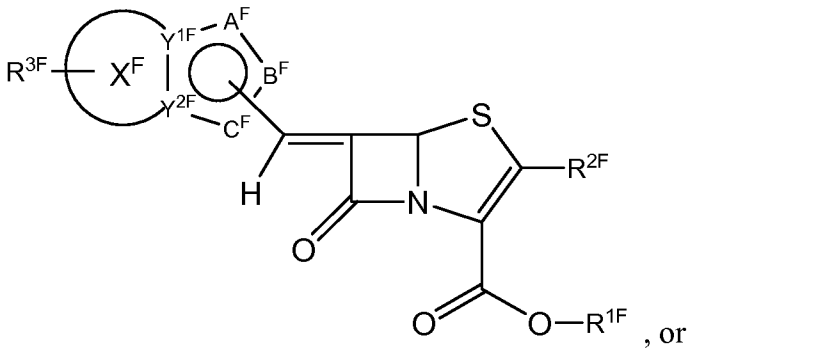
and salts thereof.

[0112] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in U.S. 7,271,186, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:

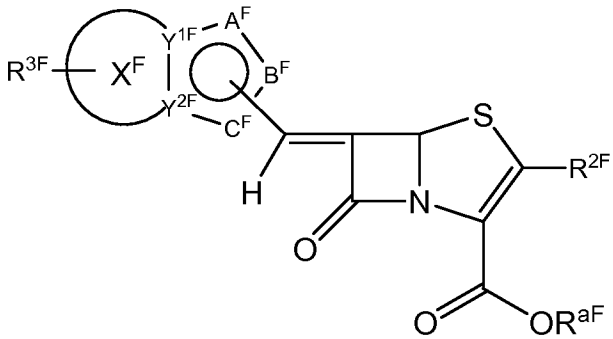


wherein, R^{1E} is a substituent selected from hydrogen, alkyl, alkenyl, cycloalkenyl, and heterocyclyl moieties, providing R^{1E} is not methyl and R^{1E} is not phenyl; and wherein R^{2E} is a substituent selected from heterocyclyl, cycloalkenyl, alkenyl and alkyl moieties.

[0113] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in U.S. Pub. No. 2011/0288063, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



, or



wherein, R^{1F} is the residue of a carboxy protecting group;

R^{aF} is hydrogen or a pharmaceutically-acceptable salt forming agent or a pharmaceutically-acceptable ester residue readily hydrolyzable *in vivo*;

R^{2F} is selected from the group consisting of: (a) Hydrogen, (b) straight or branched chain alkyl, (c) hydroxymethyl, (d) alkoxymethyl, (e) aminocarbonyloxymethyl, (f) aryl, (g) heteroaryl and (h) heterocyclyl;

heteroaryl means a 5- or 6-membered unsaturated aromatic ring containing from 1 to 4 of any one or more of the hetero atoms selected from O, S and N; heterocyclyl means a 5-membered saturated ring containing one hetero atom;

X^F is a bridged bicyclic ring system having optionally one or two hetero atoms selected from O, S and N; the ring X^F may be optionally substituted with R^{3F} wherein

R^{3F} is selected from (a) hydrogen, (b) alkyl, (c) hydroxy, (d) alkoxy, (e) hydroxymethyl, (f) alkoxymethyl, (g) halogen, (h) cyano, (i) carboxy, (j) alkoxycarbonyl, (k) amino, (l) aminoalkyl, (m) mono- or diallylamino, (n) mono- or dialkylaminoalkyl, (o) acylamino, (p) sulfonylamino, (q) substituted or unsubstituted amidino, (r) substituted or unsubstituted urea, (s) substituted or unsubstituted thiourea, (t) substituted or unsubstituted carboxamido, (u) substituted or unsubstituted thiocarboxamido, (v) substituted or unsubstituted aryl, (w) substituted or unsubstituted aralkyl, (x) substituted or unsubstituted heteroaryl, (y) substituted or unsubstituted heteroarylalkyl and (z) substituted or unsubstituted heterocyclylalkyl;

the heteroaryl groups mentioned in items (x) and (y) means a 5- or 6-membered unsaturated aromatic ring containing from 1 to 4 of any one or more of the hetero atoms selected from O, S and N, wherein the said heteroaryl groups could be bonded via carbon, or a nitrogen-containing heteroaryl group could be bonded via nitrogen;

the bridged bicyclic ring systems containing a NH ring atom may be optionally substituted on the said nitrogen by a substituent selected from: (a) alkyl, (b) alkenyl, (c) alkynyl, (d) cycloalkyl, (e) cycloalkylalkyl, (f) cycloalkenyl, (g) cycloalkenylalkyl, (h) aryl, (i) arylalkyl, (j) heteroaryl, (k) heteroarylalkyl, (l) heterocyclyl, (m) heterocyclylalkyl (n) or a protecting group;

Y^{1F} and Y^{2F} may independently be C or N;

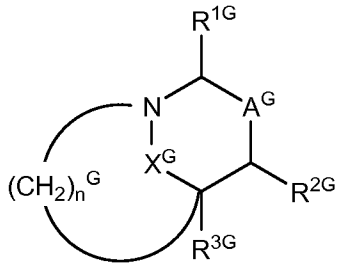
A^F, B^F or C^F form part of a heteroaryl ring where one of A^F, B^F or C^F is a carbon atom to which the remainder of the molecule is attached, and A^F, B^F and C^F are independently selected from CR^{4F}, O, N, S or NR^{5F};

R^{4F} is hydrogen; and

R^{5F} is selected from the group consisting of: (a) hydrogen, (b) straight or branched lower alkyl, (c) lower alkenyl, (d) lower alkynyl, (e) hydroxy alkyl, (f) alkoxy alkyl, (g)

aminocarbonyloxy alkyl, (h) cyano alkyl, (i) aminoalkyl, (j) mono- or dialkylaminoalkyl, (k) alkoxycarbonylalkyl, (l) carboxyalkyl, (m) substituted or unsubstituted carboxamidoalkyl, (n) cycloalkylalkyl, (o) substituted or unsubstituted thiocarboxamidoalkyl, (p) substituted or unsubstituted amidinoalkyl, (q) substituted or unsubstituted guanidinoalkyl, (r) substituted or unsubstituted aminocarbonylaminoalkyl, (s) acylaminoalkyl, (t) aralkyl, (u) heteroarylalkyl and (v) heterocyclylalkyl.

[0114] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in U.S. Pub. No. 2005/0020572, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



,

wherein, R^{1G} is hydrogen, COOH, CN, $COOR^{G}$, $CONR^{6G}R^{7G}$, $(CH_2)_n{}^{G}R^{5G}$ or $C(=NR^{6G})NHR^{7G}$;

R^{G} is selected from the group consisting of alkyl containing 1 to 6 carbon atoms optionally substituted by a pyridyl or carbamoyl radical, -CH_2-alkenyl containing 3 to 9 carbon atoms, aryl containing 6 to 10 carbon atoms and aralkyl containing 7 to 11 carbon atoms, wherein the nucleus of said aryl or aralkyl is optionally substituted by OH, NH_2, NO_2, alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms or by one or more halogen atoms;

R^{6G} and R^{7G} are identical or different and are independently selected from the group consisting of hydrogen, alkyl containing 1 to 6 carbon atoms, aryl containing 6 to 10 carbon atoms and aralkyl containing 7 to 11 carbon atoms optionally substituted by a carbamoyl, ureido or dimethylamino radical, and alkyl containing 1 to 6 carbon atoms substituted by a pyridyl radical;

n^{1G} is 1 or 2;

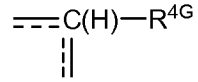
R^{5G} is selected from the group consisting of COOH, CN, OH, NH_2, $CO\text{-}NR^{6G}R^{7G}$, $COOR^{G}$, OR^{G}, OCHO, $OCOR^{G}$, $OCOOR^{G}$, $OCONHR^{G}$, $OCONH_2$, NHR^{G}, NHCOH, $NHCOR^{G}$, $NHSO_2R^{G}$, $NH\text{-}COOR^{G}$, $NH\text{-}CO\text{-}NHR^{G}$ and $NHCONH_2$, wherein R^{G}, R^{6G} and R^{7G} are as defined above;

R^{2G} is hydrogen or $(CH_2)_n{}^{1G}{}_1R^{5G}$ wherein n^{1G} is 0, 1 or 2, and

R^{5G} is as defined above;

R^{3G} is hydrogen or alkyl containing 1 to 6 carbon atoms;

A^G is a bond between the two carbons which carry R^{1G} and R^{2G},



group wherein R^{4G} is hydrogen or $(CH_2)_n{}^{1G}{}_1R^{5G}$ and n^{1G} and R^{5G} are as defined above, and the dotted line is an optional bond with one of the two carbons which carry R^{1G} and R^{2G};

n^G is 1 or 2;

X^G is a divalent -C(O)-B^G- group linked to the nitrogen atom by the carbon atom wherein B^G is a divalent -O-$(CH_2)_n{}^{2G}$- group linked to the carbonyl by the oxygen atom, a divalent -NR^{8G}-$(CH_2)_n{}^{2G}$- or -NR^{8G}-O- group linked to the carbonyl by the nitrogen atom, n^{2G} is 0 or 1, and wherein B^G is -NR^{8G}-$(CH_2)_n{}^{2G}$-, R^{8G} is selected from the group consisting of hydrogen, OH, R^G, OR^G, Y^G, OY^G, Y^{1G}, OY^{1G}, Y^{2G}, OY^{2G}, Y^{3G}, $OCH_2CH_2SO_m{}^GR^G$, $OSiR^{aG}R^{bG}R^{cG}$ and $SiR^{aG}R^{bG}R^{cG}$ and wherein B^G is -NR^{8G}-O-, R^{8G} is selected from the group consisting of hydrogen, R, Y^G, Y^{1G}, Y^{2G}, Y^{3G} and $SiR^{aG}R^{bG}R^{cG}$, wherein R^{aG}, R^{bG} and R^{cG} is each independently a linear or branched alkyl containing 1 to 6 carbon atoms or aryl containing 6 to 10 carbon atoms, R^G is as defined above and m^G is 0, 1 or 2;

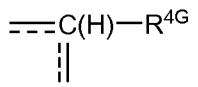
Y^G is selected from the group consisting of COH, COR^G, $COOR^G$, $CONH_2$, $CONHR^G$, CONHOH, $CONHSO_2R^G$, CH_2COOH, CH_2COOR^G, $CH_2CONHOH$, $CH_2CONHCN$, CH_2tetrazole, protected CH_2tetrazole, CH_2SO_3H, $CH_2SO_2R^G$, $CH_2PO(OR^G)_2$, $CH_2PO(OR^G)(OH)$, $CH_2PO(R^G)(OH)$ and $CH_2PO(OH)_2$;

Y^{1G} is selected from the group consisting of SO_2R^G, SO_2NHCOH, SO_2NHCOR^G, $SO_2NHCOOR^G$, $SO_2NHCONHR^G$, $SO_2NHCONH_2$ and SO_3H;

Y^{2G} is selected from the group consisting of $PO(OH)_2$, $PO(OR^G)_2$, $PO(OH)(OR^G)$ and $PO(OH)(R^G)$;

Y^{3G} is selected from the group consisting of tetrazole, tetrazole substituted by R^G, squarate, NH or NR^G-tetrazole, NH or NR^G-tetrazole substituted by R^G, $NHSO_2R^G$ and $NR^GSO_2R^G$ wherein R^G is as defined above; and

R^{1G}, R^{2G} and R^{3G} are not simultaneously hydrogen when n^G is 1, A^G is



,

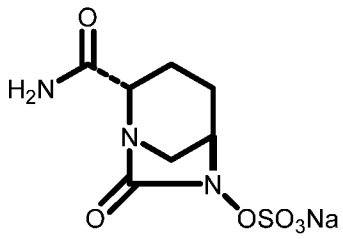
wherein R^{4G} is hydrogen and

X^G is -C(O)-O-$(CH_2)_n{}^{G2}$ wherein n^{G2} is 0 or 1, or

X^G is -CO-NR^{8G}-$(CH_2)_n{}^{G2}$ wherein n^{G2} is 1 and R^{8G} is isopropyl, or

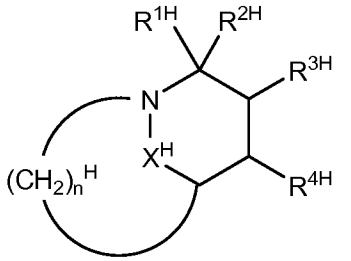
X^G is -CO-NR^{8G}-$(CH_2)_n{}^{G2}$ wherein n^{G2} is 0 and R^{8G} is hydrogen or phenyl.

[0115] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein include the compound NXL104, having the following formula:



NXL104

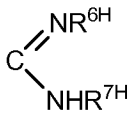
[0116] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in U.S. Pub. No. 2004/0157826, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



,

wherein, either:

a) R^{1H} is a radical selected from the group consisting of hydrogen, COOH, COOR, CN, $(CH_2)_n{}^{1H}R^{5H}$, $CONR^{6H}R^{7H}$ and



R^H is selected from the group consisting of an alkyl radical containing from 1 to 6 carbon atoms, optionally substituted with one or more halogen atoms or with a pyridyl radical; a $-CH_2-$alkenyl radical containing in total from 3 to 9 carbon atoms; a (poly)alkoxyalkyl group containing 1 to 4 oxygen atoms and 3 to 10 carbon atoms; an aryl radical containing from 6 to 10 carbon atoms or an aralkyl radical containing from 7 to 11 carbon atoms, the nucleus of the aryl or aralkyl radical being optionally substituted with a radical selected from the group consisting of OH, NH_2, NO_2, alkyl containing from 1 to 6 carbon atoms, alkoxy containing from 1 to 6 carbon atoms and one or more halogen atoms;

R^{5H} is selected from the group consisting of COOH, CN, OH, NH_2, CO-N,

$R^{6H}R^{7H}$, $COOR^H$ and OR^H radicals, R^H being as defined above, R^{6H} and R^{7H} are individually selected from the group consisting of hydrogen, an alkyl radical containing from 1 to 6 carbon atoms, an alkoxy radical containing from 1 to 6 carbon atoms, an aryl radical

containing from 6 to 10 carbon atoms, an aralkyl radical containing from 7 to 11 carbon atoms and an alkyl radical containing from 1 to 6 carbon atoms which is substituted with a pyridyl radical;

n^{1H} is equal to 1 or 2,

R^{3H} and R^{4H}, together with the carbons to which they are attached, form a phenyl or a 5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, which is substituted with one or more R^{1H} groups, R^{1H} being a radical selected from the group consisting of: $-(O)_a{}^H-(CH_2)_b{}^H-(O)_a{}^H-CONR^{6H}R^{7H}$, $-(O)_a{}^H-(CH_2)_b{}^H-OSO_3H$, $-(O)_a{}^H-(CH_2)_b{}^H-SO_3$, $-(O)_a{}^H-SO_2R^H$, $-(O)_a{}^H-SO_2-CHa^Hl_3$, $-(O)_a{}^H-(CH_2)_b{}^H-NR^{6H}R^{7H}$, $-(O)_a{}^H-(CH_2)_b{}^H-NH-COOR^H$, $-(CH_2)_b{}^H-COOH$, $-(CH_2)_b{}^H-COOR^H$, $-OR^{H}"$, OH, $-(CH_2)_b{}^H-$ phenyl, and $-(CH_2)_b{}^H-$5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur,

each of said phenyl and said heterocycle being optionally substituted with one or more substituents selected from halogen, alkyl containing from 1 to 6 carbon atoms, alkoxy containing from 1 to 6 carbon atoms and CF_3,

R^H, R^{6H} and R^{7H} being as defined above,

$R^{H}"$ being selected from alkyl radicals containing from 1 to 6 carbon atoms substituted with one or more radicals selected from hydroxy, protected hydroxy, oxo, halogen and cyano radicals,

a^H being equal to 0 or 1 and b being an integer from 0 to 6,

provided that, when $R^{1H}$is OH, R^{1H} is $CONR^{6H}R^{7H}$ in which one of R^{6H} and R^{7H} is an alkoxy containing from 1 to 6 carbon atoms; or

b) R^{4H} is hydrogen or $(CH_2)_n{}^{1H}{}_1$ R^{5H}, wherein $n^{1H}{}_1$, is 0, 1 or 2 and R^{5H} is as defined above,

and R^{1H} and R^{3H}, together with the carbons to which they are attached, form a substituted phenyl or heterocycle, as defined above;

and, in both cases a) and b),

R^{2H} is selected from the group consisting of hydrogen, halogen, R^H, $S(O)_m{}^HR^H$, OR^H, $NHCOR^H$, $NHCOOR^H$ and $NHSO_2R^H$, R being as defined above and m^H being 0, 1 or 2,

X^H is a divalent group $-C(O)-B^H-$ linked to the nitrogen atom by the carbon atom,

B^H is a divalent group selected from 1) $-O-(CH_2)_n"^H-$ linked to the carbonyl by the oxygen atom, 2) $-NR^{8H}-(CH_2)_n"^H-$ and 3) $-NR^{8H}-O-$ linked to the carbonyl by the nitrogen atom, $n"^H$ is 0 or 1 and R^{8H} is a radical selected from the group consisting of hydrogen, OH, R^H, OR^H, Y^H, OY^H, Y^{1H}, OY^{1H}, Y^{2H}, OY^{2H}, Y^{3H}, $O-CH_2-CH_2-S(O-)m^H-R^H$, $SiR^{aH}R^{bH}R^{cH}$ and

$OSiR^{aH}R^{bH}R^{cH}$, wherein each of R^{aH}, R^{bH} and R^{cH} is a linear or branched alkyl containing from 1 to 6 carbon atoms or an aryl containing from 6 to 10 carbon atoms, and R^H and m^H are as defined above;

Y^H is selected from the group consisting of COH, COR^H, $COOR^H$, $CONH_2$, $CONHR^H$, CONHOH, $CONHSO_2R^H$, CH_2COOH, CH_2COOR^H, CHF-COOH, CHF-$COOR^H$, CF_2-COOH, CF_2-$COOR^H$, CN, CH_2CN, $CH_2CONHOH$, $CH_2CONHCN$, CH_2tetrazole, protected CH_2tetrazole, CH_2SO^{3H}, $CH_2SO_2R^H$, $CH_2PO(OR^H)_2$, $CH_2PO(OR^H)(OH)$, $CH_2PO(R^H)(OH)$ and $CH_2PO(OH)_2$;

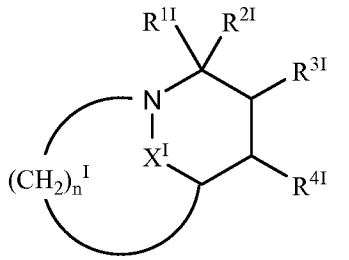
Y^{1H} is selected from the group consisting of SO_2R^H, SO_2NHCOH, SO_2NHCOR^H, $SO_2NHCOOR^H$, $SO_2NHCONHR^H$, $SO_2NHCONH_2$ and SO^{3H};

Y^{2H} is selected from the group consisting of $PO(OH)_2$, $PO(OR^H)_2$, $PO(OH)(OR^H)$ and $PO(OH)(R^H)$;

Y^{3H} is selected from the group consisting of tetrazole, tetrazole substituted with R^H, squarate, NH or NR^Htetrazole, NH or NR^Htetrazole substituted with R^H, $NHSO_2R^H$, $NR^HSO_2R^H$, CH_2tetrazole and CH_2tetrazole substituted with R^H, R^H being as defined above, and

n^H is 1 or 2, or one of its salts with a base or an acid.

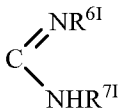
[0117] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in U.S. 7,439,253 incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



,

wherein, either:

a) R^{1I} is a radical selected from the group consisting of hydrogen, COOH, $COOR^I$, CN, $(CH_2)_n{}^IR^{5I}$, $CONR^{6I}R^{7I}$ and



R^I is selected from the group consisting of an alkyl radical containing from 1 to 6 carbon atoms, optionally substituted with one or more halogen atoms or with a pyridyl radical; a -CH_2-alkenyl radical containing in total from 3 to 9 carbon atoms; a (poly)alkoxyalkyl group containing 1 to 4 oxygen atoms and 3 to 10 carbon atoms; an aryl radical containing from 6 to 10 carbon atoms or an aralkyl radical containing from 7 to 11 carbon atoms, the aryl or aralkyl

radical being optionally substituted with a radical selected from the group consisting of OH, NH_2, NO_2, alkyl containing from 1 to 6 carbon atoms, alkoxy containing from 1 to 6 carbon atoms and one or more halogen atoms;

R^{5I} is selected from the group consisting of COOH, CN, OH, NH_2, $CO\text{-}NR^{6I}R^{7I}$, $COOR^I$ and OR^I radicals, R^I being as defined above,

R^{6I} and R^{7I} are individually selected from the group consisting of hydrogen, an alkyl radical containing from 1 to 6 carbon atoms, an alkoxy radical containing from 1 to 6 carbon atoms, an aryl radical containing from 6 to 10 carbon atoms, an aralkyl radical containing from 7 to 11 carbon atoms and an alkyl radical containing from 1 to 6 carbon atoms which is substituted with a pyridyl radical;

n'^I is equal to 1 or 2,

R^{3I} and R^{4I}, together with the carbons to which they are attached, form a phenyl or a 5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, which is substituted with one or more R'^I groups, R'^I being a radical selected from the group consisting of:

$-(O)_a{}^I\text{-}(CH_2)_b{}^I\text{-}(O)_a{}^ICONR^{6I}R^{7I}$, $-(O)_a{}^I\text{-}(CH_2)_b{}^I\text{-}OSO_3H$, $-(O)_a{}^I\text{-}(CH_2)_b{}^I\text{-}SO_3H$, $-(O)_a{}^I\text{-}SO_2R^I$, $-(O)_a{}^I\text{-}SO_2\text{-}CH_a{}^Il_3$, $-(O)_a{}^I\text{-}(CH_2)_b{}^I\text{-}NR^{6I}R^{7I}$, $-(O)_a{}^I\text{-}(CH_2)_b{}^I\text{-}NH\text{-}COOR^I$, $-(CH_2)_b{}^I\text{-}COOH$, $-(CH_2)_b{}^I\text{-}COOR^I$, $-OR''^I$, OH, $-(CH_2)_b{}^I$-phenyl, $-O\text{-}(CH_2)_2\text{-}O\text{-}CH_3$, $-O\text{-}CH_2$-(2,2-dimethyl-1,3-dioxolan-4-yl), -CO-NH phenyl,

$-(CH_2)_b{}^I$-5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, each of said phenyl and said heterocycle being optionally substituted with one or more substituents selected from halogen, alkyl containing from 1 to 6 carbon atoms, alkoxy containing from 1 to 6 carbon atoms and CF_3,

R^I, R^{6I} and R^{7I} being as defined above,

R''^I being selected from alkyl radicals containing from 1 to 6 carbon atoms substituted with one or more radicals selected from hydroxy, protected hydroxy, oxo, halogen and cyano radicals,

a^I being equal to 0 or 1 and b^I being an integer from 0 to 6,

provided that, when R'^I is OH, R^{1I} is $CONR^{6I}R^{7I}$ in which one of R^{6I} and R^{7I} is an alkoxy containing from 1 to 6 carbon atoms; or

b) R^{4I} is hydrogen or $(CH_2)_n{}'^I{}_1R^{5I}$, wherein $n'^I{}_1$, is 0, 1 or 2 and R^{5I} is as defined above,

and R^{1I} and R^{3I}, together with the carbons to which they are attached, form a substituted phenyl or heterocycle, as defined above;

and, in both cases a) and b), R^{2I} is selected from the group consisting of hydrogen, halogen, R^I, $S(O)_m{}^IR^I$, OR^I, $NHCOR^I$, $NHCOOR^I$ and $NHSO_2R^I$, R^I being as defined above and m^I being 0, 1 or 2,

X^I is a divalent group -C(O)-B^I- linked to the nitrogen atom by the carbon atom,

B^I is a divalent group selected from 1) -NR^{8I}-$(CH_2)_n{}''^I$-linked to the carbonyl by the nitrogen atom, n''^I is 0 and R^{8I} is a radical selected from the group consisting of hydrogen, OH, R^I, OR^I, Y^I, OY^I, Y^{1I}, OY^{1I}, Y^{2I}, OY^{2I}, Y^{3I}, O-CH_2-CH_2-S(O-)$_m{}^I$-R^I, $SiR^{aI}R^{bI}R^{cI}$ and $OSiR^{aI}R^{bI}R^{cI}$, wherein each of R^{aI}, R^{bI} and R^{cI} is a linear or branched alkyl containing from 1 to 6 carbon atoms or an aryl containing from 6 to 10 carbon atoms, and R^I and m^I are as defined above;

Y^I is selected from the group consisting of COH, COR^I, $COOR^I$, $CONH_2$, $CONHR^I$, CONHOH, $CONHSO_2R^I$, CH_2COOH, CH_2COOR^I, CHF-COOH, CHF-$COOR^I$, CF_2-COOH, CF_2-$COOR^I$, CN, CH_2CN, $CH_2CONHOH$, $CH_2CONHCN$, CH_2tetrazole, protected CH_2tetrazole, CH_2SO_3H, $CH_2SO_2R^I$, $CH_2PO(OR^I)_2$, $CH_2PO(OR^I)(OH)$, $CH_2PO(R^I)(OH)$ and $CH_2PO(OH)_2$;

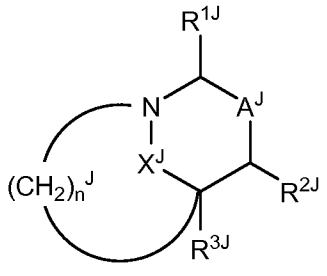
Y^{1I} is selected from the group consisting of SO_2R^I, SO_2NHCOH, SO_2NHCOR^I, $SO_2NHCOOR^I$, $SO_2NHCONHR^I$, $SO_2NHCONH_2$ and SO_3H;

Y^{2I} is selected from the group consisting of $PO(OH)_2$, $PO(OR^I)_2$, $PO(OH)(OR^I)$ and $PO(OH)(R^I)$;

Y^{3I} is selected from the group consisting of tetrazole, tetrazole substituted with R^I, squarate, NH or NR^Itetrazole, NH or NR^Itetrazole substituted with R^I, $NHSO_2R^I$, $NR^ISO_2R^I$, CH_2tetrazole and CH_2tetrazole substituted with R^I, R^I being as defined above,

and n^I is 1, or one of its salts with a base or an acid.

[0118] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in U.S. 7,612,087, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



,

wherein, R^{1J} is hydrogen, COOH, CN, $COOR^J$, $CONR^{6J}R^{7J}$, $(CH_2)_n{}'^JR^{5J}$ or $C(=NR^{6J})NHR^{7J}$;

R^J is selected from the group consisting of alkyl containing 1 to 6 carbon atoms optionally substituted by a pyridyl or carbamoyl radical, -CH_2-alkenyl containing 3 to 9 carbon atoms, aryl containing 6 to 10 carbon atoms and aralkyl containing 7 to 11 carbon atoms, wherein the nucleus of said aryl or aralkyl is optionally substituted by OH, NH_2, NO_2, alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms or by one or more halogen atoms;

R^{6J} and R^{7J} are identical or different and are independently selected from the group consisting of hydrogen, alkyl containing 1 to 6 carbon atoms, aryl containing 6 to 10 carbon atoms and aralkyl containing 7 to 11 carbon atoms optionally substituted by a carbamoyl, ureido or dimethylamino radical, and alkyl containing 1 to 6 carbon atoms substituted by a pyridyl radical;

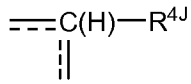
n'^J is 1 or 2;

R^{5J} is selected from the group consisting of COOH, CN, OH, NH_2, CO-$NR^{6J}R^{7J}$, $COOR^J$, OR^J, OCHO, $OCOR^J$, $OCOOR^J$, $OCONHR^J$, $OCONH_2$, NHR^J, NHCOH, $NHCOR^J$, $NHSO_2R^J$, NH-$COOR^J$, NH-CO-NHR^J and $NHCONH_2$ wherein R^J, R^{6J} and R^{7J} are as defined above;

R^{2J} is hydrogen or $(CH_2)_{n'^J_1}R^{5J}$ wherein n'^J_1 is 0, 1 or 2, and R^{5J} is as defined above;

R^{3J} is hydrogen or alkyl containing 1 to 6 carbon atoms;

A^J is a



group wherein R^{4J} is hydrogen or $(CH_2)_{n'^J_1}R^{5J}$ and n'^J_1 and R^{5J} are as defined above, and the dotted line is an optional bond with one of the two carbons which carry R^{1J} and R^{2J};

n^J is 1;

X^J is a divalent -C(O)-B^J- group linked to the nitrogen atom by the carbon atom wherein B^J is a divalent -O-$(CH_2)_{n''^J}$- group linked to the carbonyl by the oxygen atom, a divalent -NR^{8J}-$(CH_2)_{n''^J}$- or -NR^{8J}-O- group linked to the carbonyl by the nitrogen atom, n''^J is 0, and wherein B^J is -NR^{8J}-$(CH_2)_{n''^J}$-, R^{8J} is selected from the group consisting of hydrogen, OH, R^J, OR^J, Y^J, OY^J, Y^{1J}, OY^{1J}, Y^{2J}, OY^{2J}, Y^{3J}, $OCH_2CH_2SO_{m^J}R^J$, $OSiR^{aJ}R^{bJ}R^{cJ}$ and $SiR^{aJ}R^{bJ}R^{cJ}$ and wherein B^J is -NR^{8J}-O-, R^{8J} is selected from the group consisting of hydrogen, R, Y^J, Y^{1J}, Y^{2J}, Y^{3J} and $SiR^{aJ}R^{bJ}R^{cJ}$, wherein R^{aJ}, R^{bJ} and R^{cJ} is each independently a linear or branched alkyl containing 1 to 6 carbon atoms or aryl containing 6 to 10 carbon atoms, R^J is as defined above and m^J is 0, 1 or 2;

Y^J is selected from the group consisting of COH, COR^J, $COOR^J$, $CONH_2$, $CONHR^J$, CONHOH, $CONHSO_2R^J$, CH_2COOH, CH_2COOR^J, $CH_2CONHOH$, $CH_2CONHCN$,

CH_2tetrazole, protected CH_2tetrazole, CH_2SO_3H, $CH_2SO_2R^J$, $CH_2PO(OR^J)_2$, $CH_2PO(OR^J)(OH)$, $CH_2PO(R^J)(OH)$ and $CH_2PO(OH)_2$;

$Y_1{}^J$ is selected from the group consisting of SO_2R^J, SO_2NHCOH, SO_2NHCOR^J, $SO_2NHCOOR^J$, $SO_2NHCONHR^J$, $SO_2NHCONH_2$ and SO_3H;

$Y_2{}^J$ is selected from the group consisting of $PO(OH)_2$, $PO(OR^J)_2$, $PO(OH)(OR^J)$ and $PO(OH)(R^J)$;

$Y_3{}^J$ is selected from the group consisting of tetrazole, tetrazole substituted by R^J, squarate, NH or NR^J-tetrazole, NH or NR^J-tetrazole substituted by R^J, $NHSO_2R^J$ and $NRSO_2R^J$ wherein R^J is as defined above; and

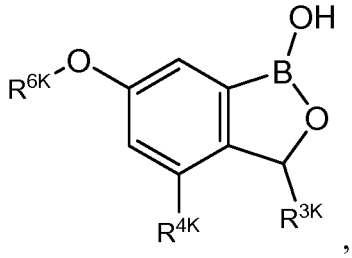
R^{1J}, R^{2J} and R^{3J} are not simultaneously hydrogen when n^J is 1,

R^{4J} is hydrogen and

X^J is $-C(O)-O-(CH_2)_n{}^{"J}$ wherein $n^{"J}$ is 0, or

X^J is $-CO-NR^{8J}-(CH_2)_n{}^{"J}$ wherein $n^{"J}$ is 0 and R^{8J} is hydrogen or phenyl.

[0119] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in Int. Pub. WO2011017125, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



,

wherein, R^{3K} is $-(CH_2)_m{}^K C(O)OR^{3aK}$,

m^K is an integer selected from 1, 2, 3, 4, 5, or 6;

R^{3aK} is selected from the group consisting of H, unsubstituted alkyl, and phenyl substituted alkyl;

R^{4K} is selected from the group consisting of unsubstituted alkyl, $-OR^{4bK}$,

$-(CH_2)_n{}^K-O-(CH_2)p^KCH_3$, and halogen

n^K is an integer selected from 1, 2, 3, 4, 5, or 6;

p^K is an integer selected from 0, 1, 2, 3, 4, 5, or 6;

R^{4bK} is H or substituted or unsubstituted alkyl;

R^{6K} is selected from the group consisting of H, substituted or unsubstituted alkyl, $-C(O)OR^{6aK}$, $-C(O)NR^{6aK}R^{6bK}$, $-S(O_2)R^{6cK}$, and A^K;

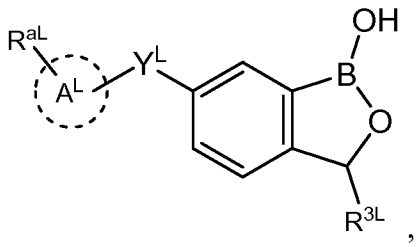
R^{6aK} is H or unsubstituted alkyl;

R^{6bK} is H or unsubstituted alkyl;

R^{6cK} is selected from the group consisting of unsubstituted alkyl, NH_2 and heteroaryl, optionally substituted with unsubstituted alkyl A is selected from the group consisting of substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

or a salt, hydrate or solvate thereof.

[0120] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in Int. Pub. WO2009140309, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



,

wherein, A^L is a member selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

Y^L is a member selected from O and $-S(O)_2NH-$

wherein the sulfur in $-S(O)_2NH-$ is covalently attached to A^L;

R^{3L} is a member selected from H, cyano and substituted alkyl;

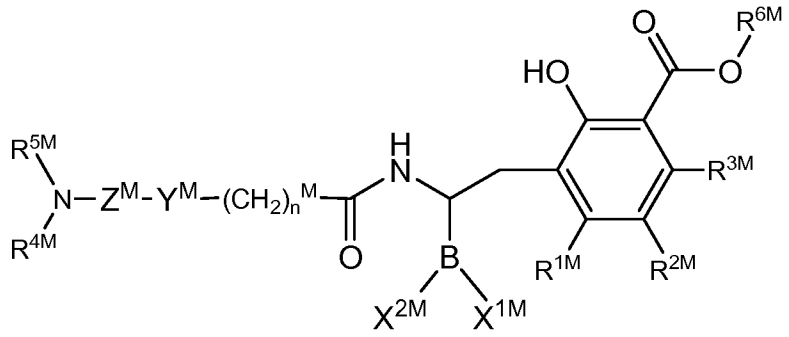
R^{aL} is a member selected from H, $-OR^{10L}$, $-NR^{10L}R^{11L}$, $-SR^{10L}$, $-S(O)R^{10L}$, $-S(O)_2R^{10L}$, $-S(O)_2NR^{10L}R^{11L}$, $-C(O)R^{10L}$, $-C(O)OR^{10L}$, $-C(O)NR^{10L}R^{11L}$, nitro, cyano, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

each R^{10L} and each R^{11L} is a member independently selected from H, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

with the proviso that R^{10L} and R^{11L}, together with the nitrogen to which they are attached, are optionally combined to form a 5- to 7- membered substituted or unsubstituted heterocycloalkyl ring; with the proviso that when Y^L is O, R^L is a member selected from cyano and substituted alkyl;

with the proviso that when Y^L is $-S(O)_2NH-$, R^{3L} is H, and R^{aL} is not H or unsubstituted alkyl or halosubstituted alkyl and salts thereof.

[0121] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in Int. Pub. WO2010130708, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



wherein, R^{1M}, R^{2M}, and R^{3M} are independently hydrogen, or selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, optionally substituted: C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 alkenyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocyclyl, amino, sulfide, and sulfone;

n^M is O, 1, or 2;

Y^M is selected from the group consisting of: (a) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino, imino, amidino, sulfido, and sulfoxido, (b) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino, imino, amidino, sulfido, and sulfoxido, and (c) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, imino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said imino group, amidino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said amidino group, sulfido, and sulfoxido;

R^{4M} is hydrogen, or selected from the group consisting of: (a) C_1-C_5 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: alkyl, alkenyl, alky ny I_1 cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino

wherein any of the C_1-C_5 carbons comprise part of said oxyimino group, imino wherein any of the C_1-C_5 carbons comprise part of said imino group, amidino wherein any of the C_1-C_5 carbons comprise part of said amidino group, sulfido, and sulfoxido, (b) C_3-C_6 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, imino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said imino group, amidino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said amidino group, sulfide and sulfoxido, (c) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, alkenyf, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino, imino, amidino, sulfido, and sulfoxido, and (d) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, imino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said imino group, amidino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said amidino group, sulfido, and sulfoxido;

R^{5M} is a lone pair of electrons, hydrogen, or selected from the group consisting of: (a) C_1-C_5 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_5 carbons comprise part of said oxyimino group, imino wherein any of the C_1-C_5 carbons comprise part of said imino group, amidino wherein any of the C_1-C_5 carbons comprise part of said amidino group, sulfido, and sulfoxido, (b) C_3-C_6

cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, imino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said imino group, amidino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said amidino group, sulfido, and sulfoxido, (c) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino, imino, amidino, sulfido, and sulfoxido, and (d) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, imino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said imino group, amidino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said amidino group, sulfido, and sulfoxido;

or R^{4M} and Y^{M} together form a ring of between 5 and 7 atoms where said ring is optionally fused or spiro in relation to the ring system of Y^{M}, said ring optionally being partially saturated or aromatic and optionally containing 1-2 additional heteroatoms selected from the group consisting of N, O, S, and a combination thereof;

or R^{4M} and R^{5M} together form a ring of between 3 and 7 atoms where said ring is optionally substituted, said ring optionally being saturated, partially unsaturated or aromatic and optionally containing 1-2 additional heteroatoms selected from the group consisting of N, O, S, and a combination thereof;

R^{6M} is hydrogen or an ester prodrug of the carboxylic acid;

Z^{M} is a bond;

or Z^M is optionally substituted: C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 sulfido, C_3-C_6 cycloalkyl, C_3-C_6 heterocyclyl where the bond to Y is through a carbon atom of said heterocyclyl ring, heteroaryl where the bond to Y is through a carbon atom of said heteraryl ring, oxyimino, imino, or amidino where the carbon of said oxyimino, imino, or amidino group is attached to Y;

or Z^M and Y^M together form a ring of 5-7 atoms where said ring is optionally fused or spiro in relation to the ring system of Y^M, said ring optionally being partially saturated or aromatic and optionally containing 1-3 heteroatoms selected from the group consisting of N, O, S, and a combination thereof;

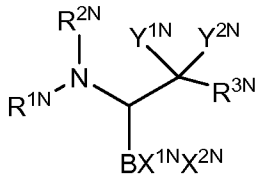
or Z^M and R^{4M} together form a ring of 4-7 atoms where said ring optionally is saturated, partially unsaturated, or aromatic and optionally contains 1-2 additional heteroatoms selected from the group consisting of N, O, S, and a combination thereof;

X^{1M} and X^{2M} are independently hydroxyl, halogen, $NR^{4M}R^{5M}$, C_1-C_6 alkoxy, or when taken together X^{1M} and X^{2M} form a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms selected from the group consisting of N, O, S, and a combination thereof, or when taken together X^{1M} and X^{2M} form a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms selected from the group consisting of N, O, S, and a combination thereof, or when taken together X^{1M} and X^{2M} form a cyclic boron amide-ester where said chain contains from 2-20 carbon atoms and, optionally, 1-3 heteroatoms selected from the group consisting of N, O, S, and a combination thereof, or X^{1M} is hydroxyl and X^{2M} is replaced by the ortho-hydroxyl oxygen of the phenyl ring such that a 6-membered ring is formed;

or a salt thereof;

provided that when R^{1M}, R^{2M}, R^{3M}, R^{4M}, R^{5M} and R^{6M} are hydrogen, X^{1M} and X^{2M} are hydroxyl, n^M is 0, Y^M is phenyl, and Z^M is CH_2 then Z^M cannot be at the meta-position of the phenyl ring relative to the rest of the molecule.

[0122] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in Int Pub. WO2009064413, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



wherein, R^{1N} is $-C(O)R^{4N}$; $-C(O)NR^{4N}R^{5N}$; $-C(O)OR^{4N}$; $-S(O)_2R^{4N}$, $-C(=NR^{4N}R^{5N})R^{4N}$, $-C(=NR^{4N}R^{5N})NR^{4N}R^{5N}$, hydrogen, or is selected from the group consisting of: (a) aryl group

substituted with from O to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (b) heteroaryl group substituted with from O to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (c) heterocyclic group substituted with from O to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido;

R^{2N} is hydrogen, or is selected from the group consisting of: (a) C_1-C_6 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_6 carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_7 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy,

heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

R^{3N} is an aryl or heteroaryl group substituted with from 1 to 4 substituents selected from the group consisting of hydroxyl, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, amino, aminocarbonyl, carbonyl, aminosulfonyl, alkylaryl, aryl, aryloxy, carboxyl, cyano, guanidino, halogen, heteroaryl, heterocyclyl, sulfido, sulfonyl, sulfoxido, sulfonic acid, sulfate, and thiol, provided that, when one of the substituents is a carboxylic acid group located at the 3-position relative to the group containing Y^{1N} and Y^{2N}, one of the remaining substituents is not a hydroxyl or amino group located at the 2- or 6-position relative to the group containing Y^{1N} and Y^{2N};

R^{4N} is selected from the group consisting of: (a) C_1-C_{10} alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_{10} carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_{10} cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one

attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

R^{5N} is hydrogen or is selected from the group consisting of: (a) C_1-C_6 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_{10} carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_7 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group

consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

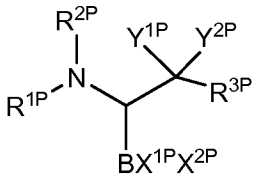
X^{1N} and X^{2N} are independently hydroxyl, halogen, $NR^{4N}R^{5N}$, C_1-C_6 alkoxy, or when taken together X^{1N} and X^{2N} form a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or when taken together X^{1N} and X^{2N} form a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or when taken together X^{1N} and X^{2N} form a cyclic boron amide-ester where said chain contains from 2-20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or X^{1N} and $R^{1N}N$ together form a cyclic ring where said ring contains 2 to 10 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, and X^{2N} is hydroxyl, halogen, $NR^{4N}R^{5N}$, C_1-C_6 alkoxy, or X^{1N} and R^{3N} together form a cyclic ring where said ring contains 2 to 10 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, and X^{2N} is hydroxyl, halogen, $NR^{4N}R^{5N}$, or C_1-C_6 alkoxy;

Y^{1N} and Y^{2N} are independently hydrogen, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, amino, aminosulfonyl, aminocarbonyl, carbonyl, alkylaryl, aryl, aryloxy, carboxyl, cyano, halogen, heteroaryl, heteroaryloxy, heterocyclyl, sulfido, sulfonyl, or sulfoxido, or taken together Y^{1N} and Y^{2N} form a cyclic structure containing from 3-12 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S;

or a salt thereof;

provided that, when $R^{1N}N$ is $-C(O)R^{4N}$, $R^{2N}N$ is hydrogen, R^{3N} is a phenyl group having one substitution consisting of a carboxylic acid group located at the 3-position relative to the group containing Y^{1N} and Y^{2N}, X^{1N} and X^{2N} are hydroxyl, and Y^{1N} and Y^{2N} are hydrogen, R^{4N} is not unsubstituted C_1 alkyl or C_1 alkyl having one substitution consisting of a phenyl group.

[0123] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in Int. Pub. WO2009064414, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



wherein, R^{1P} is $-C(O)R^{4P}$; $-C(O)NR^{4P}R^{5P}$; $-C(O)OR^{4P}$; $-S(O)_2R^{4P}$, $-C(=NR^{4P}R^{5P})R^{4P}$, $-C(=NR^{4P}R^{5P})NR^{4P}R^{5P}$, hydrogen, or is selected from the group consisting of: (a) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (b) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (c) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido;

R^{2P} hydrogen, or is selected from the group consisting of: (a) C_1-C_6 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein

any of the C_1-C_6 carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_7 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxide), and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

R^{3P} is an aryl or heteroaryl group substituted with from 1 to 4 substituents wherein one of the substituents is a hydroxyl or amino group located at the 2 position relative to the group containing Y^{1P} and Y^{2P}, and wherein the remaining substituents are selected from the group consisting of hydroxyl, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, amino, aminocarbonyl, carbonyl, aminosulfonyl, alkylaryl, aryl, aryloxy, carboxyl, cyano, guanidino, halogen, heteroaryl, heterocyclyl , sulfido, sulfonyl, sulfoxido, sulfonic acid, sulfate, and thiol;

R^{4P} is selected from the group consisting of: (a) C_1-C_{10} alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl,

halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_{10} carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_{10} cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

R^{5P} is hydrogen or is selected from the group consisting of: (a) C_1-C_6 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl,

heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_{10} carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_7 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

X^{1P} and X^{2P} are independently hydroxyl, halogen, $NR^{4P}R^{5P}$, C_1-C_6 alkoxy, or when taken together X^{1P} and X^{2P} form a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or when taken together X^{1P} and X^{2P} form a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or when taken together X^{1P} and X^{2P} form a cyclic boron amide-ester where said chain contains from 2-20 carbon atoms and,

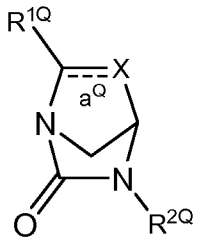
optionally, 1-3 heteroatoms which can be O, N, or S, or X^{1P} and R^{1P} together form a cyclic ring where said ring contains 2 to 10 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, and X^{2P} is hydroxyl, halogen, $NR^{4P}R^{5P}$, C_1-C_6 alkoxy, or X^{1P} and R^{3P} together form a cyclic ring where said ring contains 3 to 10 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, and X^{2P} is hydroxyl, halogen, $NR^{4P}R^{5P}$, or C_1-C_6 alkoxy;

Y^{1P} and Y^{2P} are independently hydrogen, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, amino, aminosulfonyl, aminocarbonyl, carbonyl, alkylaryl, aryl, aryloxy, carboxyl, cyano, halogen, heteroaryl, heteroaryloxy, heterocyclyl, sulfido, sulfonyl, or sulfoxido, or taken together Y^{1P} and Y^{2P} form a cyclic structure containing from 3-12 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S;

or a salt thereof;

provided that, when R^{1P} is $-C(O)R^{4P}$, R^{2P} is hydrogen, R^{3P} is a phenyl group having two substituents consisting of a hydroxyl at the 2-position and a carboxylic acid at the 3-position relative to the group containing Y^{1P} and Y^{2P}, X^{1P} and X^{2P} are hydroxyl or X^{1P} is hydroxyl and X^{2P} is replaced by the ortho-hydroxyl oxygen of R^{3P} such that a 6-membered ring is formed, and Y^{1P} and Y^{2P} are hydrogen, R^{4P} is not unsubstituted C_1 alkyl.

[0124] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in Int. Pub. WO2009091856, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



or a pharmaceutically acceptable salt thereof, wherein the bond identified as a^Q is a single bond or a double bond;

when bond a^Q is a single bond, X is CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $CH\text{-}CH_5$, $CH_2\text{-}CH\text{-}CH$, or $CH{=}CH\text{-}CH_2$;

when bond a^Q is a double bond, X is CH, $CH\text{-}CH_2$, or $CH\text{-}CH{=}CH$;

R^{1Q} is $C(O)N(R^{3Q})R^{4Q}$, $C(O)OR^{3Q}$, or $C(O)OR^{5Q}$;

R^{2Q} is SO_3M^Q, OSO_3M^Q, SO_2NH_2, PO_3M^Q, OPO_3M^Q, $CH_2CO_2M^Q$, $CF_2CO_2M^Q$, or CF_3;

M^Q is H or a pharmaceutically acceptable cation;

R^{3Q} is (1) C 1-8 alkyl substituted with a total of from 1 to 4 substituents selected from the group consisting of zero to 2 $N(R^{AQ})R^{BQ}$, zero to 2 R^{CQ}, and zero to 1 of $AryA^Q$, $HetA^Q$, or $HetB^Q$, (2) $CycA^Q$, (3) $HetA^Q$, (4) $AryA^Q$, (5) $HetB^Q$, or (6) $AryB^Q$;

R^{4Q} is H or C 1-8 alkyl optionally substituted with $N(R^{AQ})R^{BQ}$;

or alternatively, when R^{1Q} is $C(O)N(R^{3Q})R^{4Q}$, R^{3Q} and R^{4Q} together with the N atom to which they are both attached form a 4- to 9-membered, saturated monocyclic ring optionally containing 1 heteroatom in addition to the nitrogen attached to R^{3Q} and R^{4Q} selected from N, O, and S, where the S is optionally oxidized to S(O) or $S(O)_2$; wherein the monocyclic ring is optionally fused to, bridged with, or spiro to a 4- to 7-membered, saturated heterocyclic ring containing from 1 to 3 heteroatoms independently selected from N, O and S, where the S is optionally oxidized to S(O) or $S(O)_2$, to form a bicyclic ring system, wherein the monocyclic ring or the bicyclic ring system so formed is optionally substituted with 1 or 2 substituents each of which is independently: (1) C_{1-6} alkyl, (2) C_{1-6} fluoroalkyl, (3) $(CH_2)_{1-2}G$, wherein G is OH, O-C_{1-6} alkyl, O-C_{1-6} fluoroalkyl, $N(R^{AQ})R^{BQ}$, $C(O)N(R^{AQ})R^{BQ}$, $C(O)R^{AQ}$, CO_2R^{AQ}, or SO_2R^{AQ}, (4) O-C_{1-6} alkyl, (5) O-C_{1-6} fluoroalkyl, (6) OH, (7) oxo, (8) halogen, (9) $N(R^{AQ})R^{BQ}$, (10) $C(O)N(R^{AQ})R^{BQ}$, (11) $C(O)R^{AQ}$, (12) C(O)-C_{1-6} fluoroalkyl, (13) $C(O)OR^{AQ}$, or (14) $S(O)_2R^{AQ}$;

R^{5Q} is C_{1-8} alkyl substituted with 1 or 2 substituents each of which is independently $N(R^{AQ})C(O)$-$AryA^Q$;

$CycA^Q$ is C_{4-9} cycloalkyl which is optionally substituted with a total of from 1 to 4 substituents selected from zero to 2 $(CH_2)_n{}^QN(R^{AQ})R^{BQ}$ and zero to 2 $(CH_2)_n{}^QR^{CQ}$;

$HetA^Q$ is a 4- to 9-membered saturated or mono-unsaturated heterocyclic ring containing from 1 to 3 heteroatoms independently selected from N, O and S, wherein any ring S is optionally oxidized to S(O) or S $(O)_2$ and either 1 or 2 ring carbons are optionally oxidized to C(O); wherein the ring is optionally fused with a C_{3-7} cycloalkyl; and wherein the optionally fused, saturated or mono-unsaturated heterocyclic ring is optionally substituted with a total of from 1 to 4 substituents selected from zero to 2 $(CH_2)_n{}^QN(R^{AQ})R^{BQ}$ and zero to 2 $(CH_2)_n{}^QR^{CQ}$;

$AryA^Q$ is phenyl which is optionally substituted with a total of from 1 to 4 substituents selected from zero to 2 $(CH_2)_n{}^QN(R^{AQ})R^{BQ}$ and zero to 2 $(CH_2)_n{}^QR^{CQ}$;

$HetB^Q$ is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms selected from 1 to $_3$ N atoms, zero or 1 O atom, and zero or 1 S atom; wherein the heteroaromatic ring is optionally fused with a 5- to 7-membered, saturated heterocyclic ring containing 1 or 2 heteroatoms independently selected from N, O and S, wherein any ring S is optionally oxidized to S(O) or $S(O)_2$ and either 1 or 2 non-fused ring carbons are optionally oxidized to C(O); and wherein the optionally fused heteroaromatic ring is optionally substituted with a total of from 1 to 4 substituents selected from zero to 2 $(CH_2)_n{}^QN(R^{AQ})R^{BQ}$ and zero to 2 $(CH_2)_n{}^QR^{CQ}$;

$AryB^Q$ is a bicyclic ring system which is phenyl fused with a 5- to 7-membered saturated heterocyclic ring containing from 1 to 3 heteroatoms independently selected from N, O and S, wherein any ring S is optionally oxidized to S(O) or $S(O)_2$, and wherein the bicyclic ring system is optionally substituted with a total of from 1 to 4 substituents selected from zero to 2 2 $(CH_2)_n{}^QN(R^{AQ})R^{BQ}$ and zero to 2 $(CH_2)_n{}^QR^{CQ}$;

each n^Q is independently an integer which is 0, 1, 2, or 3;

each R^{AQ} is independently H or C_{1-8} alkyl;

each R^{BQ} is independently H or C_{1-8} alkyl;

each R^{CQ} is independently C_{1-6} alkyl, OH, O-C_{1-8} alkyl, OC(O)-C_{1-8} alkyl, $C(=NH)NH_2$, NH-$C(=NH)NH_2$, halogen, CN, $C(O)R^{AQ}$, $C(O)OR^{AQ}$, $C(O)N(R^{AQ})R^{BQ}$, SO_2R^{AQ}, $SO_2N(R^{AQ})R^{BQ}$, pyridyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl; and

provided that:

(A) when R^{1Q} is $C(O)OR^{3Q}$ and R^{3Q} is $AryA^Q$, then $AryA^Q$ is not (i) unsubstituted phenyl, (ii) phenyl substituted with NH_2, (iii) phenyl substituted with OH, (iii) phenyl substituted with O-C_{1-6} alkyl, (iv) phenyl substituted with one or more halogens, or (v) phenyl substituted with C_{1-6} alkyl;

(B) when R^{1Q} is $C(O)OR^{3Q}$ and R^{3Q} is C_{1-6} alkyl substituted with $HetB^Q$, then $HetB^Q$ is not pyridyl;

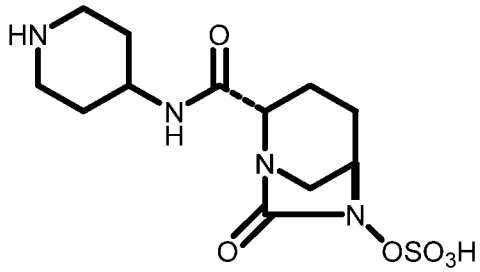
(C) when R^{1Q} is $C(O)OR^{3Q}$ and R^{3Q} is CH_2-$AryA^Q$ or CH_2CH_2-$AryA^Q$, then $AryA^Q$ is not (i) unsubstituted phenyl, (ii) phenyl substituted with NH_2, OH, O-C_{1-6} alkyl, or C_{1-6} alkyl, or (iii) phenyl substituted with one or more halogens;

(D) when R^{1Q} is $C(O)N(R^{3Q})R^{4Q}$, R^{3Q} is $AryA^Q$, CH_2-$AryA^Q$ or CH_2CH_2-$AryA^Q$, and R^{4Q} is H or C_{1-6} alkyl, then $AryA^Q$ is not unsubstituted phenyl, phenyl substituted with $N(CH_3)_2$, or phenyl substituted with $C(O)NH_2$;

(E) when R^{1Q} is $C(O)N(R^{3Q})R^{4Q}$, R^{3Q} is C_{1-6} alkyl substituted with $HetB^Q$, and R^{4Q} is H or C_{1-6} alkyl then $HetB^Q$ is not pyridyl; and

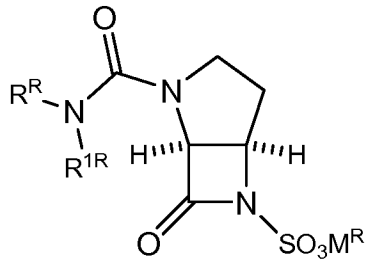
(F) when R^{1Q} is $C(O)OR^{3Q}$ and R^{3Q} is C_{1-6} alkyl substituted with R^{CQ}, then R^{CQ} is not $C(O)NH_2$.

[0125] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein include the compound MK-7655, having the following formula:



MK-7655

[0126] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in Int. Pub. WO2008039420, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



or a pro-drug or pharmaceutically acceptable salt thereof,

wherein, R^R represents a 7-, 8-, or 9-membered saturated or unsaturated ring optionally containing from 1 to 3 heteroatoms independently selected from N, O and S, wherein the ring is optionally substituted with one or more R^{aR} groups;

R^{IR} represents hydrogen or methyl;

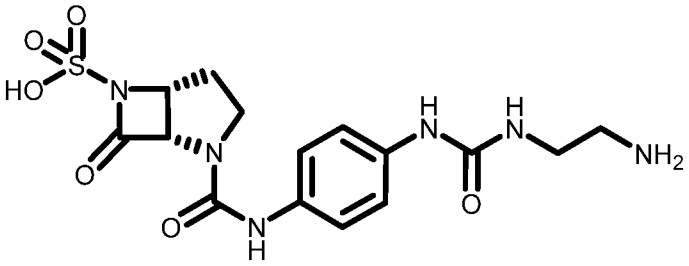
each R^{aR} independently represents hydrogen, C_{1-6} alkyl, halo, $-(CH_2)_n{}^RCN$, $-(CH2)_n{}^RNO_2$, $-(CH_2)_n{}^ROR^{bR}$, $-(CH_2)_n{}^RSR^{bR}$, $-(CH_2)_n{}^RN(R^{bR})_2$, $-(CH_2)_n{}^RC(O)N(R^{bR})_2$, $-(CH_2)_n{}^RSO_2N(R^{bR})_2$, $-(CH_2)_n{}^RCO_2R^{bR}$, $-(CH_2)n^RC(O)R^{bR}$, $-(CH_2)_n{}^ROC(O)R^{bR}$, $-(CH_2)_n{}^RNHC(O)R^{bR}$, $-(CH_2)_n{}^RNHC(O)_2R^{bR}$, $-(CH_2)_n{}^RNHSO_2R^{bR}$, $-(CH_2)_n{}^RC(=NH)NH_2$, or $-(CH_2)_n{}^RC(=NH)H$; or two R^{aR} groups on the same ring carbon atom are optionally taken together to form oxo; or two R^{aR} groups on the same ring sulfur atom are optionally taken together with the sulfur to represent SO; or four R^{aR} groups on the same ring sulfur atom are optionally taken together with the sulfur to represent SO_2;

each n^R is independently 0, 1, 2, 3, or 4;

each R^{bR} independently represents hydrogen or C_{1-4} alkyl; and

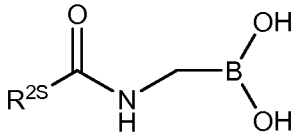
M^R represents hydrogen or a pharmaceutically acceptable cation or, when the compound contains an internal base which is capable of being protonated by a sulfonic acid, M^R is optionally a negative charge.

[0127] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein include compound BAL-29880, having the following formula:

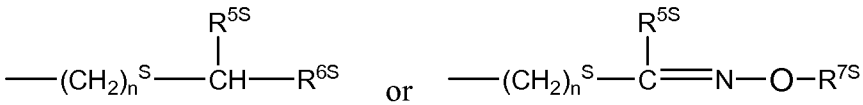


BAL-29880

[0128] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in Int. Pub. WO0222137, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



wherein, R^{2S} is H, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkyl-cycloalkyl, heteroalkyl-cycloalkyl, alkyl-heterocycloalkyl, heteroalkyl-heterocycloalkyl, alkenyl, heteroalkenyl, cyclic alkene, heterocyclic alkene, alkyl-cyclic alkene, heteroalkyl-cyclic alkene, cyclic alkene-alkyl, cyclic alkene-heteroalkyl, alkyl-heterocyclic alkene, heterocyclic alkene-alkyl, heterocyclic alkene-heteroalkyl, heteroalkyl-heterocyclic alkene, alkyl-O-cyclic alkene, alkyl-O-heterocyclic alkene, alkyl-S-cyclic alkene, alkyl-S-heterocyclic alkene, or



each R^{2S} may be unsubstituted or substituted with one or more R^{3S} groups;

each R^{3S} is independently alkyl, heteroalkyl, cyclic alkene, cyclic alkene substituted with one or more R^{4S} groups, heterocyclic alkene, heterocyclic alkene substituted with one or more R^{4S} groups, halogen, $-NH_2$, =NH, =N, =N-OH, =O, -OH, -O-C(O)H, -O-alkyl,-COOH, $-(CH_2)_m{}^S$-COOH, $=CH-(CH_2)_m{}^S$-COOH, -CN, $=N-O-CH_3$, $=N-O-C(CH_3)_2$-COOH, $=N-O-C(CH_3)_2$-C(O)-O-alkyl, $-(CH_2)_m{}^S-NH_2$, $=C(COOH)-C(O)-NH_2$, -C(O)-O-alkyl, -C(O)-O-cyclic alkene, -S-alkyl, $-SO_3H$, or $-SO_2-CH_3$;

each R^{4S} is independently alkyl, halogen, =NH, $-NH_2$,$-(CH_2)_m{}^S-NH_2$, =O, -OH, $-(CH_2)_m{}^S$-OH, -COOH, $-(CH_2)_m{}^S$-COOH, $-C(=O)NH_2$, $-SO_3H$, or $-SO_2-CH_3$;

R^{5S} is cyclic alkene or heterocyclic alkene, each of which may be unsubstituted or substituted with one or more R^{4S} groups;

R^{6S} is alkyl or heteroalkyl, each of which may be unsubstituted or substituted with one or more R^{4S} groups;

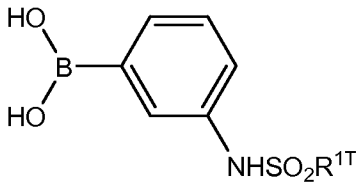
R^{7S} is H or R^{7S} is alkyl or heteroalkyl, each of which may be unsubstituted or substituted with one or more R^{4S} groups;

m^S is 1-4; and

n^S is 0-2;

or a pharmaceutically-acceptable salt thereof.

[0129] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in Int. Pub. WO2000035904, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



wherein, R^{1T} is N-lower alkyl, a cyclic alkene or a heterocyclic alkene, wherein the cyclic alkene and heterocyclic alkene may be substituted with one or more substituents R^{2T}; and

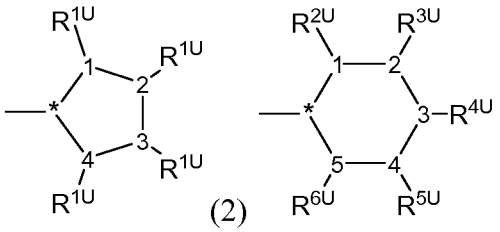
each R^{2T} is independently H, a halogen atom, lower, alkyl, lower alkyl substituted with one or more halogen atoms, NH_2, NO, NO_2, N-lower alkyl, N-lower alkyl substituted with one or more halogen atoms, OH, O-lower alkyl, O-lower alkyl substituted with one more halogen atoms, CO-lower alkyl, CO-lower alkyl substituted with one or more halogen atoms, COOH, lower alkyl-COOH, COO-lower alkyl, $CONH_2$, CON-lower alkyl, SO_3H, SO_2NH_2, SO_2N-lower alkyl, or $B(OH)_2$, except that R^{2T} cannot be N-lower alkyl when R^{1T} is naphthalene;

or a pharmaceutically-acceptable salt thereof.

[0130] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in Int. Pub. WO98/56392, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:

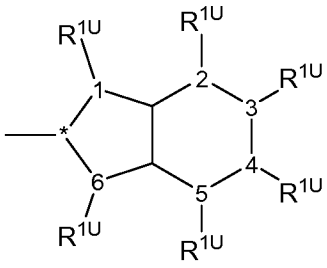
$$\mathbf{(OH)_2\ B\ -\ R^U}$$

wherein, R^U is naphthalene, phenanthrene, or has one of the following formulas:

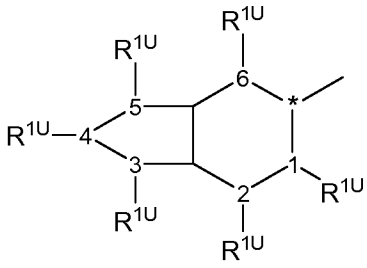


(2)

(3)



(4)



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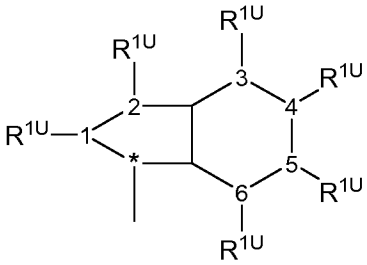

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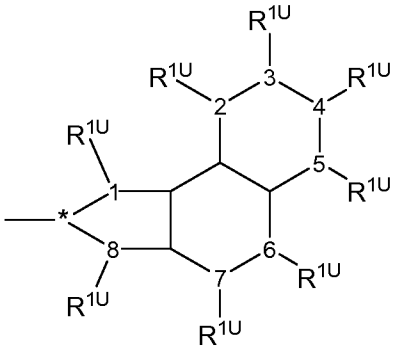
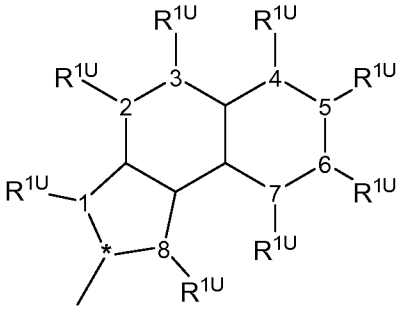
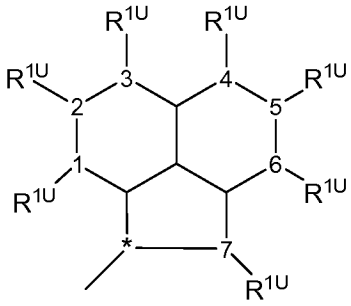


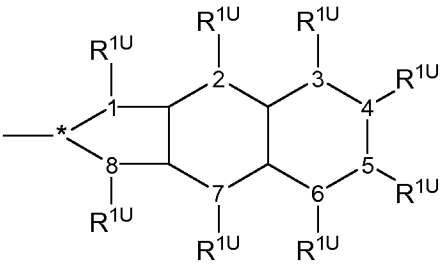
(7)



(8)



(9)



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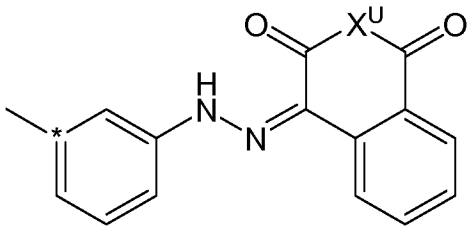
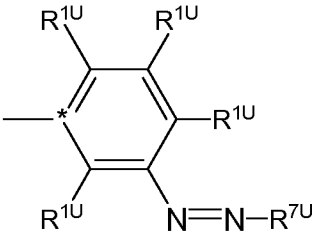
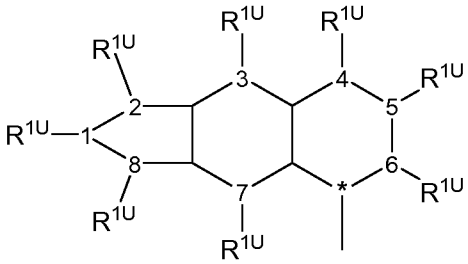


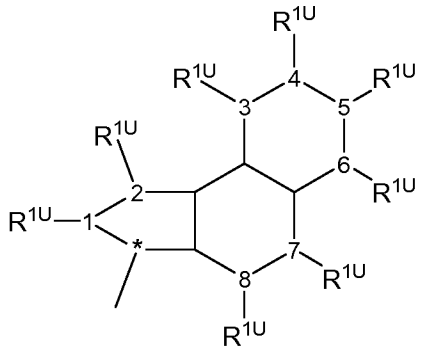
(11)



(12)



(13)



(14)

wherein, ring system (2), (3), (4), (5), (6), (7), (8), (9) or (10) is aromatic or nonaromatic;

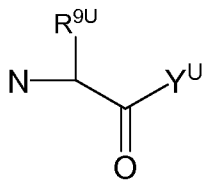
the atom center * is (R) or (S) in the case of chiral compounds; positions 1, 2, 3, 4, 5, 6, 7 or 8 each independently is C, N, O or S;

R^{1U} through R^{6U} each independently is a lone pair, H, $B(OH)_2$, a halogen atom, CF_3, CH_2CF_3, CCl_3, CH_2CCl_3, CBR^{3U}, CH_2CBR^{3U}, NO_2, lower alkyl, CO_2H, CHCHCOOH, CH2CH_2CH_2COOH, SO_3H, PO_3H, OSO_3H, OPO_3H, OH, NH_2, $CONH_2$, $COCH_3$, OCH_3, or phenyl boronic acid, except that R^{2U}, R^{3U}, R^{4U}, R^{5U} and R^{6U} cannot all simultaneously be H, R^{2U} cannot be lower alkyl when R^{3U}, R^{4U}, R^{5U} and R^{6U} are H, R^{3U} cannot be NH_2, OH or lower alkyl when R^{2U}, R^{4U}, R^{5U} and R^{6U} are H, and R^{4U} cannot be lower alkyl when R^{2U}, R^{3U}, R^{5U} and R^{6U} are H;

R^{7U} is a lone pair of electrons, H, $B(OH)_2$, a halogen atom, CF_3, CCl_3, CBR^{3U}, CH_2CF_3, CH_2CCl_3, CH_2CBR^{3U}, NO_2, $CONH_2$, $COCH_3$, OCH_3, lower alkyl, aryl, aryl substituted with one or more substituents R^{8U}, heteroaryl, or heteroaryl substituted with one or more substituents R^{8U};

each R^{8U} is independently a lone pair, H, $B(OH)_2$, a halogen atom, CF_3, CCl_3, CBR^{3U}, CH_2CF_3, CH_2CCl_3, CH_2CBR^{3U}, NO_2, lower alkyl, O, N, S, OH, NH_2, $N(CH_3)_2$, $N(CH_3)CH_2CH_3$, $NCOCH_3$, COOH, CHCHCOOH, $CH_2CH_2CH_2COOH$, $CONH_2$, $COCH_3$, OCH_3, OCl or phenyl boronic acid;

X^U is O, NH, NCH_3 or

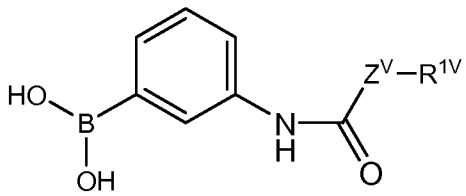


Y^U is OH, NH_2, NCH_3, $N(CH_3)_2$, $NHCOCH_3$ or $NHCOCH_2COOH$; and

R^{9U} is a lone pair of electrons, H, B $(OH)_2$, a halogen atom, CF_3, CCl_3, CBR^{3U}, CH_2CF_3, CH_2CCl_3, CH_2CBR^{3U}, NO_2, CO_2H, CHCHCOOH, $CH_2CH_2CH_2COOH$, SO_3H, PO_3H, OSO_3H, OPO_3H, OH, NH_2, $CONH_2$, $COCH_3$, OCH_3, phenyl boronic acid, lower alkyl, or a side chain of a standard amino acid;

or a pharmaceutically-acceptable salt thereof.

[0131] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in Int. Pub. WO200035905, incorporated herein by reference in its entirety. Some embodiments include compounds having the following formula:



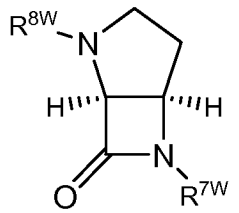
wherein, R^{1V} is lower alkyl, lower alkyl substituted with one or more halogen atoms, a cyclic alkene, or a heterocylic alkene, wherein the cyclic alkene or heterocyclic alkene may be substituted with one or more substituents R^{2V};

each R^{2V} is independently H, a halogen atom, lower alkyl, lower alkyl substituted with one or more halogen atoms, NH_2, NO, NO_2, CN, N-lower alkyl, N-lower alkyl substituted with one or more halogen atoms, OH, O-lower alkyl, O-lower alkyl substituted with one or more halogen atoms, CO-lower alkyl, CO-lower alkyl substituted with one or more halogen atoms, COOH, lower alkyl-COOH, $CONH_2$, CON-lower alkyl, SO_3H, SO_2NH_2, or SO_2N-lower alkyl; and

Z^V is a bond, O, S, lower alkyl radical, or lower heteroalkyl radical;

or a pharmaceutically-acceptable salt thereof.

[0132] Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein are described in Int. Pub. WO2007065288 and U.S. Pub. No. 2010/0056478, the disclosures of which are incorporated herein by reference in their entireties. Some embodiments include compounds having the following formula:



wherein, R^{7W} signifies SO_3H, OSO_3H or $OCR^{jW}R^{jW'}COOH$,

wherein R^{jW} and $R^{j'W}$ are independently selected from hydrogen; alkyl; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen; benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen; alkylamino and alkoxyalkyl;

R^{8W} is alkoxycarbonylamino, the acyl residue of an α or β-amino acid, or a residue of the formula Q^W-$(X^W)_r{}^W$-Y^W-, wherein Q^W is a 3-6 membered .ring which optionally contains nitrogen, sulphur and/or oxygen and which is optionally fused to a phenyl ring or to a 5-6 membered heterocyclic ring and which is optionally substituted with 1 to 4 substituents selected from alkyl, allyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino, carboxamide which may be substituted, carboxylic acid, carbonylalkoxy, aminocarbonyl, alkylaminocarbonyl , halogen, ha1ogenomethyl, dihalogenomethyl, trihalogenomethyl, sulfamide, substituted sulfamide with substituents selected from alkyl, allyl, phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl , amino, alkylamino and halogen and benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, halogen and benzyl, urea which may be substituted with alkyl, aminoalkyl or alkylhydroxyl and carbamate which may be substituted with alkyl, aminoalkyl or alkylhydroxyl,

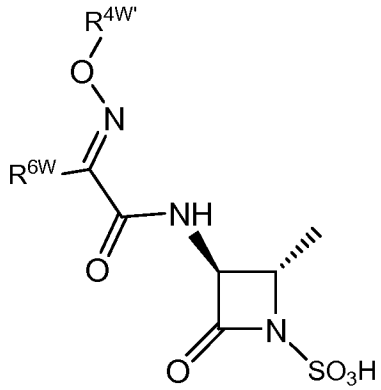
X^W signifies a linear spacer of from 1 to 6 atoms length and containing carbon, nitrogen, oxygen and/or sulphur atoms, of which up to 2 atoms can be nitrogen atoms and 1 atom can be oxygen or sulphur,

r^W is an integer of from 0 to 1; and

Y^W is selected from -CO-, -CS-, -NHCO- and -SO_2-;

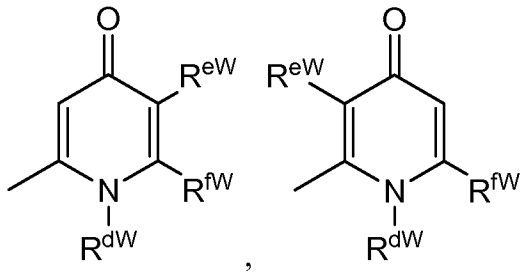
or a pharmaceutically acceptable salt thereof.

[0133] More embodiments include compounds having the following formula:



wherein, $R^{4W'}$ signifies hydrogen, alkyl, $C(R^{xW'})$ $(R^{yW'})$ $Z^{W'}$,

wherein $R^{xW'}$ and $R^{yW'}$ are independently selected from hydrogen, alkyl and (C_3-C_6) cycloalkyl; and $Z^{W'}$ signifies COOH or a group of one of the following two formulae

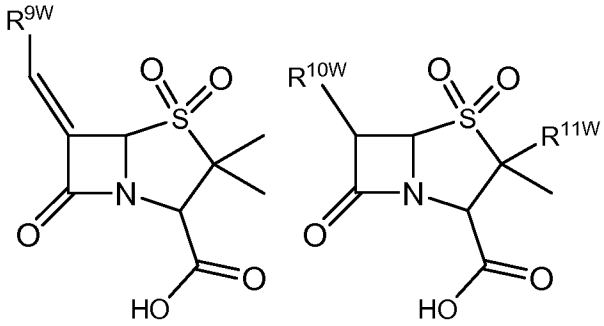


wherein, R^{dW} is hydrogen; amino; monoalkylamino ; alkyl; alkoxycarbony; benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen, diphenylmethyl; trityl; or ORg whereby R^{gW} is hydrogen, alkyl, benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino and halogen; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino and halogen;

R^{eW} and R^{fW} are independently selected from hydrogen; alkyl; benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino and halogen; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino and halogen; OR^{gW} whereby R^{gW} is hydrogen, alkyl, benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino and halogen; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino and halogen; diphenylmethyl; trityl or alkoxycarbonyl; or, when R^{eW} and R^{fW} are vicinal substituents, R^{eW} and R^{fW} taken together may also be -O-CH=CH-CH_2-, -O-CH_2-CH_2-O-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -CH=CH-CH=CH- or -CH=C(OH)-C(OH)=CH-;

$R^{6W'}$ signifies phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen; or a 5-6 membered heteroaromatic ring which may be substituted with amino, alkyl amino, carbonylamino or halogen.

[0134] More embodiments include compounds having the following formula:



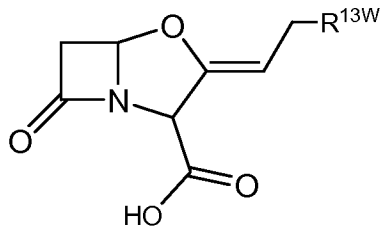
wherein, R^{9W} signifies COOH or a 5-6 membered monocyclic or polycyclic heteroaromatic group;

R^{10W} signifies hydrogen or halogen;

R^{11W} signifies CH_2R^{12W}; $CH{=}CHR^{12W}$ wherein R^{12W} is hydrogen, halogen, cyano, carboxylic acid, carboxamide which may be substituted, alkoxycarbonyl or a 5-6 membered heteroaromatic ring which is optionally substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl , amino, alkylamino, dialkylamino and halogen; or which is optionally fused with a 5-6 membered heteroaromatic ring; $CH{=}NR^{12W'}$ wherein $R^{12W'}$ is amino, alkylamino, dialkylamino, aminocarbonyl , hydroxy, alkylhydroxy,

or a pharmaceutically acceptable salt thereof.

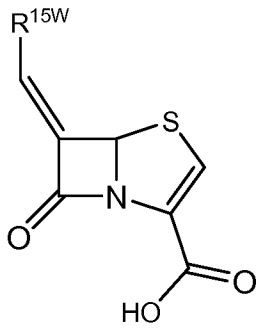
[0135] More embodiments include compounds having the following formula:



wherein, R^{13W} signifies OR^{14W}; $S(O)_n{}^WR^{14W}$ or a 5-6 membered heteroaromatic ring which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen; whereby n^W = 0, 1 or 2, and R^{14W} is hydrogen, alkyl, (C_2-C_7) alkene, (C_2-C_7) alkyne or a 5-6 membered heteroaromatic ring which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen,

or a pharmaceutically acceptable salt thereof.

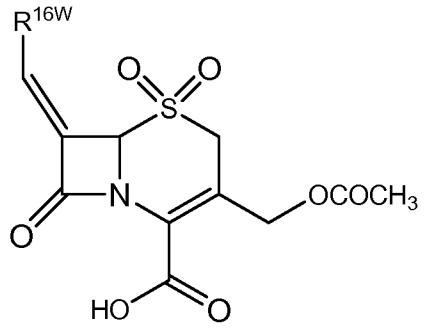
[0136] More embodiments include compounds having the following formula:



wherein, R^{15W} signifies a 5-6 membered heteroaromatic ring which maybe substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl , amino, alkylamino, dialkylamino and halogen; or which is optionally fused with a 5-6 membered heteroaromatic ring and/or which is optionally bound to the exo-methylene group over a -CH=CH- spacer being preferably in the (E) -configuration,

or a pharmaceutically acceptable salt thereof.

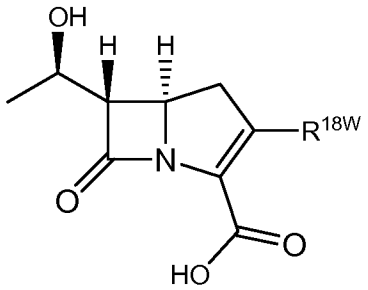
[0137] More embodiments include compounds having the following formula:



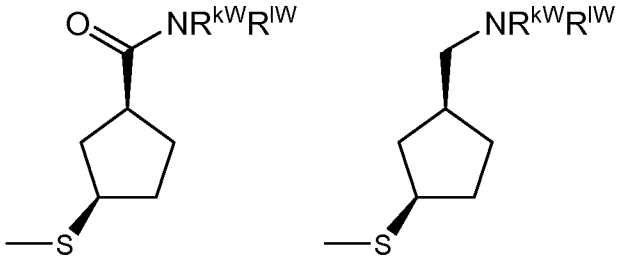
wherein, R^{16W} signifies $COOR^{17W}$, whereby R^{17W} signifies hydrogen or alkyl; or a 5-6 membered heteroaromatic ring which is optionally fused with a 5-6 membered heteroaromatic ring being optionally substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl , amino, alkylamino, dialkylamino , halogen; and/or being optionally bound to the exo-methylene group over a -CH=CH- spacer being preferably in the (E)-configuration,

or a pharmaceutically acceptable salt thereof.

[0138] More embodiments include compounds having the following formula:

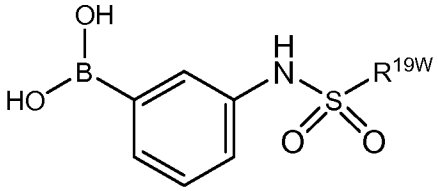


wherein, R^{18W} signifies -S-alkyl , -S-(CH_2) 2-NH-CH=NH or a group of one of the following two formulae



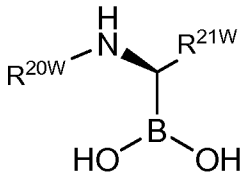
wherein R^{kW} and R^{lW} are individually selected from hydrogen, alkyl, 2-, 3-, 4-carboxyphenyl and sulfamoyl, or a pharmaceutically acceptable salt thereof.

[0139] More embodiments include compounds having the following formula:



wherein R^{19W} signifies a 5-6 membered heteroaromatic ring which may be substituted with amino, alkylamino, dialkylamino or alkylsulfoxide, or a pharmaceutically acceptable salt thereof.

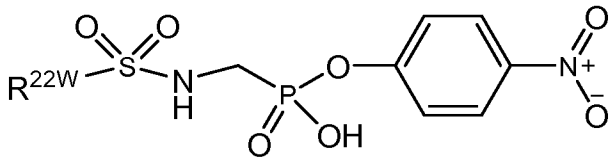
[0140] More embodiments include compounds having the following formula:



wherein, R^{20W} and R^{21W} are independently selected from a 5-6 membered heteroaromatic ring; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkyl- hydroxyl, amino, alkylamino, dialkylamino and halogen and benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen,

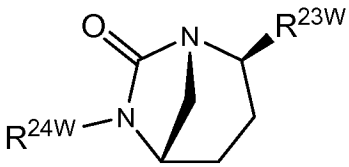
or a pharmaceutically acceptable salt thereof.

[0141] More embodiments include compounds having the following formula:



wherein, R^{22W} is selected from a 5-6 membered heteroaromatic ring which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen and which is optionally fused with a 5-6 membered heteroaromatic ring; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen; and benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen.

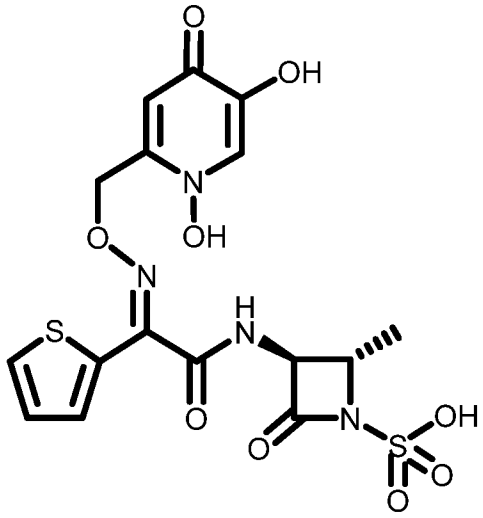
[0142] More embodiments include compounds having the following formula:



wherein, R^{23W} signifies hydrogen, carboxylic acid, alkoxycarbonyl or carboxamide which may be substituted, and

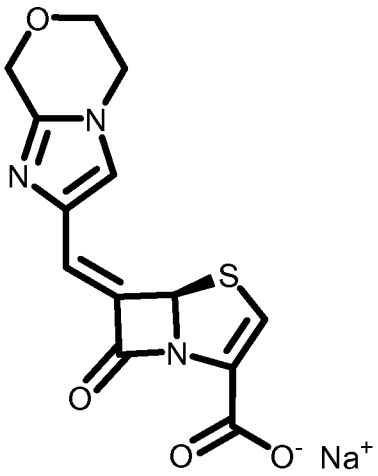
R^{24W} signifies SO_3H, OSO_3H or $OCR^{jW}R^{jW'}COOH$, wherein R^{jW} and $R^{jW'}$ are independently selected from hydrogen, alkyl, phenyl which may be substituted, benzyl which may be substituted, aminoalkyl and alkoxy.

Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein include compound SYN-2190, having the following formula:



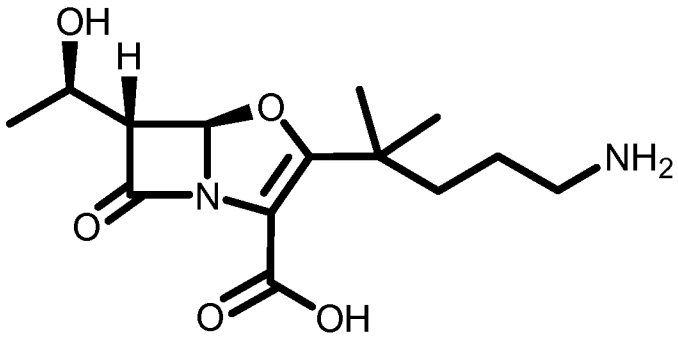
SYN-2190

Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein include compound BLI-489, having the following formula:



BLI-489

Some β-lactamase inhibitors useful with the methods, compositions and compounds provided herein include compound AM-112, having the following formula:



AM-112

[0143] The following examples of specific β-lactamse inhibitors are used for the purposes of illustration only, and should not be considered as limiting.

EXAMPLES

General procedures

[0144] Materials used in preparing the cyclic boronic acid 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.

[0145] 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.

[0146] 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.

[0147] 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.

[0148] 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.

[0149] (^{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.

[0150] 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

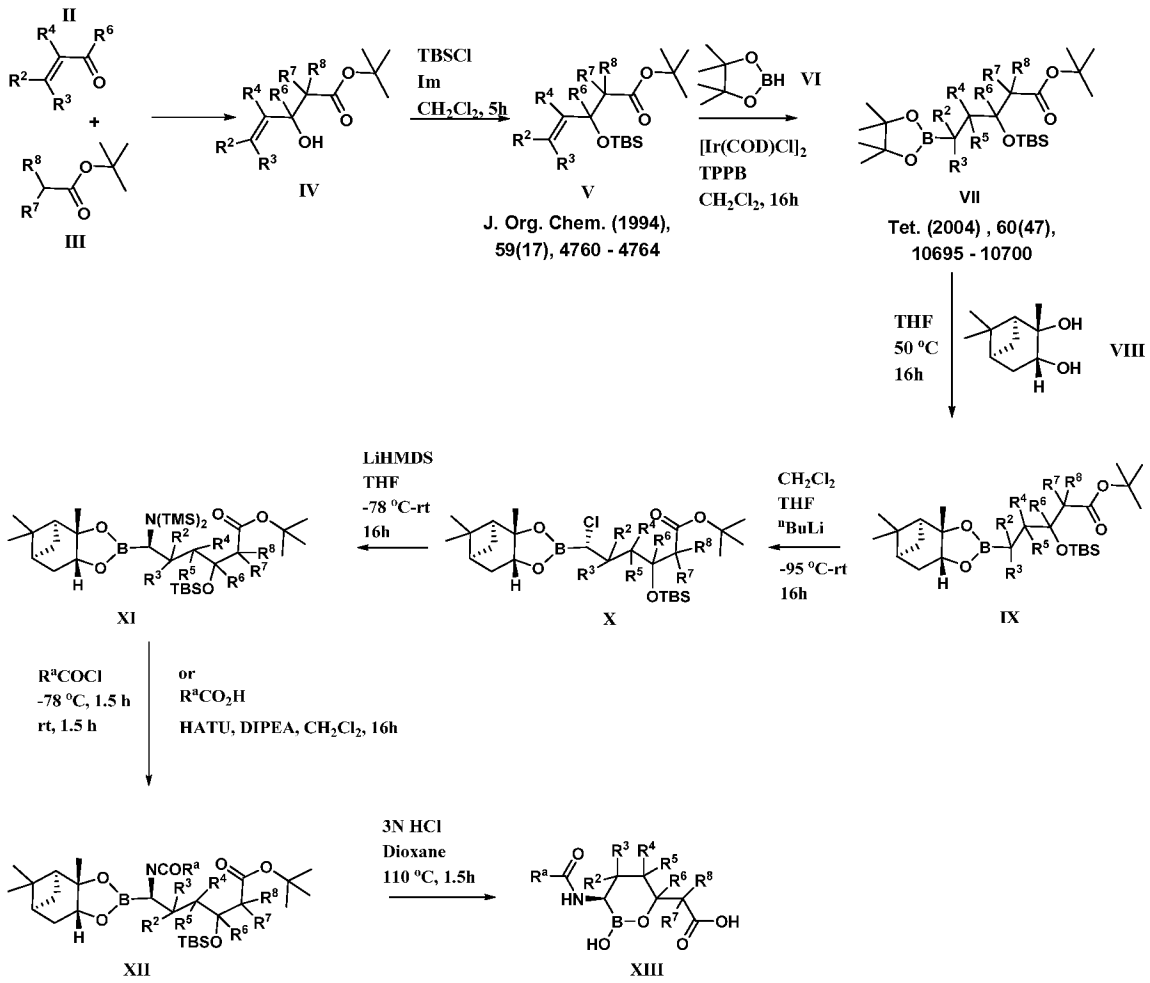
EtOH	= ethanol
HATU	= 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCl	= hydrochloric acid
HOBt	= hydroxybenzotriazole
Im	= imidazole
LiHMDS	= lithium bis(trimethylsilyl)amide
MeCN	= acetonitrile
$NaHCO_3$	= sodium bicarbonate
Na_2SO_4	= sodium sulfate
NMM	= N-methylmorpholine
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

[0151] 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.

Formula (I)

[0152] 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.

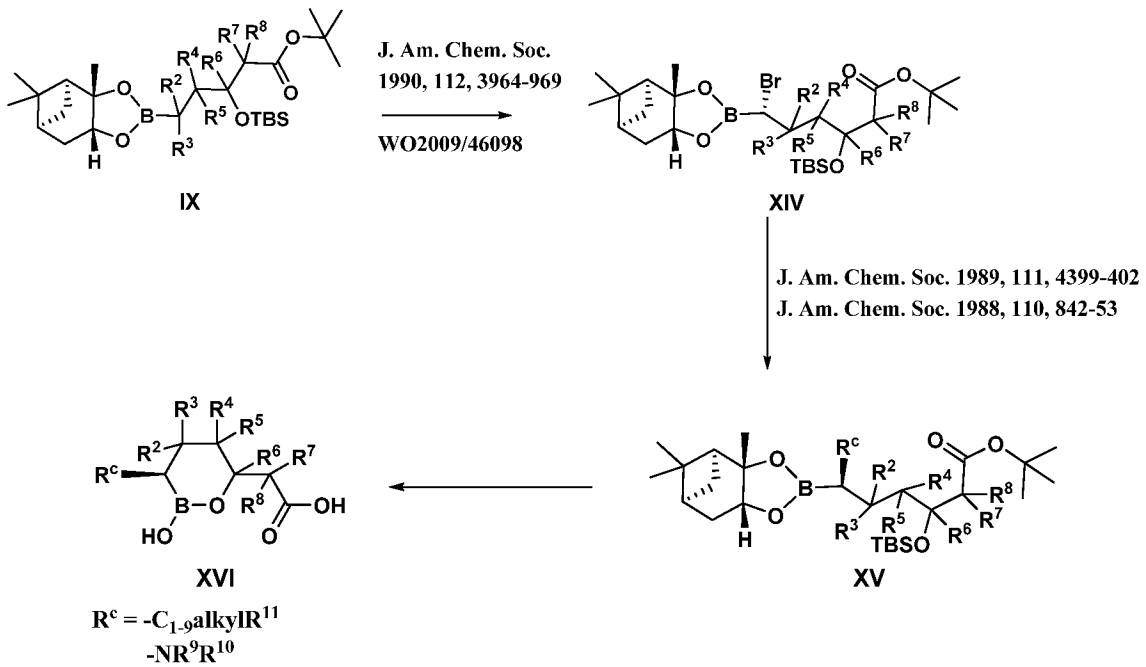
Scheme 1



[0153] 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). 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).

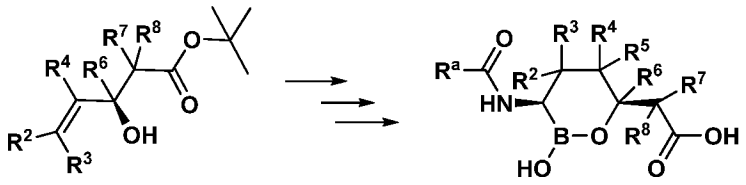
Scheme 2



[0154] 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.

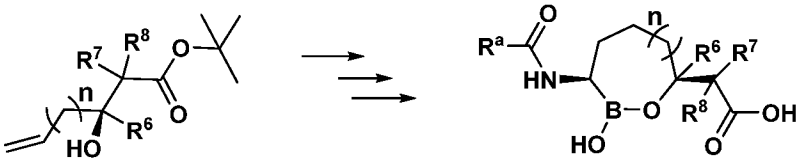
Scheme 3



XVII **XVIII**

[0155] 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.

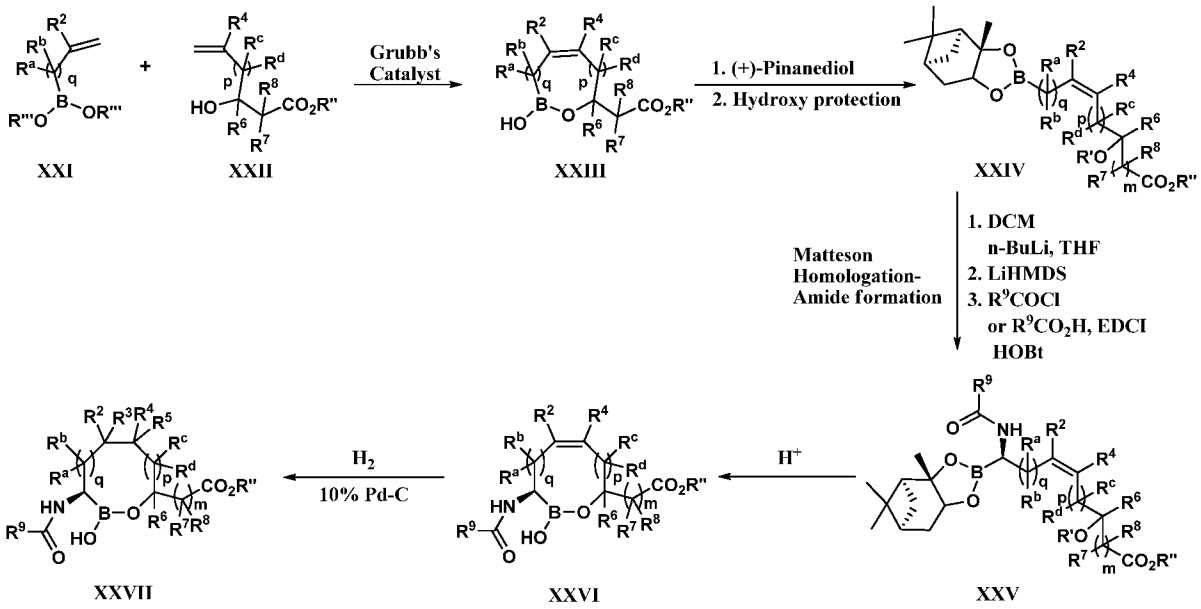
Scheme 4



XIX **XX**

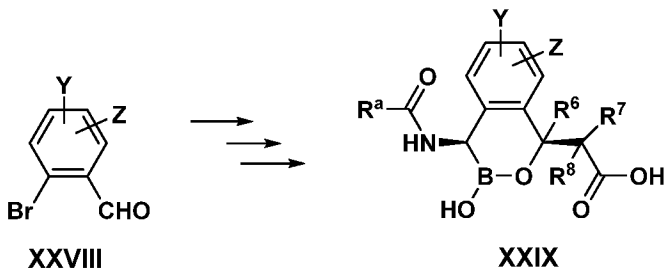
[0156] The sequence shown in Scheme 1 also allows for varied ring sizes in formula **I** such as 7- and 8-membered rings. For example, a seven-membered analog **XX** where n = 1 can be achieved by using the corresponding allyl intermediate (**XIX**) as a starting material (Scheme 4). Such allyl derivatives 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



[0157] 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**.

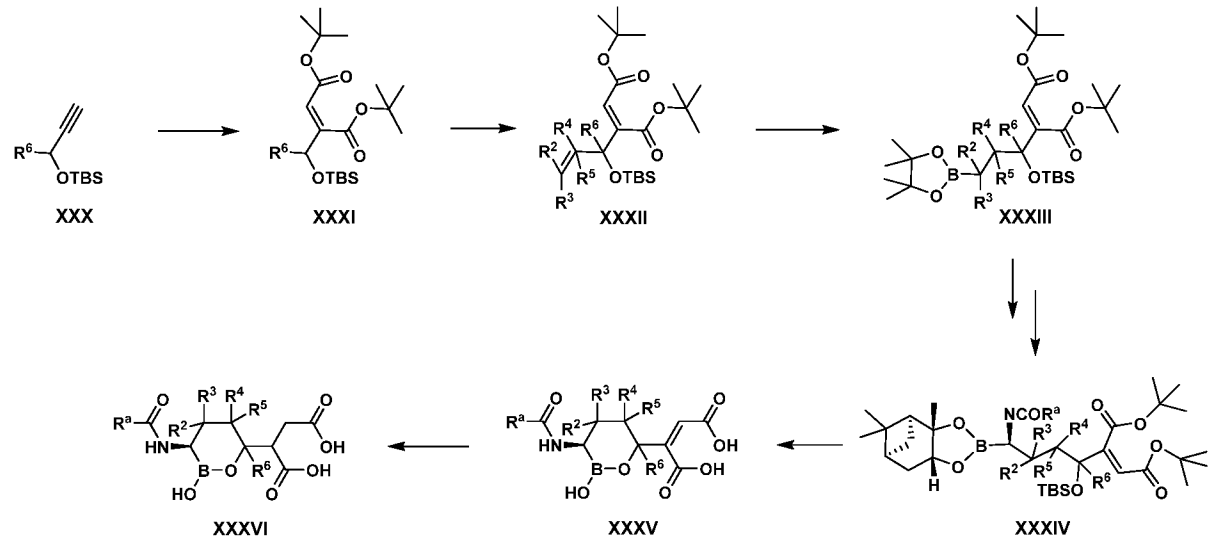
Scheme 6



[0158] 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

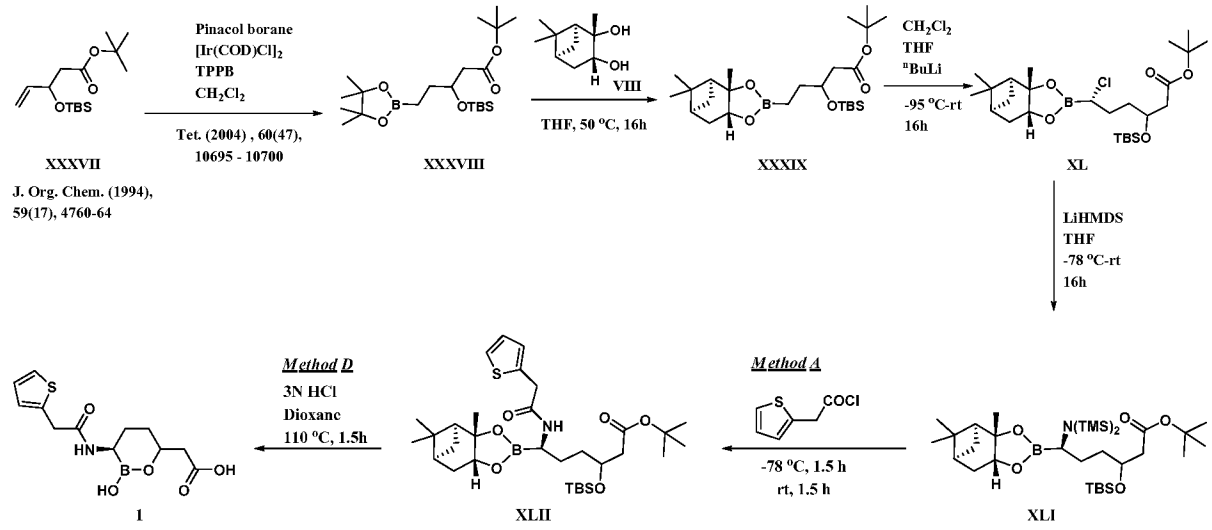


[0159] Compounds of formula I where R^7 and R^8 are substituted as maleate (**XXXV**) or succinate (**XXXVI**) may be made following the sequence shown in Scheme 7. Maleate intermediates such as **XXXII** can be transformed to analogs **XXXV** analogously to the steps in Scheme 1. Analogs of **XXXV** 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].

Illustrative Compound Examples

[0160] 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

[0161] 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

[0162] 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

[0163] 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

[0164] 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).

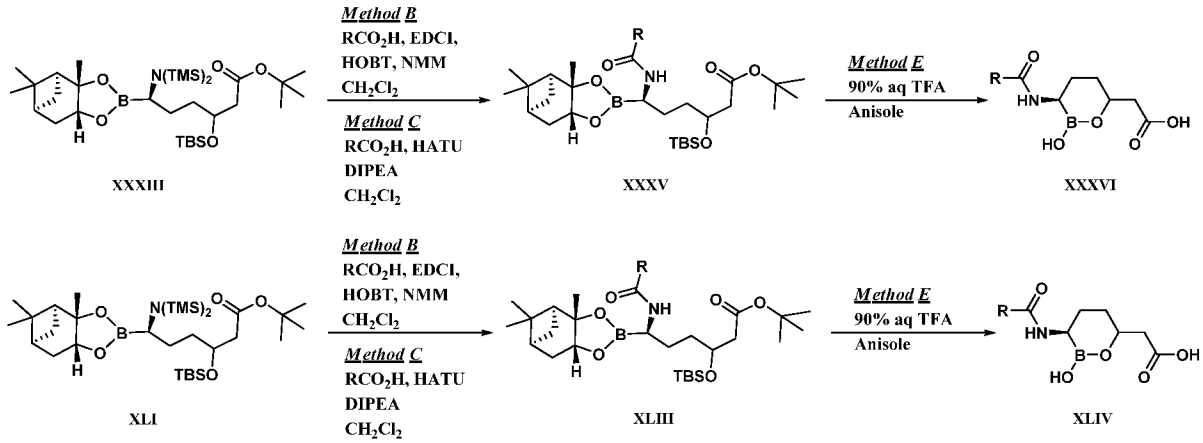
Step 6

[0165] ***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). ^{1}H 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%) $(M-H_2O)+$.

[0166] Alternative procedures for Steps 5 and 6 are shown in Scheme 9.

Scheme 9



Step5, Method B

[0167] 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

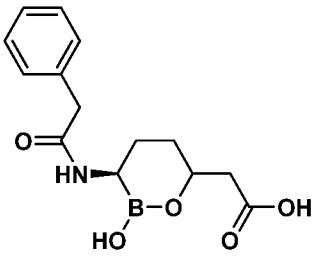
[0168] A solution of bis-silyl amide **XLI** (0.5 mmol) and acid in dry DCM (10 mL) were cooled to 0°C. Then DIPEA (1.5 mmol) was added drop wise followed HATU (0.75 mmol). The mixture was then allowed to warm to room temperature. After TLC has indicated complete conversion (~3h) of the starting materials, 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**.

Step6, Method E

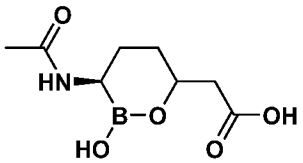
[0169] To a solution of amide **(XLIII)** (0.1 mmol) in dichloroethane (2 mL) at 0^0C was treated with pre-cooled 90% aq. TFA (4 mL) and stirred at room temperature for 3 hrs. The reaction mixture was evaporated in vacuo, azeotroped with MeCN (3 X 5 mL) and the residue was triturated with ether (5 mL). The product separated was filtered, dissolved in dioxane-water mixture and freeze dried to give the final product **XLIV** as a fluffy solid.

[0170] The following compounds are prepared in accordance with the procedure described in the above Example 1 using methods A and D.



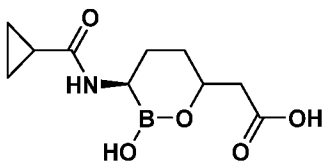
2

[0171] 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

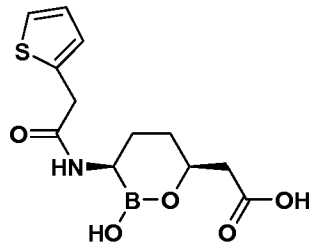
[0172] 2-((3R)-3-acetamido-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **3**. ^{1}H NMR (CD_3OD) δ ppm 1.07-1.36 (m, 1H), 1.36-1.59 (m, 1H), 1.59-1.73 (m, 1H), 1.73-2.09 (m, 1H), 2.15-2.16 (d, 3H), 2.35-2.69 (m, 3H), 4.01-4.23 (m, 1H); ESIMS found for $C_8H_{14}BNO_5$ *m/z* 198 (100%) $(M-H_2O)^+$.



4

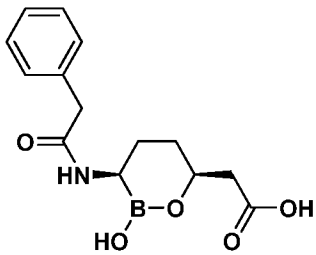
[0173] 2-((3R)-3-(cyclopropanecarboxamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **4**. ^{1}H NMR (CD_3OD) δ ppm 0.98-1.32 (m, 5H), 1.32-1.67 (m, 2H), 1.67-2.06 (m, 2H), 2.27-2.66 (m, 3H), 3.98-4.16 (m, 1H); ESIMS found for $C_{10}H_{16}BNO_5$ *m/z* 224 (100%) $(M-H_2O)^+$.

[0174] 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

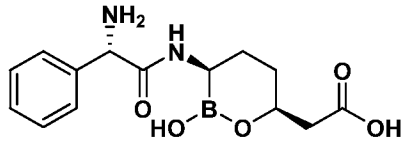
[0175] 2-((3R,6S)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-1,2-oxaborinan-6-yl)acetic acid **5**. ^{1}H NMR (CD_3OD) δ ppm 0.97-1.11 (q, 1H), 1.47-1.69 (m, 2H), 1.69-1.80 (m, 1H), 2.21-2.33 (td, 1H), 2.33-2.41 (dd, 1H), 2.58-2.67 (m, 1H), 3.97 (s, 2H), 4.06-4.14 (m, 1H), 6.97-7.04 (m, 1H), 7.04-7.08 (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

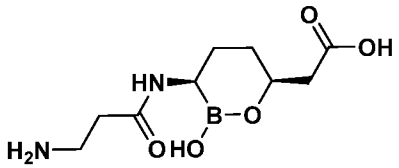
[0176] 2-((3R,6S)-2-hydroxy-3-(2-phenylacetamido)-1,2-oxaborinan-6-yl)acetic acid **6**. ^{1}H NMR (CD_3OD) δ ppm 0.86-1.02 (m, 1H), 1.44-1.53 (dd, 1H), 1.53-1.66 (td, 1H), 1.68-1.78 (m, 1H), 2.17-2.26 (dd, 1H), 2.26-2.36 (dd, 2H), 3.75 (s, 2H), 4.02-4.12 (m, 1H), 7.22-7.40 (m, 5H); ESIMS found for $C_{14}H_{18}BNO_5$ *m/z* 274 (100%) $(M-H_2O)^+$.

[0177] 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.



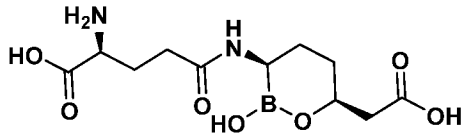
33

[0178] 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 $(M-H_2O)^+$.



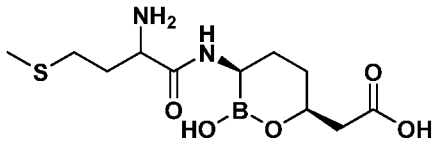
34

[0179] 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 $(M-H_2O)^+$.



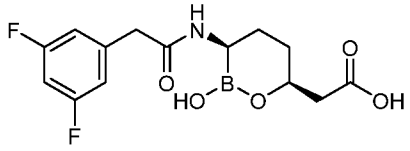
35

[0180] (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

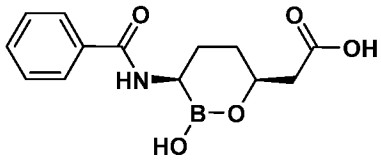
[0181] 2-((3R,6S)-3-(2-amino-4-(methylthio)butanamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **41** was isolated as the HCl salt. ^{1}H NMR (CD_3OD) δ ppm 1.45-1.65 (m, 1H), 1.65-1.75 (m, 1H), 1.75-1.86 (m, 1H), 1.86-2.05 (m, 1H), 2.09-2.20 (m, 4H), 2.46-2.73 (m, 6H), 2.84-2.86 (t, *J*=6 Hz, 1H), 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

[0182] 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 $(M\text{-}H_2O)^+$.

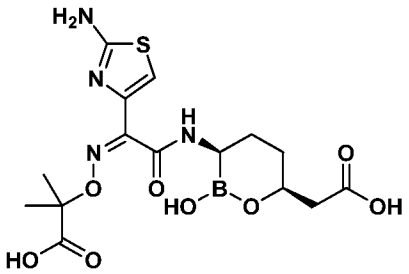
[0183] The following compounds are prepared in accordance with the procedure described in the above Example 1 starting from enantiomerically pure (R)-tert-butyl 3-hydroxypent-4-enoate (J. Am. Chem. Soc. 2007, 129, 4175-4177) using methods A and E.



37

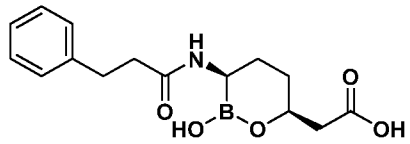
[0184] 2-((3R,6S)-3-benzamido-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **37**. ^{1}H NMR (CD_3OD) δ ppm 1.10-1.19 (q, *J*=11 Hz, 1H), 1.60-1.65 (dd, *J*=14 Hz, *J*=3 Hz, 1H), 1.71-1.80 (td, *J*=9 Hz, *J*=3 Hz, 1H), 1.91-1.96 (d, *J*=14 Hz, 1H), 2.32-2.38 (dd, *J*=15 Hz, *J*=6 Hz, 1H), 2.44-2.49 (dd, *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 $(M\text{-}H_2O)^+$.

[0185] 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.



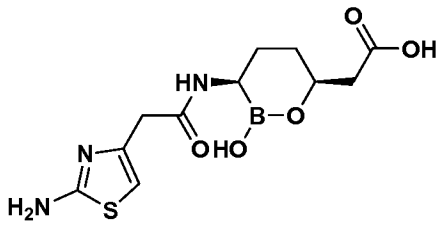
36

[0186] 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 $(M\text{-}H_2O)^+$.



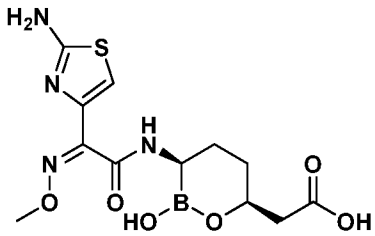
38

[0187] 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 $(M-H_2O)^+$.



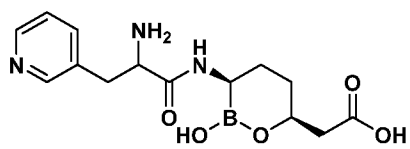
39

[0188] 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

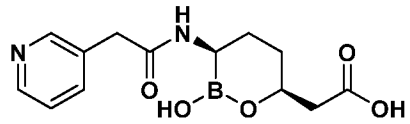
[0189] 2-((3R,6S)-3-((Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **40** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.56-1.67 (m, 2H), 1.76-1.81 (m, 1H), 1.86-1.90 (m, 1H), 2.50-2.54 (dd, *J*=17 Hz, *J*=6 Hz, 1H), 2.59-2.64 (dd, *J*=16 Hz, *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 $(M-H_2O)^+$.



42

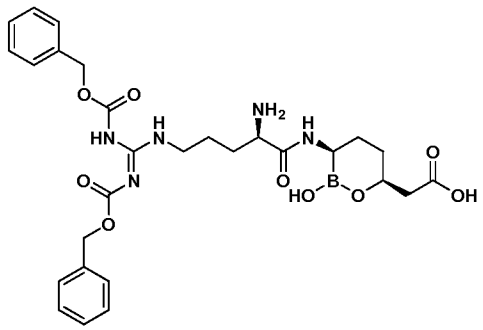
[0190] 2-((3R,6S)-3-(2-amino-3-(pyridin-3-yl)propanamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **42** was isolated as the TFA salt. ^{1}H NMR (CD_3OD/CF_3O_2D) δ ppm

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 $(M-H_2O)^+$.



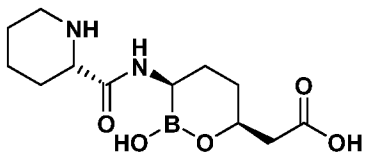
43

[0191] 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 $(M-H_2O)^+$.



44

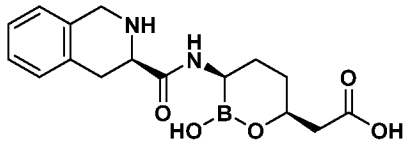
[0192] 2-((3R,6S)-3-((R)-2-amino-5-((Z)-2,3-bis(benzyloxycarbonyl)guanidino) pentanamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **44** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.28-1.34 (dd, *J*=18 Hz, *J*=12 Hz, 1H), 1.39-1.49 (m, 1H), 1.68-1.74 (m, 1H), 1.74-1.84 (m, 4H), 1.84-1.94 (m, 1H), 2.38-2.43 (dd, *J*=16 Hz, *J*=6 Hz 1H), 2.49-2.54 (dd, *J*=17 Hz, *J*=7 Hz, 1H), 2.72-2.75 (t, *J*=7 Hz, 1H), 3.90-3.99 (m, 3H), 4.28-4.31 (m, 1H), 5.11-5.17 (dd, *J*=16 Hz, *J*=13 Hz, 2H), 5.30 (s, 2H), 7.30-7.44 (m, 10H); ESIMS found for $C_{28}H_{36}BN_5O_9$ *m/z* 580 $(M-H_2O)^+$.



45

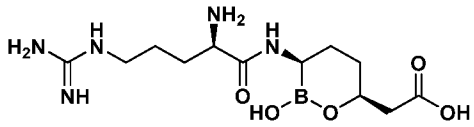
[0193] 2-((3R,6S)-2-hydroxy-3-((S)-piperidine-2-carboxamido)-1,2-oxaborinan-6-yl)acetic acid **45** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.44-1.51 (m, 1H), 1.54-1.80 (m, 5H), 1.80-1.91 (m, 2H), 1.91-1.98 (brd, *J*=12 Hz, 1H), 2.16-2.21 (dd, *J*=13 Hz, *J*=2 Hz, 1H), 2.49-2.57 (non, *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 $(M\text{-}H_2O)^+$.



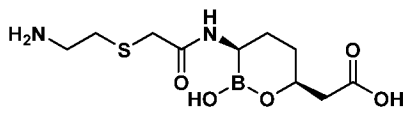
46

[0194] 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 $(M\text{-}H_2O)^+$.



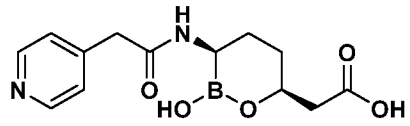
47

[0195] 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 $(M\text{-}H_2O)^+$.



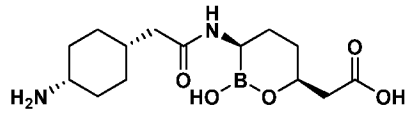
48

[0196] 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 $(M\text{-}H_2O)^+$.



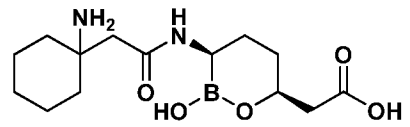
49

[0197] 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 $(M-H_2O)^+$.



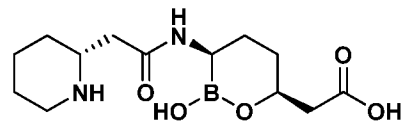
50

[0198] 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 $(M-H_2O)^+$.



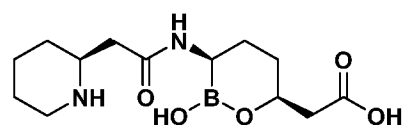
51

[0199] 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 $(M-H_2O)^+$.



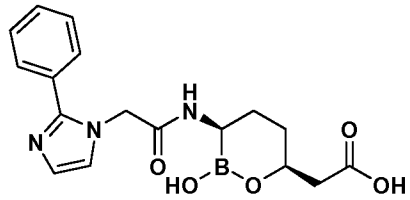
52

[0200] 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 $(M-H_2O)^+$.



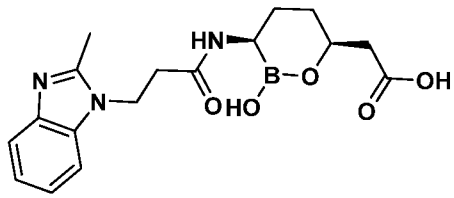
53

[0201] 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).



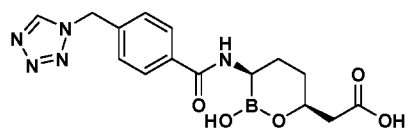
54

[0202] 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

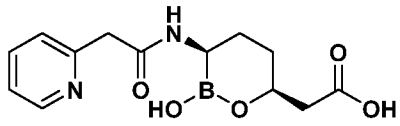
[0203] 2-((3R,6S)-2-hydroxy-3-(3-(2-methyl-1H-benzo[d]imidazol-1-yl)propanamido)-1,2-oxaborinan-6-yl)acetic acid **55**. ^{1}H NMR (CD_3OD) δ ppm 0.92-1.00 (m, 1H), 1.47-1.53 (m, 1H), 1.58-1.62 (m, 2H), 2.31-2.33 (d, *J*=7 Hz, 2H), 2.50-2.52 (t, *J*=4 Hz, 1H), 2.97 (s, 3H), 3.08-3.20 (m, 2H), 4.04-4.10 (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 $(M-H_2O)^+$.



56

[0204] 2-((3R,6S)-3-(4-((1H-tetrazol-1-yl)methyl)benzamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **56**. ^{1}H 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),

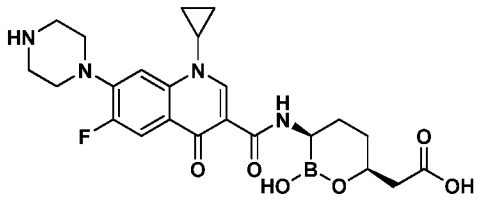
2.80-2.83 (brd, *J*=4 Hz, 1H), 4.11-4.17 (m, 1H), 5.83 (s, 2H), 7.53-7.55 (d, *J*=8 Hz, 2H), 8.02-8.05 (d, *J*=8 Hz, 2H), 9.30 (s, 1H); ESIMS found for $C_{15}H_{18}BN_5O_5$ *m/z* 342.0 $(M-H_2O)^+$.



57

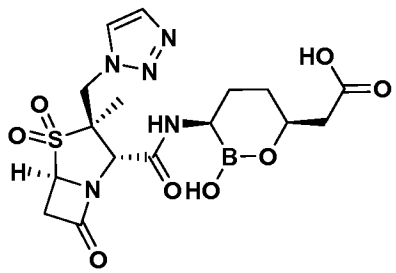
[0205] 2-((3R,6S)-2-hydroxy-3-(2-(pyridin-2-yl)acetamido)-1,2-oxaborinan-6-yl)acetic acid **57** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.21-1.32 (m, 1H), 1.59-1.67 (m, 2H), 1.67-1.75 (m, 2H), 2.29-2.40 (m, 3H), 2.67-2.72 (m, 1H), 4.14-4.21 (m, 1H), 7.62-7.66 (t, *J*=6 Hz, 1H), 7.70-7.73 (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 $(M-H_2O)^+$.

[0206] The following compounds are prepared in accordance with the procedure described in the above Example 1 using methods C and E.



58

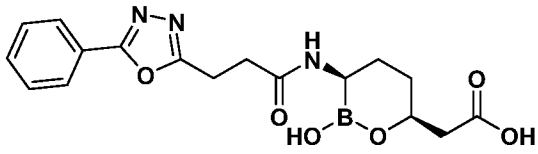
[0207] 2-((3R,6S)-3-(1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamido)-2-hydroxy-1,2-oxaborinan-6-yl)acetic acid **58** was isolated as the TFA salt. ^{1}H NMR (CD_3OD) δ ppm 1.14-1.29 (m, 3H), 1.39-1.44 (brd, *J*=7 Hz, 2H), 1.56-1.63 (dd, *J*=14 Hz, *J*=3 Hz, 1H), 1.70-1.80 (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

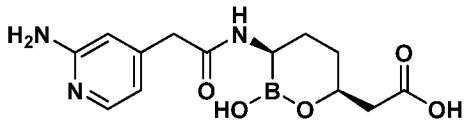
[0208] 2-[(3R,6S)-2-hydroxy-3-[(2S,3S,5R)-3-methyl-4,4,7- trioxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4λ^6- thia-1-azabicyclo[3.2.0]heptane-2-amido]-1,2- oxaborinan-6-yl] acetic acid **59**. ^{1}H NMR (CD_3OD) δ ppm 1.43 (s, 3H), 1.49-1.57 (m, 1H), 1.72-1.81 (m, 3H), 2.51-2.56

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 $(M\text{-}H_2O)^+$.



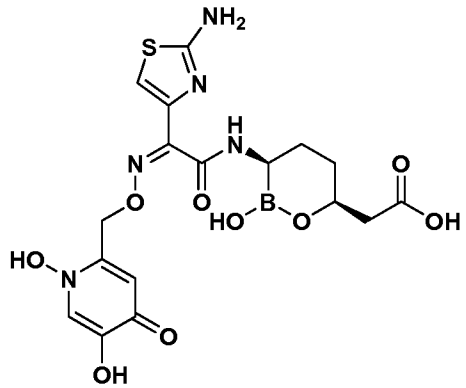
60

[0209] 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 $(M\text{-}H_2O)^+$.



61

[0210] 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 $(M\text{-}H_2O)^+$.



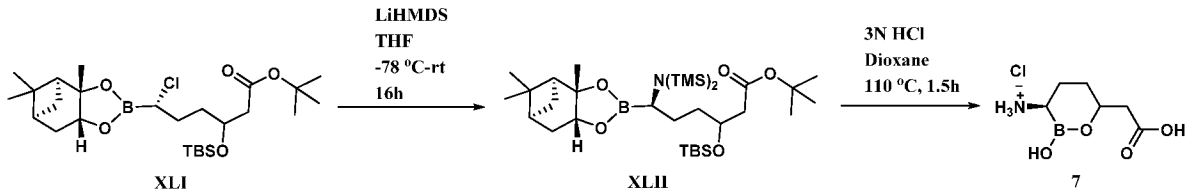
62

[0211] 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 $(M-H_2O)^+$.

[0212] 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



XLI XLII 7

Example 2

Step 1

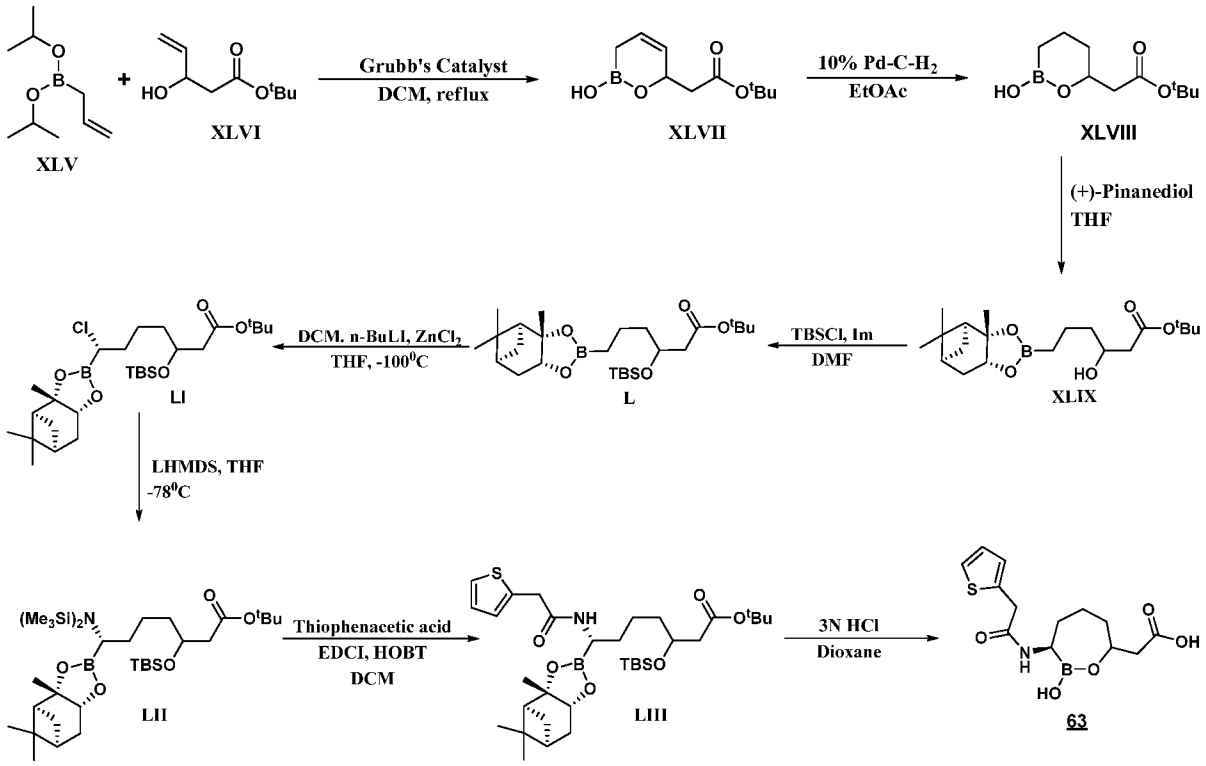
[0213] 6-(tert-butoxy)-4-[(tert-butyldimethylsilyl)oxy]-1-chloro-6-oxo-1-[(2S,6R)-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.02,6]decan-4-yl]hexane **XLI** (515 mg, 0.97 mmol) in THF (5 mL) was cooled to -78°C under nitrogen. A solution of LiHMDS (1 mL, 1.0 M in THF, 1 mmol, 1.0 eq) was added slowly 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

[0214] 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). ^1H 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).

[0215] 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

[0216] 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

[0217] 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

[0218] 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

[0219] 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

[0220] 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

[0221] 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

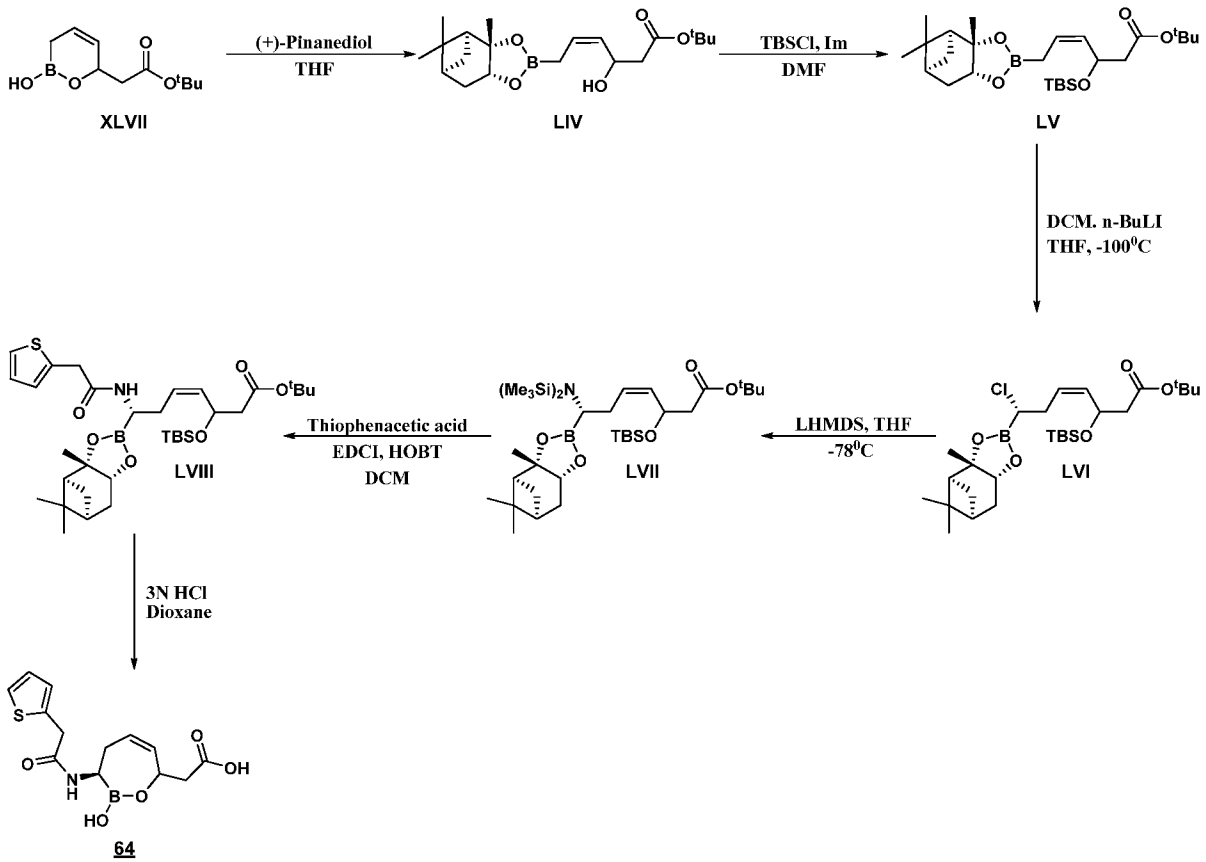
[0222] To a stirred solution of 2-thiophenacetic acid (232 mg, 1.64 mmol) in DCM (45 mL) at 0°C under nitrogen was added EDCI (391 mg, 2.05 mmol) and HOBT (221 mg, 1.64 mmol). After stirring at 0°C for 30 minutes, a solution of the bis-silyl amide **LII** intermediate (1.37 mmol) in DCM (10 mL) followed 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

[0223] 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 $(M\text{-}H_2O)^+$.

[0224] 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

[0225] 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[6.1.1.02,6]decan-4-yl]hex-4-enoate LIV (1 g, 2.75 mmol, 59.9% yield).

Step 2

[0226] 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 (Na2SO4). 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[6.1.1.02,6]decan-4-yl]hex-4-enoate LV (800 mg, 1.67 mmol, 93.9% yield).

Step 3

[0227] 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

[0228] 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

[0229] 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-

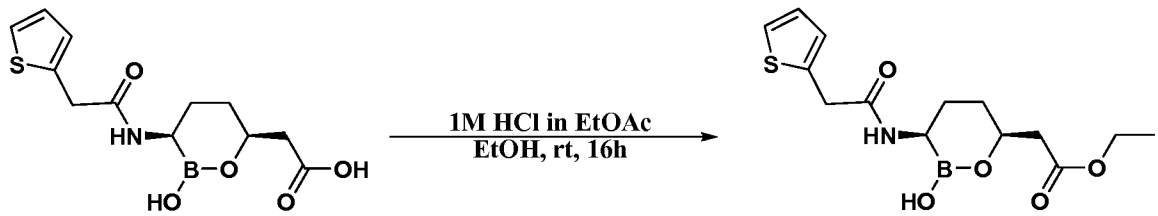
butyldimethylsilyl)oxy]-7-[2-(thiophen-2- yl)acetamido]-7-[(1R,2R,6S,8R)-6,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.02,6]decan-4-yl]hept-4- enoate LVIII (600 mg, 0.95 mmol, 63.7% yield for 2 steps).

Step 6

[0230] 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 $(M\text{-}H_2O)^+$.

[0231] 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

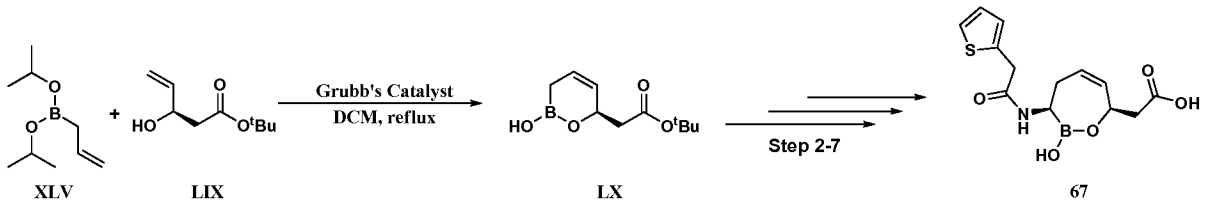
Step 1

[0232] 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). 1H NMR (CD3OD) 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 C14H20BNO5S m/z 308.1 (M-H2O)+.

[0233] 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

[0234] 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

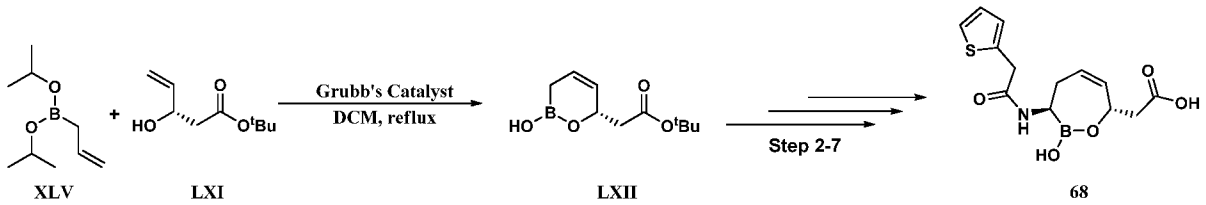
Steps 2-7

[0235] Prepared in accordance with the procedure described in the above Steps 1-6 of Example 4.

[0236] 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 $(M\text{-}H_2O)^+$.

[0237] 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



XLV LXI LXII 68

Example 7

Step 1

[0238] 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

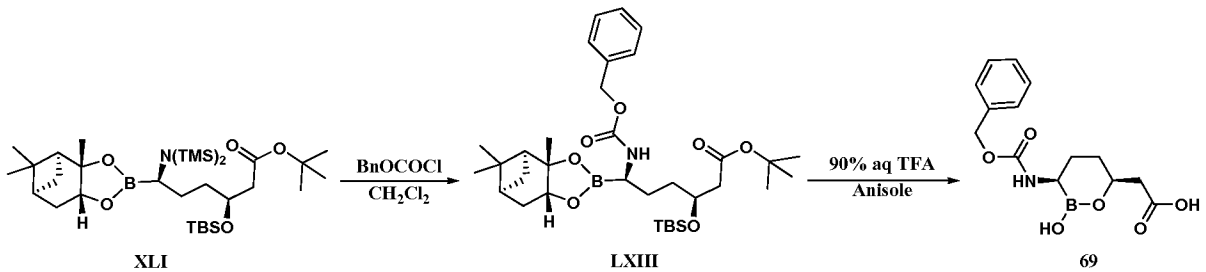
Steps 2-7

[0239] Prepared in accordance with the procedure described in the above Steps 1-6 of Example 4.

[0240] 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 $(M\text{-}H_2O)^+$.

[0241] 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

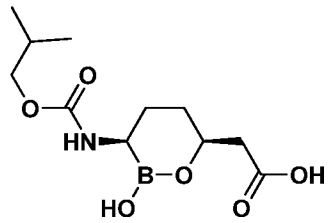
[0242] A solution of bis-silyl amide **XLI** (0.2 mmol) in DCM (5 mL) was cooled to 0°C and benzyl chloroformate (0.056 mL, 0.4 mmol) was added. Then, the cooling bath was removed and the solution stirred at ambient temperature for 16 h. The reaction was quenched with water and extracted twice with EtOAc. 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

[0243] 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 $(M-H_2O)^+$.

[0244] The following compound is prepared in accordance with the procedure described in the above Example 8.

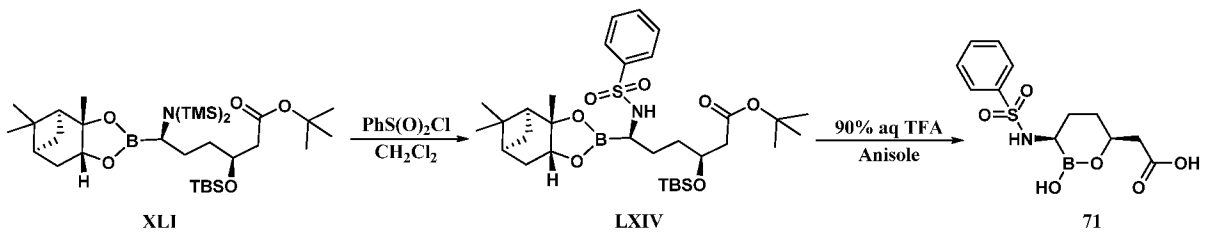


70

[0245] 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). ^1H 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 $(M-H_2O)^+$.

[0246] 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

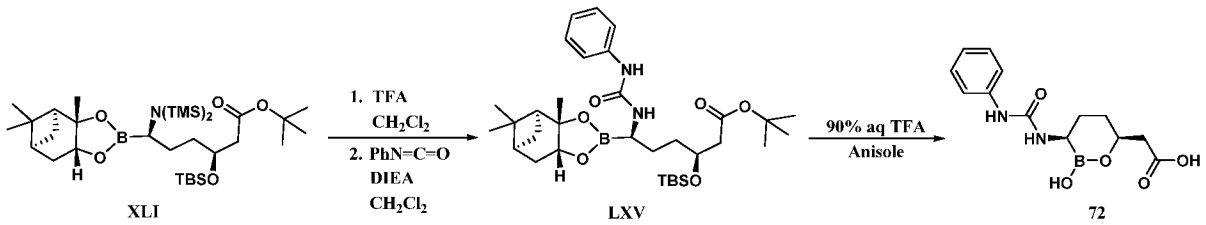
Step 1-2

[0247] Prepared in accordance with the procedure described in the above Steps 1-2 of Example 8.

[0248] 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 $(M-H_2O)^+$.

[0249] 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

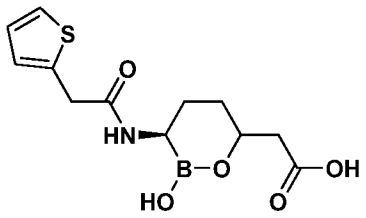
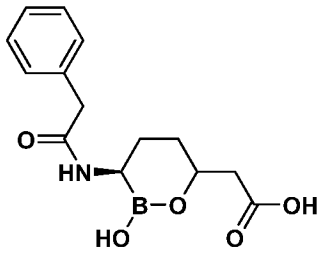
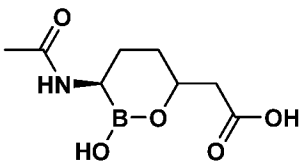
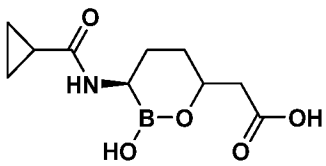
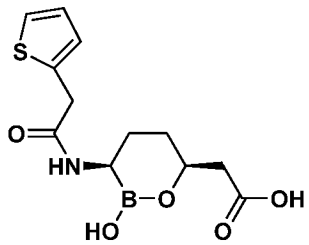
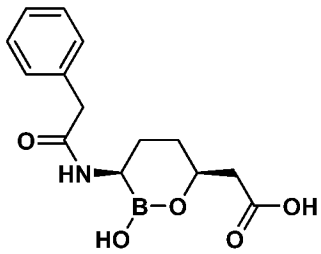
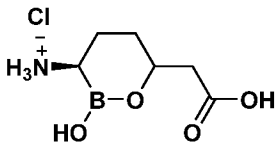
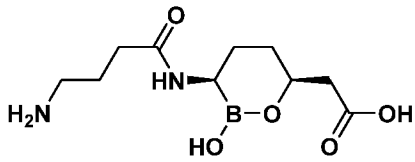
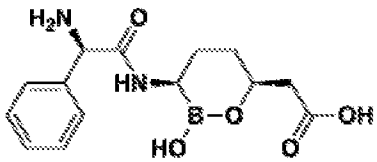
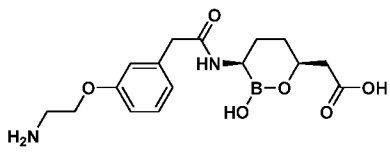
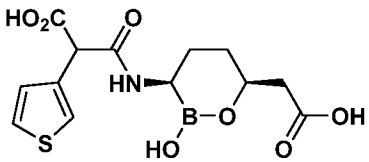
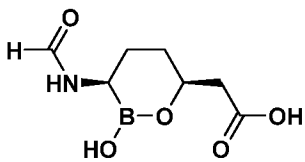
[0250] To a solution of bis-silyl amide **XLI** (0.2 mmol) in DCM (5 mL) at 0°C was added a solution of TFA in hexane (0.6 mmol). The reaction was stirred at 0°C for 20 min before adding phenyl isocayanate (0.04 mL, 0.4 mmol) followed by N,N-diisopropylethylamine (0.18 mL, 1 mmol). The cooling bath was 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).

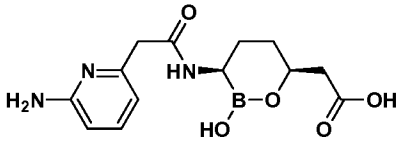
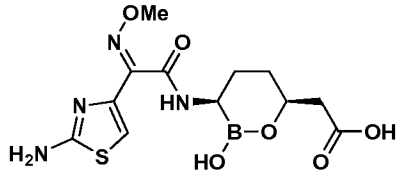
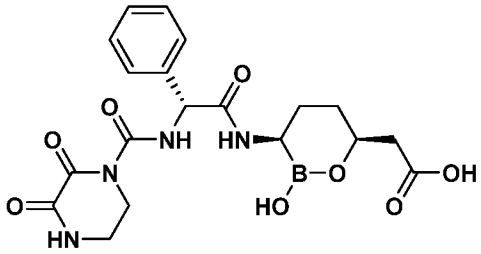
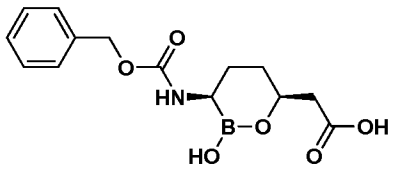
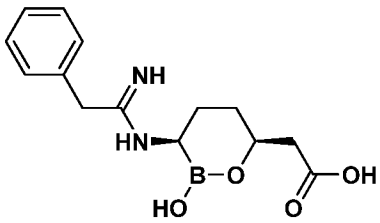
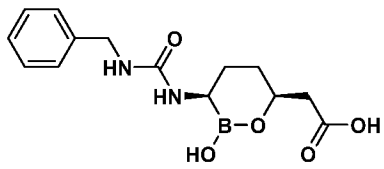
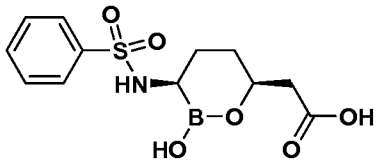
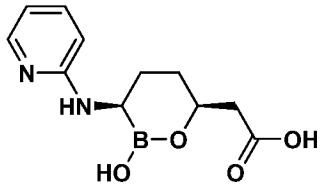
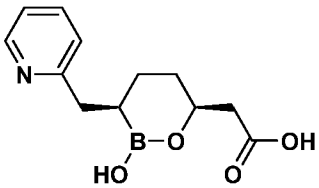
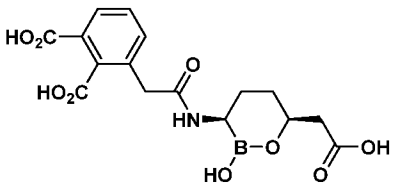
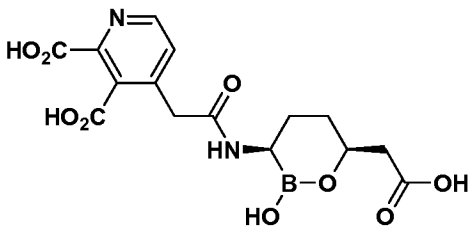
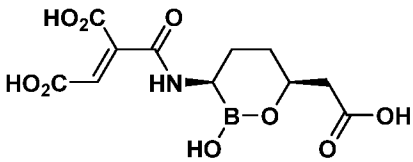
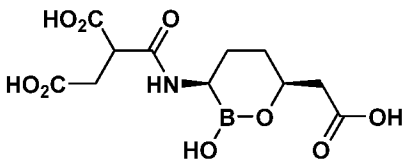
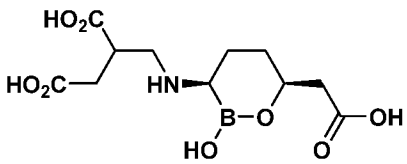
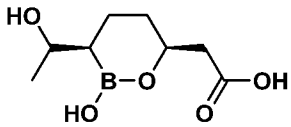
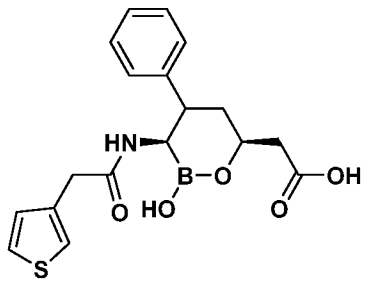
Step 2

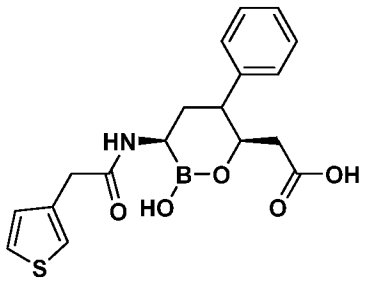
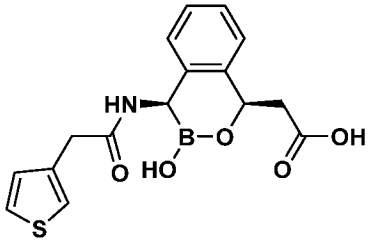
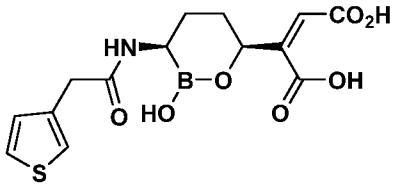
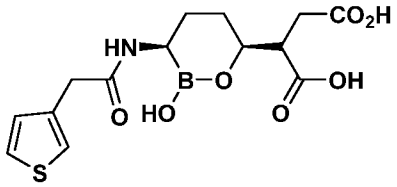
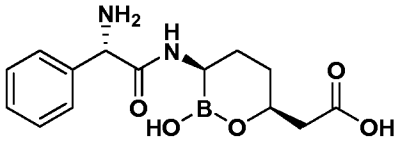
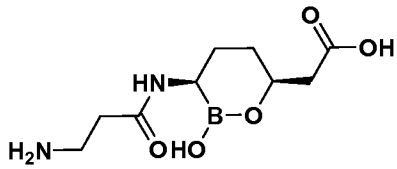
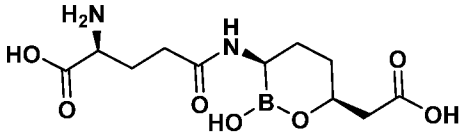
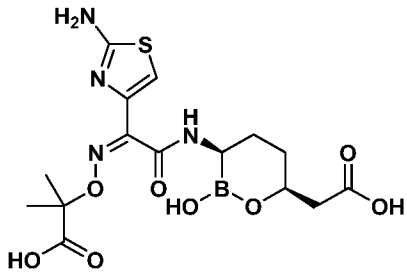
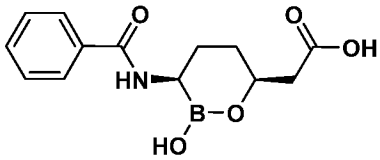
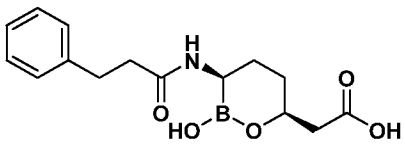
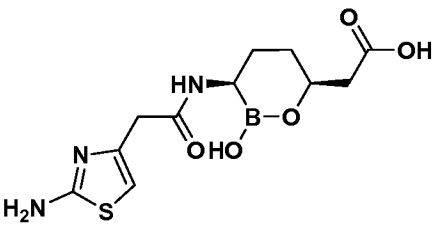
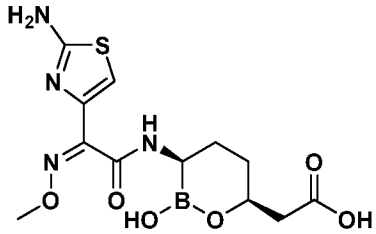
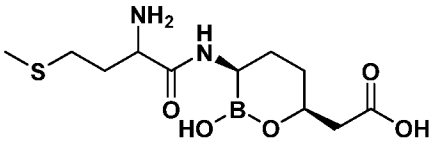
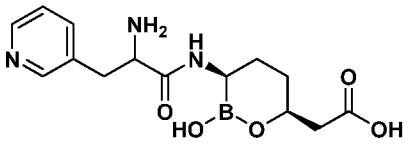
[0251] Deprotection was performed following the procedure described above in step 2 of example 8 to give 2-((3*R*,6*S*)-2-hydroxy-3-(3-phenylureido)-1,2-oxaborinan-6-yl)acetic acid **72** as a white solid (20 mg, 0.068 mmol, 86% yield). ^{1}H NMR (CD_3OD) δ ppm 1.24-1.31 (m, 1H), 1.56-1.64 (m, 2H) 1.78-1.81 (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 $(M-H_2O)^+$.

[0252] 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.

TABLE 1

Example	Structure	Example	Structure
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	

Example	Structure	Example	Structure
13		14	
15		16	
17		18	
19		20	
21		22	
23		24	
25		26	
27		28	

Example	Structure	Example	Structure
29		30	
31		32	
33		34	
35		36	
37		38	
39		40	
41		42	

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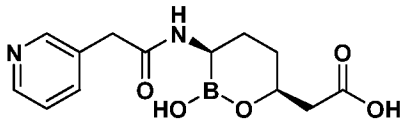
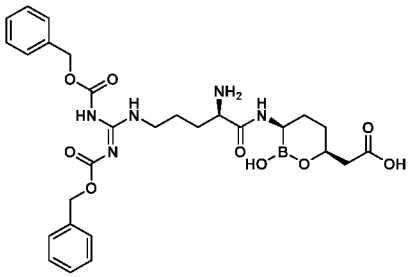
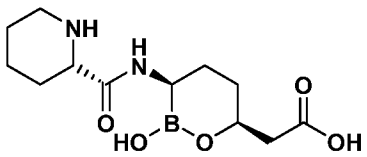
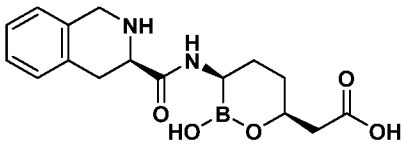
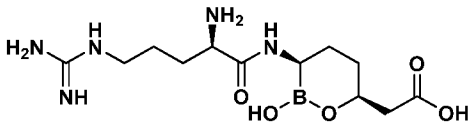
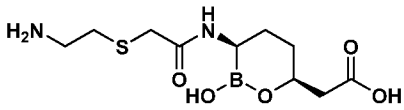
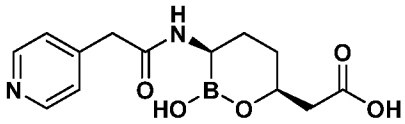
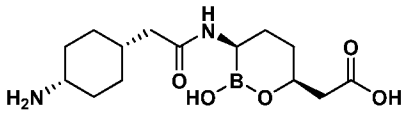
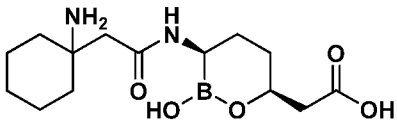
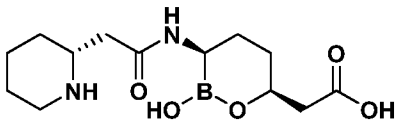
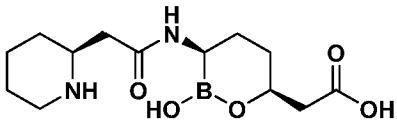
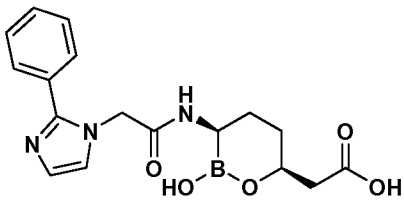
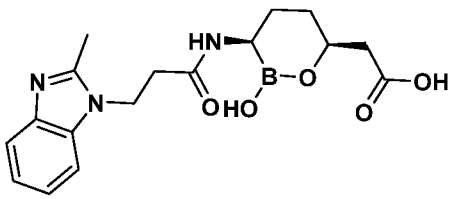
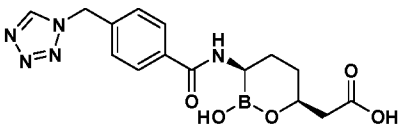
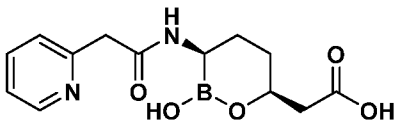
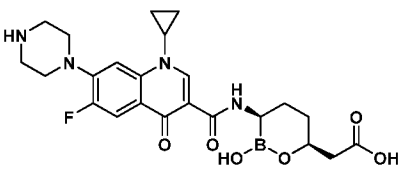
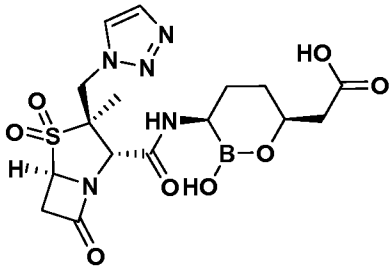
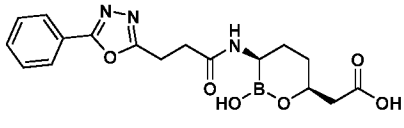
43		44	
45		46	
47		48	
49		50	
51		52	
53		54	
55		56	
57		58	
59		60	

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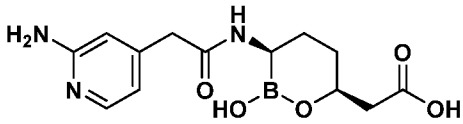
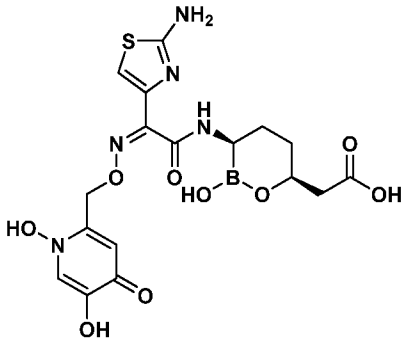
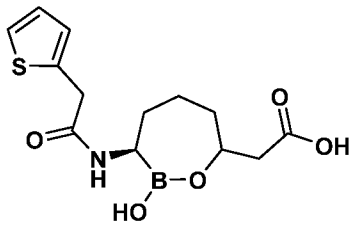
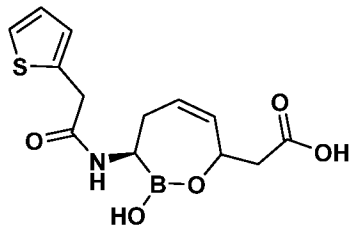
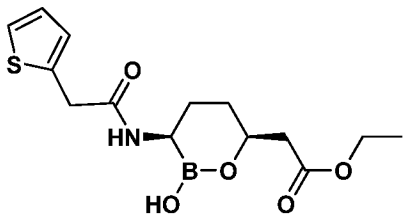
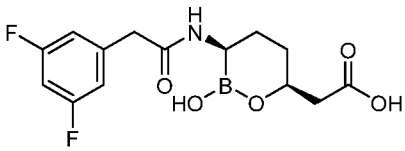
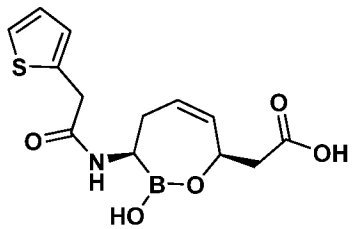
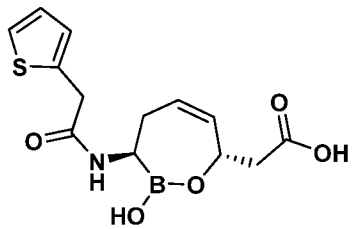
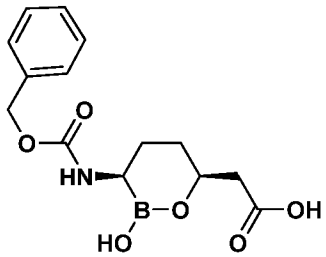
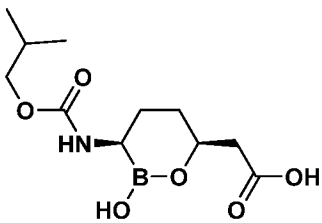
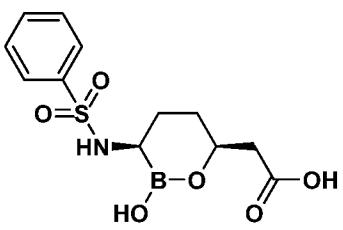
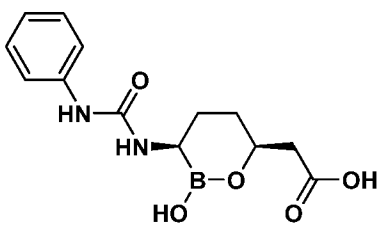
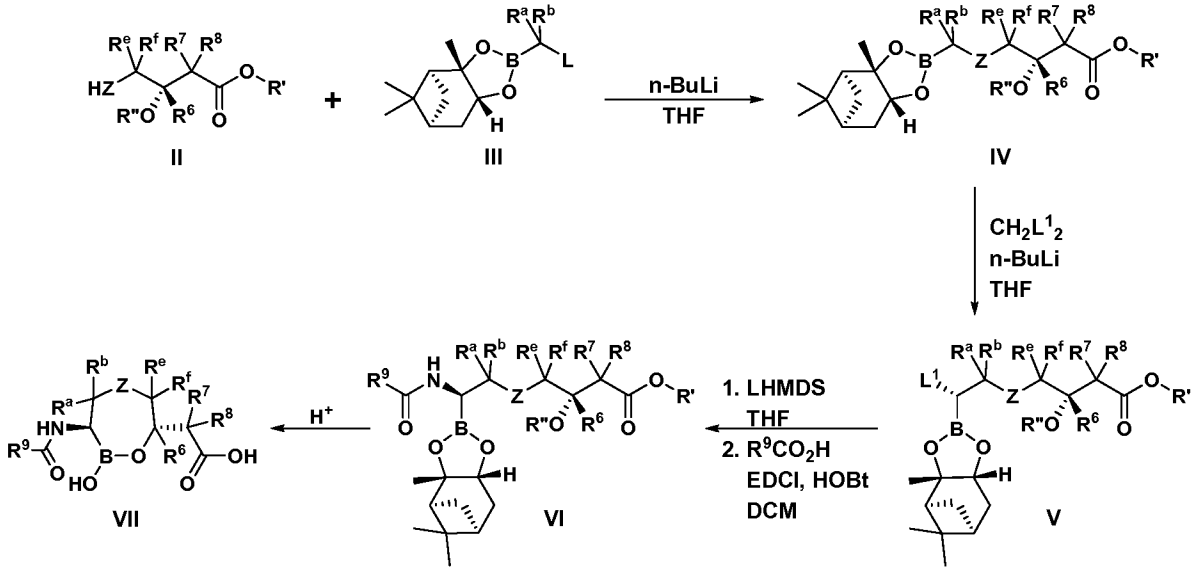
61		62	
63		64	
65		66	
67		68	
69		70	
71		72	

Formula (II)

[0253] Compounds of formula (II) where $R^{1\alpha}$ is an acylamino group, Z^{α} is -O- or -S- and X^{α} is a carboxylic acid can be prepared as depicted in Scheme 1A. In the following

schemes only, that is Schemes 1A – 7A, an element that is denoted in the text with a superscript alpha ($^{\alpha}$) is represented in the corresponding diagramed element without the superscript alpha ($^{\alpha}$). For example, in Scheme 1A, structure IV $^{\alpha}$ in the text corresponds to diagrammed structure IV.

Scheme 1A

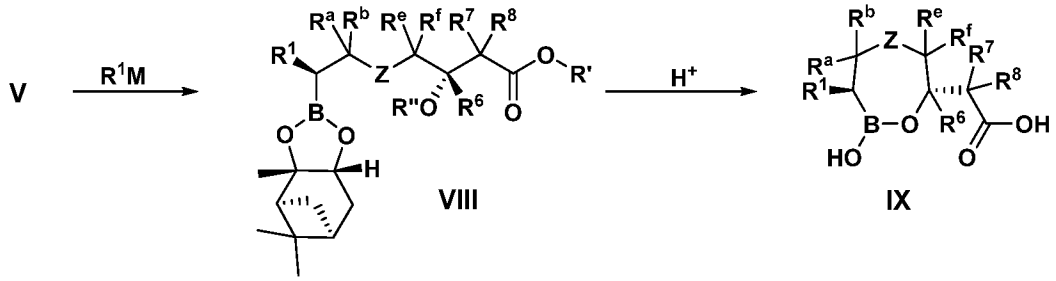


[0254] Compounds of structure **IV**$^{\alpha}$ where Z^{α} is -O- can be made via lithium alkoxide formation of alcohol **II**$^{\alpha}$ (Z = -O-) [*J. Org. Chem.* **(2010)**, *75*, 3953-3957; WO0587700] and reaction with halomethyleneboronate esters [*Tetrahedron* **(2005)**, *61*, 4427-4436; *J. Am. Chem. Soc.* **(1990)**, *112*, 3964-3969]. Compounds where Z^{α} is -S- in **IV**$^{\alpha}$ may be attained via thiol version of **II**$^{\alpha}$ (Z^{α} = -S-). Such thiol compounds can be made from the corresponding alcohol by variety of known procedures (*Tetrahedron: Asymmetry* **(1993)**, *4*, 361-8). Homologation of **IV**$^{\alpha}$ to **V**$^{\alpha}$ where $L^{1\alpha}$ is chloro is achieved via Matteson reaction conditions with good stereocontrol [WO0946098; *Tetrahedron* (1998), *54*, 10555-10607]. The chloro derivative of **V**$^{\alpha}$ can be utilized to introduce a substituted amine group at the alpha-position of boronate. Stereospecific substitution with hexamethyldisilazane gives the corresponding bis(trimethylsilyl) amide which may be reacted in situ with an acid chloride to result directly in analogs of structure **VI**$^{\alpha}$. Such analogs of **VI**$^{\alpha}$ 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). Simultaneous deprotection of the pinane ester, acid sensitive OR'$^{\alpha}$ and OR" $^{\alpha}$ groups and concomitant cyclization are achieved by heating with dilute HCl, affording the desired cyclic boronate derivatives of structure **VII**$^{\alpha}$. This transformation may also be achieved by treatment with BCl_3 or BBr_3 (WO09064414). Alternatively, the deprotection may be attained via trans-esterification with isobutyl boronic

acid in presence of dilute HCl (WO09064413) or via other known methods [*J. Org. Chem.* **(2010)**, *75*, 468-471].

[0255] Compounds of structure **IX**$^{\alpha}$ where $R^{1\alpha}$ of Formula II is an alkyl, aralkyl or aminoaryl group may be made from intermediate **V**$^{\alpha}$ as shown in Scheme 2A.

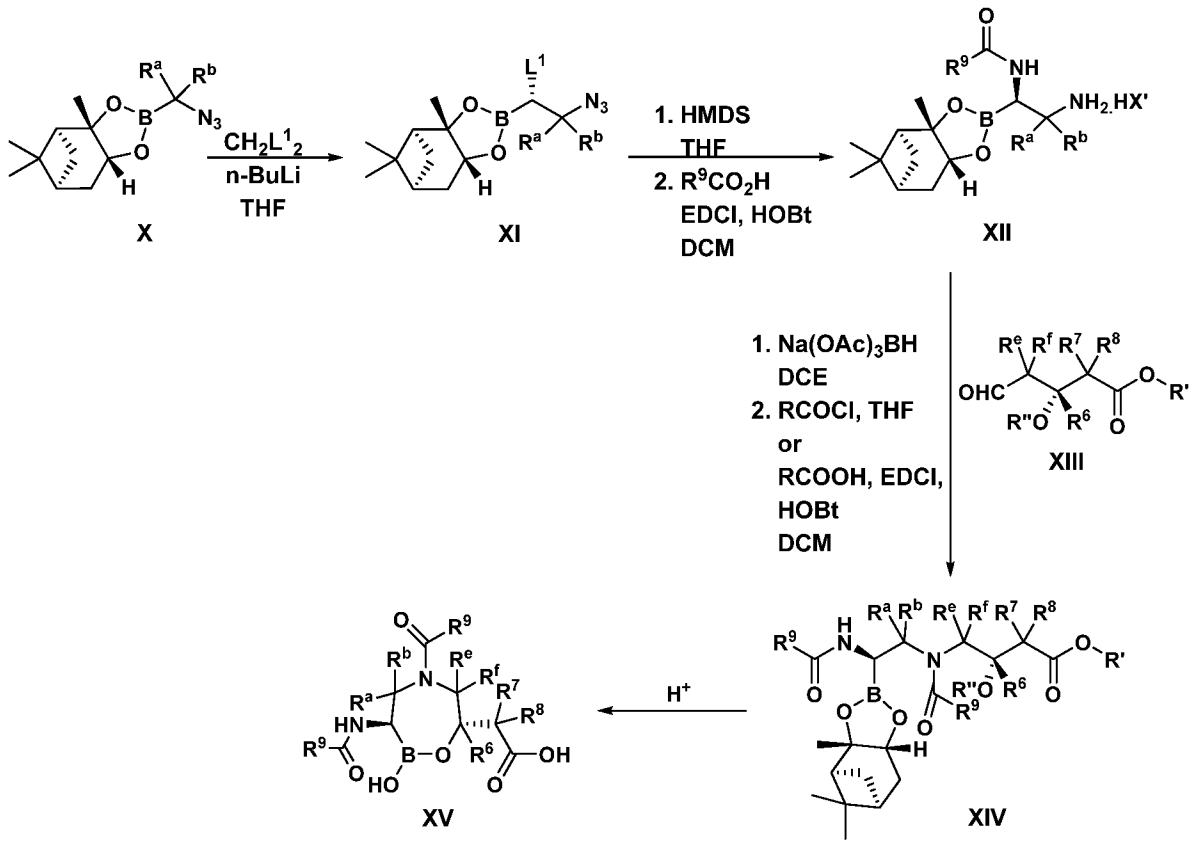
Scheme 2A



[0256] Compounds of structure **IX**$^{\alpha}$ may be made from intermediate **V**$^{\alpha}$, where $L^{1\alpha}$ preferably an iodo, or bromo group [*J. Organomet. Chem.* **(1992)**, *431*, 255-70]. Such bromo derivatives may be made as analogously to the chloro compounds of Scheme 1A, utilizing dibromomethane [*J. Am. Chem. Soc.* **(1990)**, *112*, 3964-969]. Displacement of the bromo group in **V**$^{\alpha}$ 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 **VIII**$^{\alpha}$. Deprotection and cyclization of **VIII**$^{\alpha}$ to afford **IX**$^{\alpha}$ may be achieved under the conditions described in Scheme 1A.

[0257] Compounds of formula II where $R^{1\alpha}$ is an acylamino group, Z^{α} is -N[C(=O)$R^{9\alpha}$]- and X^{α} is a carboxylic acid can be prepared as depicted in Scheme 3A.

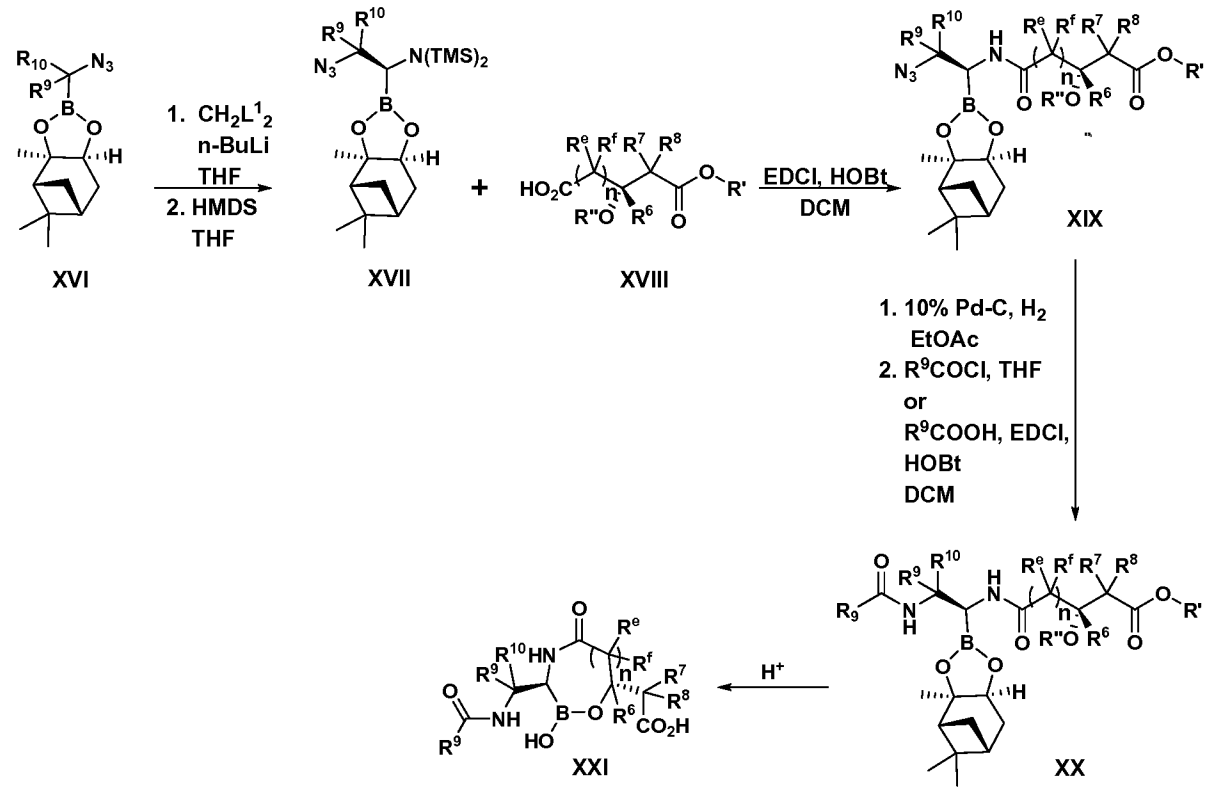
Scheme 3A



[0258] Enantiomerically pure 1,2-diamino-propyl boronate derivatives of structure **XII**$^{\alpha}$ are made utilizing Matteson protocol as described above, starting from azido-methylene boronate of structure **X**$^{\alpha}$ [*Organometallics* **(1996)**, *,15*, 152-163] via halomethylene insertion product **XI**$^{\alpha}$ [*J. Organomet. Chem.* **(2008)**, *693*, 2258-2262]. Compounds of structure **XII**$^{\alpha}$ can be further transformed to **XIV**$^{\alpha}$ by well known reductive amination transformation [*J. Org. Chem.* **(1996)**, *61*, 3849-3862] with carbonyl intermediates such as **XIII**$^{\alpha}$, followed by installation of $R^{9\alpha}CO$- group on the resulting amine. Cyclic boronates of structure **XV**$^{\alpha}$ are attained from intermediate **XIV**$^{\alpha}$ by simultaneous deprotection and cyclization in acid hydrolysis conditions described in Scheme 1A. A sequential deprotection and cyclization protocol may be followed where –OR'$^{\alpha}$ and –OR"$^{\alpha}$ of structure **XIV**$^{\alpha}$ are not acid sensitive protective groups.

[0259] Compounds of formula II where $R^{1\alpha}$ is an acylamino group, $G^{1\alpha}$ is null, $G^{2\alpha}$ is a substituted carbonyl alkyl group, Z^{α} is -N[C(=O)$R^{9\alpha}$]- and X^{α} is a carboxylic acid can be prepared as depicted in Scheme 4A.

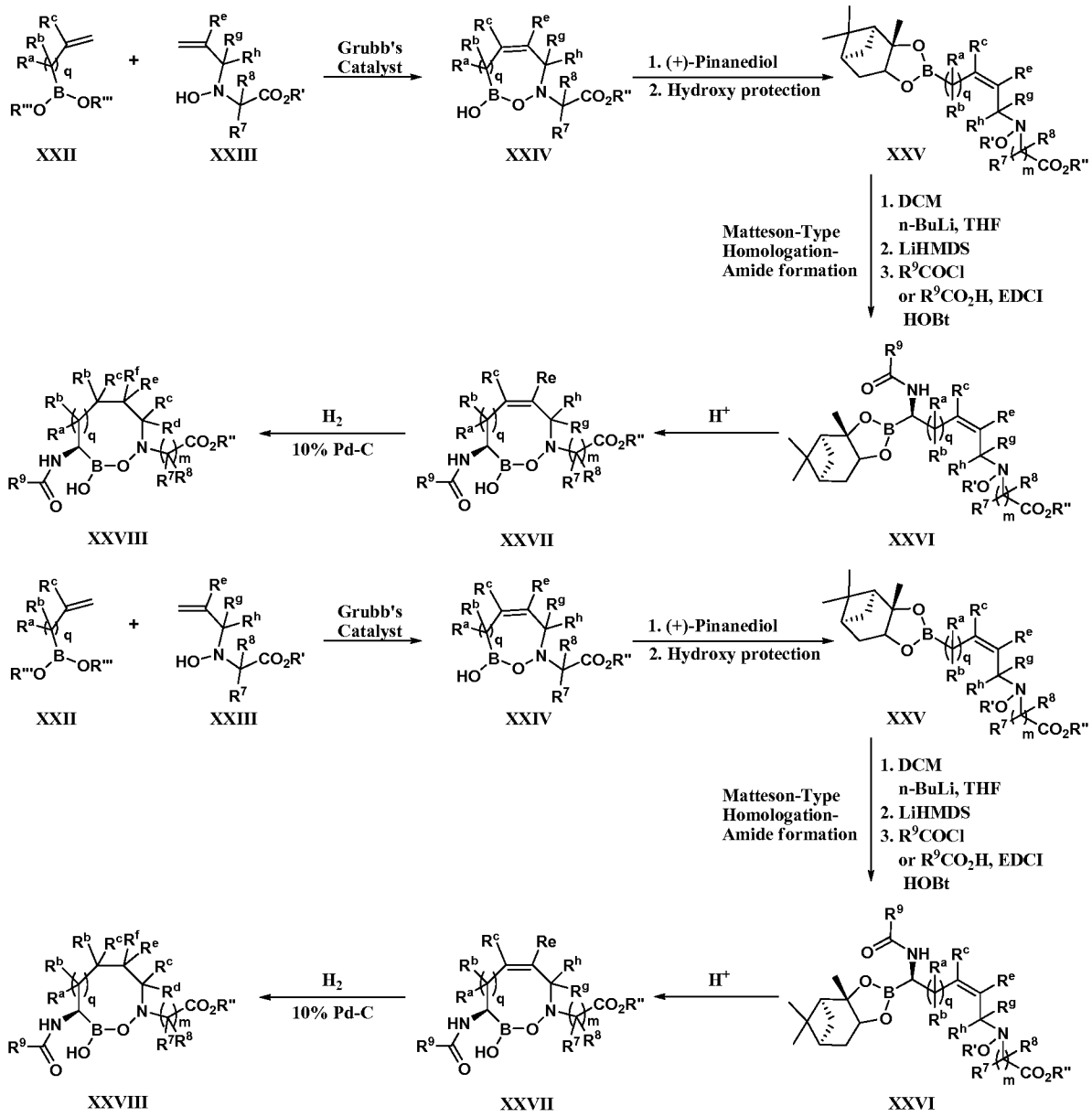
Scheme 4A



[0260] Bis-trimethylsilyl amino intermediate **XVII**$^{\alpha}$ may be made as described above in Scheme 3A starting from azidomethylene boronate **XVII** [*J. Organomet. Chem.* **(2008)**, *693*, 2258-2262]. These derivatives as **XVII**$^{\alpha}$ can be directly utilized in amide coupling reactions with carboxylic acid intermediates of structure **XVIII**$^{\alpha}$. Such intermediates of structure **XVIII**$^{\alpha}$ with suitable protective groups, where n is 0 or 1 can be obtained by procedures described earlier in both enantiomeric forms [WO0691771, *J. Org. Chem.* **(1989)**, *54*, 2085-2091]. Resulting azido-amides of structure **XIX**$^{\alpha}$ from amide coupling reaction can be then further transformed to bis-amide **XX**$^{\alpha}$. Such transformation may be achieved by reduction via hydrogenation conditions in presence of a palladium catalyst followed by acylation of the resulting amine to **XX**$^{\alpha}$. Final deprotection-cyclization to compounds of formula **XXI**$^{\alpha}$ may be achieved in single step or sequentially based on the choice of –OR'$^{\alpha}$ and –OR" $^{\alpha}$ groups of **XVIII**$^{\alpha}$ as described above.

[0261] Compounds of formula **XXVII**$^{\alpha}$ and **XXVIII**$^{\alpha}$ can be made following the sequence depicted in Scheme 5A.

Scheme 5A

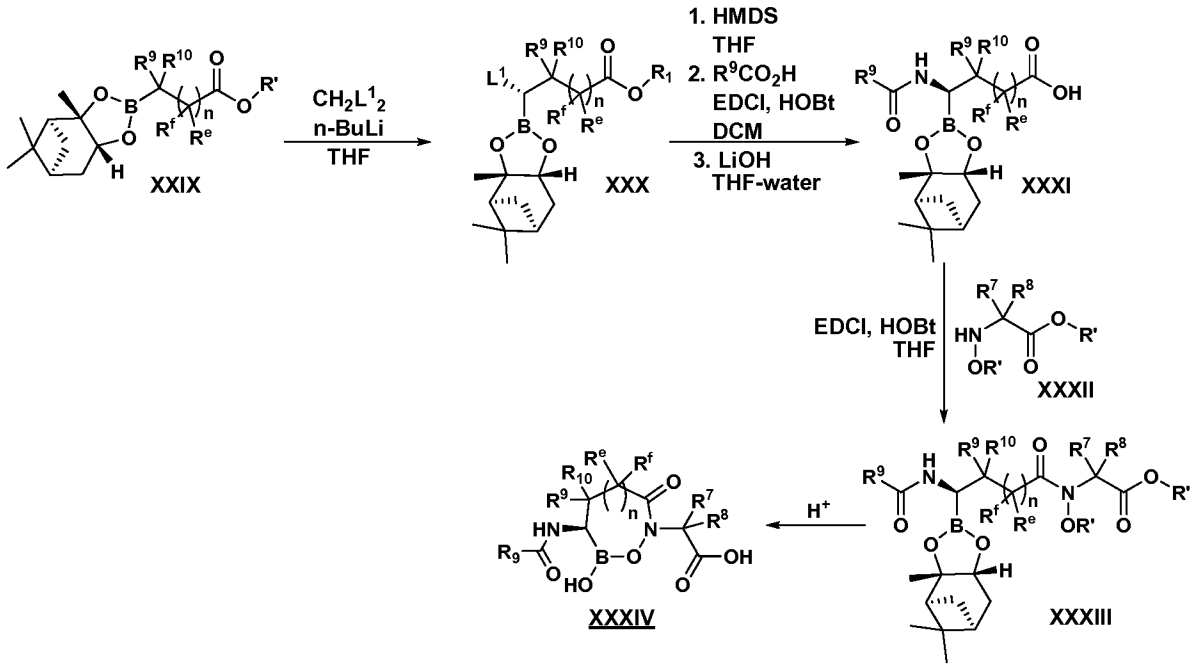


[0262] Ring-Closing Metathesis reaction (RCM) with commercially available boronated olefins (**XXII**$^{\alpha}$) and olefin substituted hydroxylamine esters (**XXIII**$^{\alpha}$) result in cyclic boronates of formula **XXIV**$^{\alpha}$ [*Angew. Chem. Int. Ed.* **(2002)**, *41*, 152-154]. Such substituted hydroxylamine acetic acid esters (**XXIII**$^{\alpha}$) may be made by alkenylation of known intermediates [*J. Org. Chem.* **(2005)**, *70*, 10494-10501]. Cyclic boronates (**XXIV**$^{\alpha}$) undergo ready esterification with chiral pinane diol of choice to give required Matteson reaction precursors, upon protection of the resulting alcohol with groups such as t-butyldimethylsilyl- or benzyl or trityl. Matteson-Type homologation followed by amide formation result in compounds of formula **XXVI**$^{\alpha}$ with high stereoselectivity, as described above in Scheme 1A. Acid mediated hydrolysis of compounds of **XXVI**$^{\alpha}$ upon deprotection give cyclic boronate (**XXVII**$^{\alpha}$). Double

bond substitution of **XXVII**$^{\alpha}$ can be further modified to other analogs or to a saturated cyclic boronate (**XXVIII**$^{\alpha}$) by catalytic hydrogenation. The above sequence can be utilized to make 7- or 8- membered rings with double bond by varying **XXII**$^{\alpha}$ where q^{α} is 0 or 1.

[0263] Compounds of formula II where $R^{1\alpha}$ is an acylamino group, $G^{1\alpha}$ is null, $G^{2\alpha}$ is a substituted alkyl carbonyl group, Z^{α} is -C($R^{9\alpha}R^{10\alpha}$)-, Y^{α} is N and X^{α} is a carboxylic acid can be prepared as depicted in Scheme 6A.

Scheme 6A



[0264] Synthesis of compounds of structure **XXXIV**$^{\alpha}$ can be attained starting from known intermediates of structure **XXX**$^{\alpha}$ (n^{α} is 0 or 1), in racemic or enatiomerically pure form. Matteson-Type homologation of **XXIX** [*Tetrahedron Lett.* **(1987)**, *28*, 4499-4502] followed by amination and amide formation result in ester derivative of **XXXI**$^{\alpha}$. Such ester can hydrolysed under mild conditions to give the carresponding carboxylic acid (**XXXI**$^{\alpha}$). Alternatively, such carboxylic acids can also be made in racemic form via azido substitution sequence [US6586615; *J. Org. Chem.* **(2001)**, *66*, 6375-6380]. Amide formation of substituted and β-hydroxylamine esters with suitable protective groups (-OR'$^{\alpha}$ as silyloxy or benzyloxy) result in the formation of compounds of structure **XXXIII**$^{\alpha}$ [*J. Chem. Soc., Perkin Trans 1,* **(1989)**, *2*, 235-9]. Cyclic boronate compounds of formula **XXXIV**$^{\alpha}$ can be obtained by deprotection-cyclization of compounds of formula **XXXIII**$^{\alpha}$, in single step or sequentially based on the choice of –OR'$^{\alpha}$ and –OR" $^{\alpha}$ groups. Enantiomercally pure compounds of **XXXIV**$^{\alpha}$ can also be attained by chiral chromatography of the racemic precursors or the final compounds.

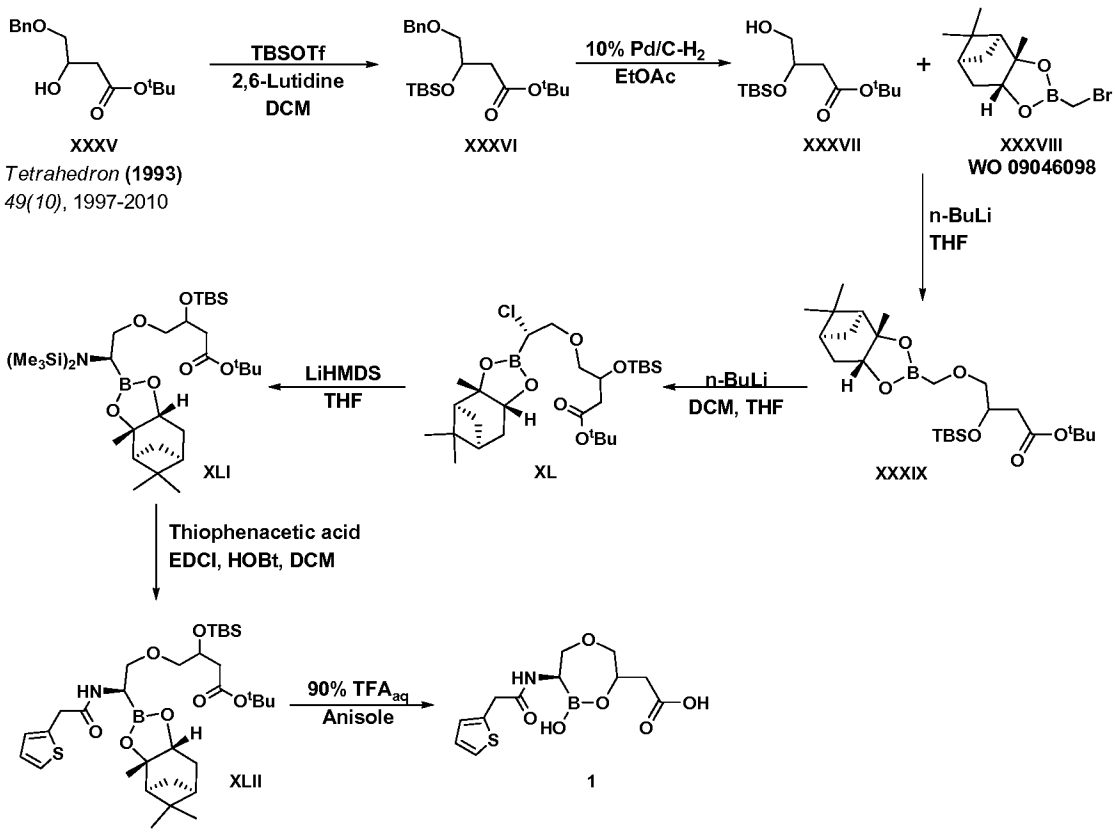
[0265] The syntheses of compounds of formulae **VII**$^{\alpha}$, **XIX**$^{\alpha}$, **XV**$^{\alpha}$ and **XXI**$^{\alpha}$ in the above sequences are described for trans-isomers. These methods can also be utilized to make cis-isomers in enantiomerically pure form by starting (as in Schemes 1A to 4A) with corresponding enantiomer.

[0266] Compounds of formula **II** where X^{α} is a carboxylic acid isostere can be prepared following the protocols described earlier in literature [*J. Med. Chem.* **(2011)**, *54*, 2529-2591].

Illustrative Compound Examples

[0267] Synthesis of 2-((3R)-2-hydroxy-3-(2-(thiophen-2-yl)acetamido)-1,5,2-dioxaborepan-7-yl)acetic acid. An example synthesis of **1**$^{\alpha}$ is depicted in Scheme 7A and Example 10.

Scheme 7A



Example 10

Step 1

[0268] To a solution of *tert*-butyl-4-(benzyloxy)-3-hydroxybutanoate **XXXV**$^{\alpha}$ [*Tetrahedron* **(1993)**, *49(10)*, 1997-2010] (2.3 g, 8.84 mmol) in DCM (100 mL) at 0°C was added 2,6-lutidine (3.07 mL, 26.52 mmol) and TBSOTf (4 mL, 4. 17.68 mmol). After stirring

for 16 h at 0°C, the reaction was diluted with EtOAc (400 mL). The mixture was washed with 1N HCl, saturated aq $NaHCO_3$, water and dried. The extract was dried (MgSO4) and concentrated under reduced pressure. Purification of the crude product by column chromatography (100% hexane→25% EtOAc/hexane) afforded *tert*-butyl 4-(benzyloxy)-3-(tert-butyldimethylsilyloxy)butanoate **XXXVI**$^{\alpha}$ (3.1 g, 8.15 mmol, 92.1% yield) as a colorless oil.

Step 2

[0269] To a solution of *tert*-butyl 4-(benzyloxy)-3-(tert-butyldimethylsilyloxy) butanoate **XXXVI**$^{\alpha}$ (3.1 g, 8.15 mmol) in EtOAc (200 mL) under a nitrogen atmosphere was added 10% palladium on carbon (600 mg). The reaction flask was evacuated and then charged with a balloon of hydrogen. The reaction mixture was then stirred at room temperature for 16 h before being filtered through Celite. The filtrate was then concentrated under reduced pressure. Purification of the crude product by column chromatography (100% DCM→50% EtOAc/DCM) afforded *tert*-butyl 3-(tert-butyldimethylsilyloxy)-4-hydroxybutanoate **XXXVII**$^{\alpha}$ (2.1 g, 7.22 mmol, 88.7% yield) as a colorless oil.

Step 3

[0270] To a solution of *tert*-butyl 3-(tert-butyldimethylsilyloxy)-4-hydroxybutanoate **XXXVII**$^{\alpha}$ (1 g mL, 3.44 mmol) in anhydrous THF (15 mL) at -78°C with an acetone/dry ice bath was added n-BuLi (2.5 M in hexanes, 1.38 mL, 3.44 mmol) slowly. The mixture was stirred at -78°C for 15 min. DMSO (0.25 mL, 3.44 mmol) was added dropwise followed by bromide intermediate **XXXVIII**$^{\alpha}$ (WO 09046098) (937 g, 3.44 mmol). The reaction was allowed to reach room temperature slowly and then was heated at 50°C overnight. The reaction mixture was then diluted with diethyl ether (200 mL) and washed with aqueous HCI (0.6 N, 200 mL). The aqueous layer was re-extracted with diethyl ether (2 x 100 mL). The organic layers were combined and concentrated *in vacuo*. Purification of the crude oil by flash chromatography (100% hexane→25% EtOAc/hexane) afforded alkoxy intermediate **XXXIX**$^{\alpha}$ (460 mg, 0.95 mmol, 27.7% yield) as a colorless oil.

Step 4

[0271] To a solution of DCM (0.13 mL, 2.15 mmol) in THF (5 mL) at -100°C was added 2.5 M n-butyl lithium in hexane (0.64 mL, 1.61 mmol) slowly under nitrogen and down the inside wall of the flask, maintaining the temperature below -90°C. The resulting white precipitate was stirred for 30 minutes before the addition of alkoxy intermediate **XXXIX**$^{\alpha}$ from step 3 (520 mg, 1.078 mmol) in THF (2 mL) at -90°C. Zinc chloride (3.77 mL, 1M in diethyl ether, 3.77 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 20 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 the chloromethylenation product **XL**$^{\alpha}$ (280 mg, 0.53 mmol, 48.9% yield).

Step 5

[0272] Chloro intermediate **XL**$^{\alpha}$ (260 mg, 0.48 mmol) in THF (4 mL) was cooled to -78°C under nitrogen. A solution of 1M LiHMDS solution in THF (0.5 mL, 0.5 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 bis(trimethylsilyl)amine product **XLI**$^{\alpha}$.

Step 6

[0273] To a stirred solution of 2-thiophenacetic acid (80 mg, 0.57 mmol) in DCM (10 mL) at 0°C under nitrogen was added EDCI (137 mg, 0.72 mmol) and HOBT (77 mg, 0.57 mmol). After stirring at 0°C for 30 minutes, a solution of the crude bis-silyl amide (**XLI**$^{\alpha}$) intermediate in DCM (5 mL) followed by *N*-methyl-morpholine (0.1 mL, 0.98 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 amide **XLII**$^{\alpha}$ (100 mg, 0.157 mmol, 32.7% yield for 2 steps).

Step 7

[0274] A solution of amide **XLII**$^{\alpha}$ (50 mg, 0.078 mmol) in anisole (2.5 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)-1,5,2-dioxaborepan-7-yl)acetic acid **1**$^{\alpha}$ (15 mg, 0.48 mmol, 61.4% yield). ^{1}H NMR (CD_3OD) δ ppm 6.98-7.00 (m, 1H), 7.00-7.09 (m, 1H), 7.33-7.35 (m, 1H); ESIMS found for $C_{12}H_{16}BNO_6S$ *m/z* 296 $(M\text{-}H_2O)^+$.

[0275] Illustrative compounds of Formula (II) are shown in Table 2. 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.

TABLE 2

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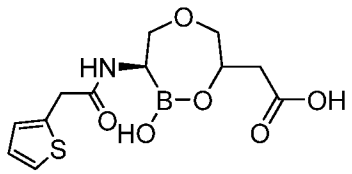
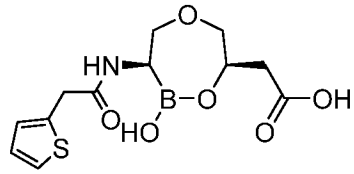
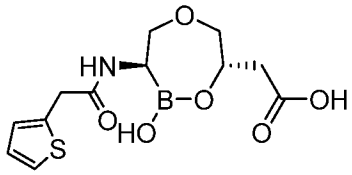
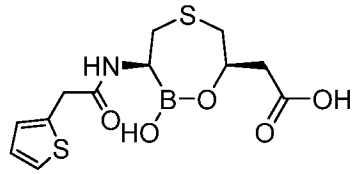
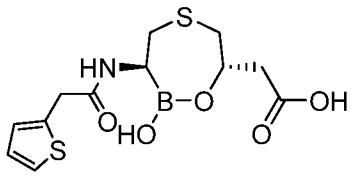
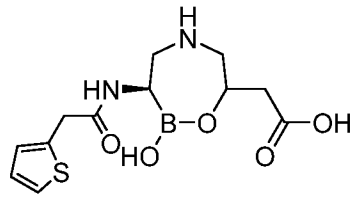
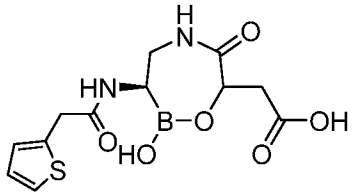
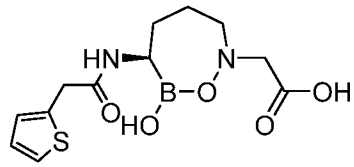
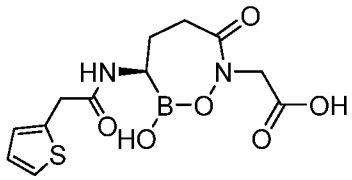
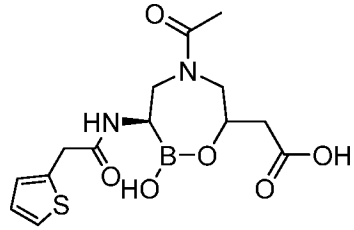
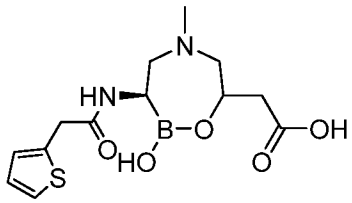
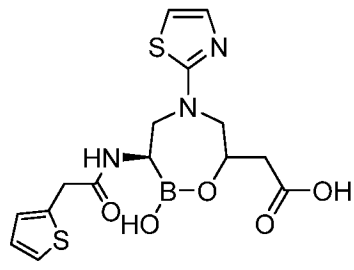
73		74	
75		76	
77		78	
79		80	
81		82	
83		84	

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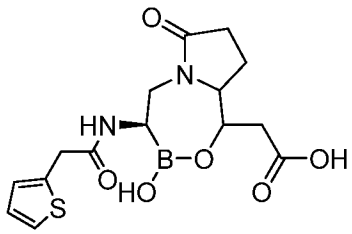
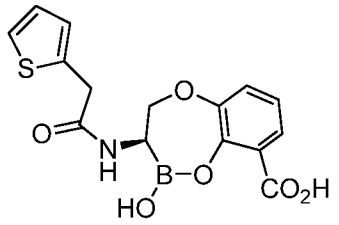
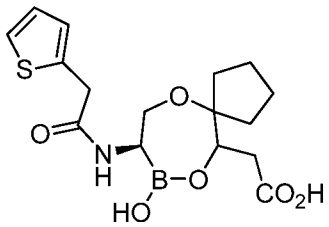
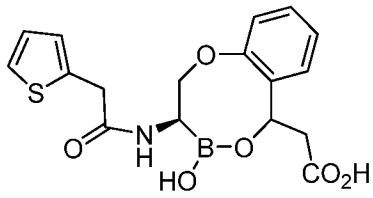
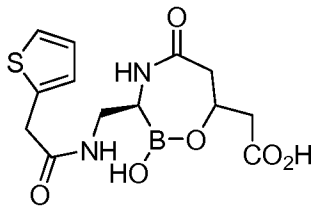
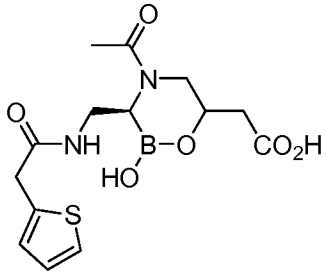
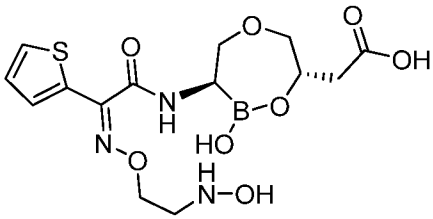
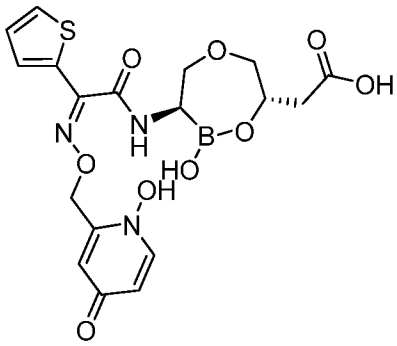
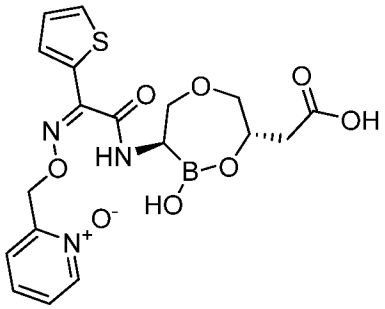
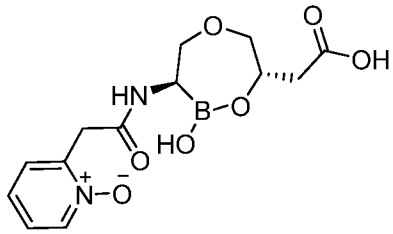
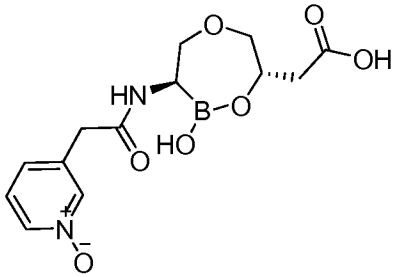
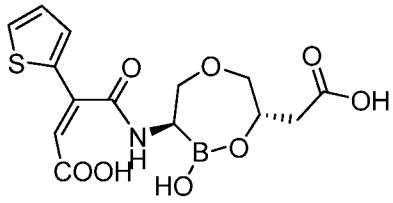
85		86	
87		88	
89		90	
91		92	
93		94	
95		96	

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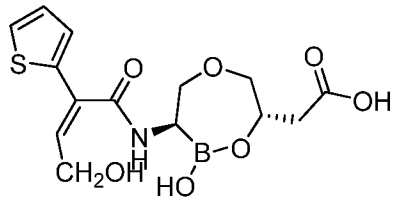
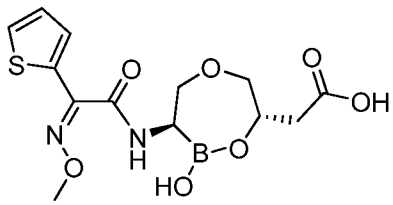
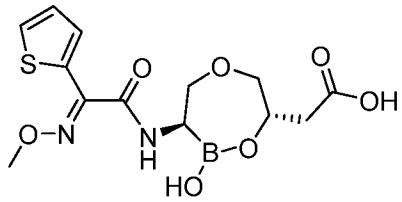
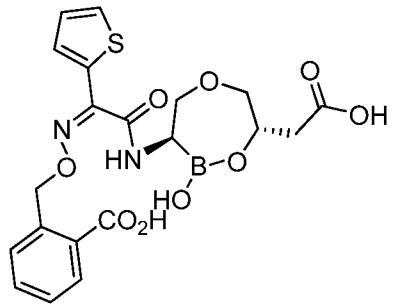
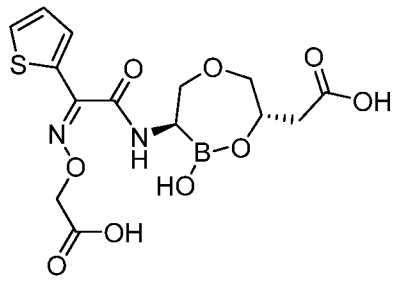
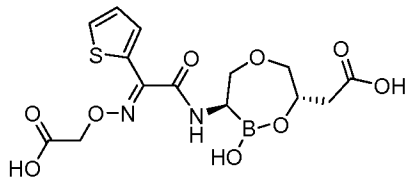
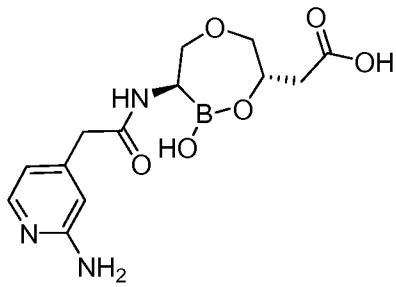
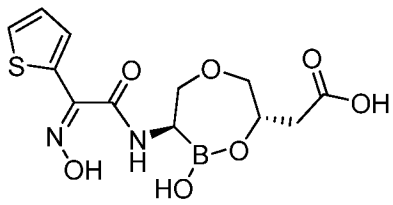
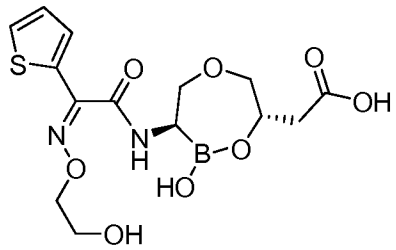
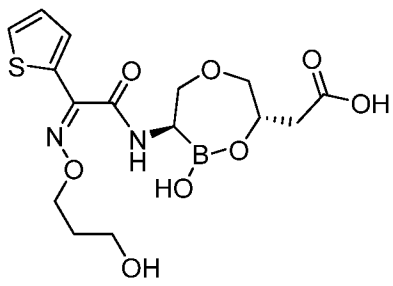
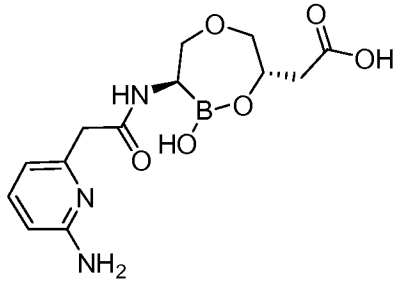
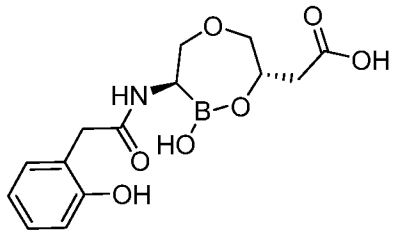
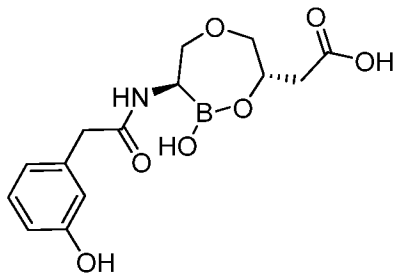
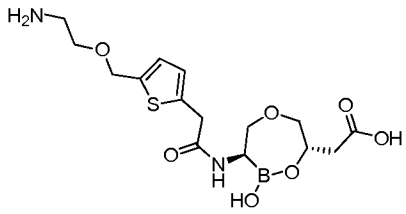
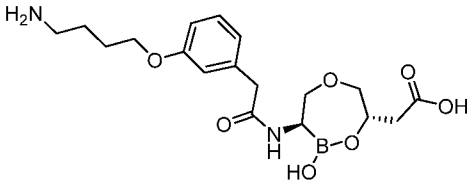
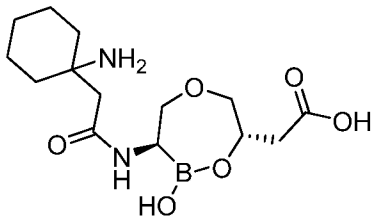
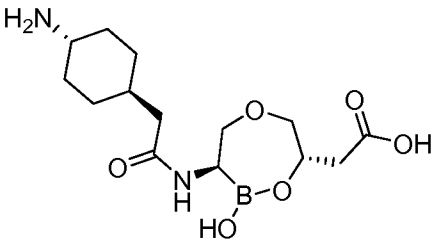
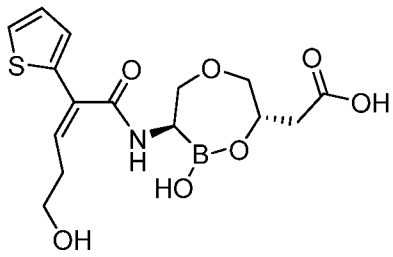
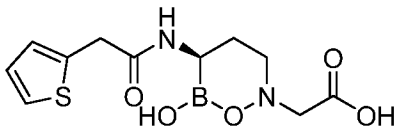
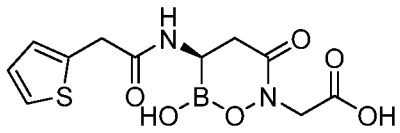
97		98	
99		100	
101		102	
103		104	
105		106	
107		108	

Example	Structure	Example	Structure
109		110	
111		112	
113		114	
115		116	

Example 11

[0276] The potency and spectrum of β-lactamase inhibitors was determined by assessing their antibiotic potentiation activity.

[0277] 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 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 CLSI (Clinical Laboratory Standards Institute) 2009. Methods for Dilution of Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Eighth Edition; Approved Standard. CLSI Document M07-A8, 2009). In this assay, multiple dilutions of two drugs, namely BLI and β-lactam (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.

[0278] The checkerboard (CB) assay is performed in microtiter plates. Biapenem is 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.

[0279] 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 derivatives showed significant potentiation of biapenem against the strains expressing class A carbapenemases: MPC8 (minimal potentiation concentration of cyclic boronic acid derivative (μg/mL) to reduce the MIC of Biapenem 8-fold) varied from 0.02 μg/mL to 0.16 μg/mL (Table 3). Cyclic boronic acid derivatives were capable of reducing biapenem MICs up to 1000-fold (Table 3).

TABLE 3

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

Strain	Organism	Description	PCR	Class	Compound	MPC8
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
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

Strain	Organism	Description	PCR	Class	Compound	MPC8
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

[0280] The activity of β-lactamase inhibitors to inhibit hydrolysis of 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.

[0281] Next, the activity of bacterial lysates was optimized for 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 biapenem in buffer A (pre-incubated at 37°C for 15 minutes) were added to each well. Hydrolysis of biapenem was measured at 296 nm. 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.

[0282] Finally, the potency of cyclic boronic acid derivativeto inhibit the cleavage of 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 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 solution of biapenem in buffer A (pre-incubated at 37°C for 15 minutes) were next added to each well and hydrolysis of biapenem was recorded at 296 nm. EC_{50} of inhibition was determined by plotting the rate of biapenem cleavage vs. cyclic boronic acid derivative concentration.

[0283] The results of these experiments are presented in Table 4. These experiments demonstrate that the described compounds are inhibitors with a broad-spectrum activity towards various β-lactamases.

TABLE 4

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.

[0284] 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 5 summarizes BLI potency of biapenem potentiation (MPC_1). Biapenem MIC for each strain is also shown.

TABLE 5

Biapenem MIC	>8	8	4	8	Biapenem MIC	>8	8	4	8
	BPM MPC_1 KP1004 KPC-2	BPM MPC_1 KP1008 KPC-2	BPM MPC_1 EC1007 KPC-3	BPM MPC_1 ECL1004 NMC-A		BPM MPC_1 KP1004 KPC-2	BPM MPC_1 KP1008 KPC-2	BPM MPC_1 EC1007 KPC-3	BPM MPC_1 ECL1004 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
44	X	X	X	Y	**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.

Example 13

[0285] Checkerboard assays were used to evaluate the ability of Compound **5** to potentiate biapenem 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 6. Compound **5** was capable to significantly potentiate biapenem.

TABLE 6

		Concentration of Compound 5 (mg/L) to potentiate biapenem (mg/L)									
Organism	**Strain**	**Enzyme**	**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	KP1008	KPC-2	Biapenem	Z	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	KP1087	KPC-2, CTX-M-15, SHV-11, TEM-1	Biapenem	Z	Z	Z	Z	Y	Y	X	X
Klebsiella oxytoca	KX1019	KPC-2, OXA-2	Biapenem	Z	Y	Y	Y	Y	Y	X	X
Klebsiella	KX1017	KPC-2,	Biapenem	Y	Y	Y	X	X	X	X	X

		Concentration of Compound 5 (mg/L) to potentiate biapenem (mg/L)									
Organism	**Strain**	**Enzyme**	**Antibiotic**	**0**	**0.16**	**0.31**	**0.625**	**1.25**	**2.5**	**5**	**10**
oxytoca		OXA-2, SHV-30									
Klebsiella oxytoca	KX1018	KPC-2, SHV-40, OXY-1	Biapenem	Z	X	X	X	X	X	NG	NG
Escherichia coli	EC1007	KPC-3	Biapenem	Z	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	ECL1059	KPC-3, SHV-12, TEM-1	Biapenem	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	KP1084	KPC-3, SHV-11, TEM-1	Biapenem	Z	Z	Z	Z	Z	Y	X	X
Klebsiella pneumoniae	KP1088	KPC-3, SHV-11, TEM-1	Biapenem	Z	Y	X	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 14

[0286] The β-lactamase inhibitor, Compound **5**, was tested for its ability to potentiate Biapenem in bacterial strains expressing the metallo-β-lactamase NDM-1, the serine β-lactamase KPC-2, and both β-lactamases. MIC values for each bacterial strain were measured for Biapenem at various concentrations of Compound 5. Table 7 summarizes the activity of Compound 5 in combination with Biapenem. The presence of Compound 5 decreased the Biapenem MIC in bacterial strains that expressed the beta-lactamase, KPC-2 alone or in combination with NDM-1.

TABLE 7

		Biapenem MIC (μg/ml)		
Organism (strain)		*Escherichia coli* (EC1061)	*Klebsiella pneumonia* (KP1004)	*Klebsiella pneumonia* (KPM1097)
Description		Donor strain	Recipient strain	Trans-conjugant
Beta-lactamase		NDM-1	KPC-2	NDM-1, KPC-2
Compound 5 (μg/ml)	**0**	0.125	8	16
	0.31	0.13	0.5	2
	0.63	0.13	0.25	1
	1.25	0.125	0.25	1
	2.5	0.06	0.06	1
	5	0.125	0.06	1
	10	0.06	≤ 0.03	1
	20	0.06	≤ 0.03	1

Example 15

[0287] The two β-lactamase inhibitors (BLIs), Compound 5 and Compound 68, were tested for their ability to potentiate the two antimicrobial compounds, Aztreonam and Tigemonan, in bacterial strains expressing the β-lactamases: NDM-1, CMY-6, SHV-11, CTX-M-15, and TEM-1. MIC values for each bacterial strain were measured for each antimicrobial compound at various concentrations of each BLI. Table 8 summarizes the activity of each BLI in combination with Aztreonam or Tigemonan. The presence of each BLI decreased the Aztreonam or Tigemonan MICs in bacterial strains that expressed the beta-lactamase, NDM-1 and CMY-6.

TABLE 8

			Antibiotic MIC (μg/ml) in the presence of BLI (μg/ml)							
Organism/Strain (β-lactamase)	**Antibiotic**	**BLI**	**0**	**0.31**	**0.63**	**1.25**	**2.5**	**5**	**10**	**20**
E. coli. / EC1061 (NDM-1 CMY-6)	Aztreonam	Compound 5	16	4	4	2	2	0.5	0.5	0.5
E. coli. / EC1061 (NDM-1 CMY-6)	Tigemonam	Compound 5	8	ND	1	1	1	0.5	0.5	1
E. coli. / EC1061 (NDM-1 CMY-6)	Tigemonam	Compound 68	16	0.5	0.5	0.5	0.5	0.5	0.5	ND
K. pneumoniae/	Aztreonam	Compound 5	256	256	128	32	16	8	4	2

KP1081 (NDM-1, CMY-6, SHV-11, CTX-M-15, TEM-1)										
K. pneumoniae/ KP1081 (NDM-1, CMY-6, SHV-11, CTX-M-15, TEM-1)	Tigemonam	Compound 5	16	ND	4	4	4	4	4	4
K. pneumoniae/ KP1081 (NDM-1, CMY-6, SHV-11, CTX-M-15, TEM-1)	Tigemonam	Compound 68	16	8	8	4	4	4	4	ND

Example 16

[0288] Tigemonnam was administered by IP route with and without the BLI, Compound A (also known as Compound 68) in a neutropenic mouse thigh infection model. The infection comprised E. coli EC1061 (contains NDM-1 and CMY-6, as shown in Table 8). The results are summarized in FIG. 1. Tigemonam MIC = 8 mg/L; 0.5 mg/L with 0.31 μg/ml Compound A (also known as Compound 68).

[0289] While the present invention has been described in some detail for purposes of clarity and understanding, one skilled in the art will appreciate that various changes in form and detail can be made without departing from the true scope of the invention.

[0290] 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.

[0291] 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.

[0292] The above description discloses several methods and materials of the present invention. This invention is susceptible to modifications in the methods and materials, 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

invention 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.

[0293] 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.

WHAT IS CLAIMED IS:

1. A method of increasing sensitivity of a bacterial infection to treatment with an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase, said method comprising:

identifying a bacterial infection as including bacteria that comprises a serine β-lactamase and a metallo β-lactamase; and

contacting said bacteria with an effective amount of a β-lactamase inhibitor.

2. The method of claim 1, wherein contacting said bacteria with an effective amount of a β-lactamase inhibitor comprises administering the β-lactamase inhibitor to a subject having said bacterial infection.

3. A method of treating a bacterial infection that includes bacteria comprising a serine β-lactamase and a metallo β-lactamase, said method comprising:

contacting said bacteria with a β-lactamase inhibiting effective amount of a β-lactamase inhibitor and an antibacterially effective amount of an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase.

4. The method of claim 3, further comprising identifying said bacterial infection as including bacteria that comprises a serine β-lactamase and a metallo β-lactamase.

5. The method of claim 3, wherein contacting said bacteria with a β-lactamase inhibiting effective amount of a β-lactamase inhibitor and an antibacterially effective amount of an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase comprises administering the β-lactamase inhibitor and the antimicrobial compound resistant to degradation by a metallo β-lactamase to a subject having said bacterial infection.

6. The method of claim 5, wherein said administering comprises administering a pharmaceutical composition comprising said β-lactamase inhibitor and said antimicrobial compound resistant to degradation by a metallo β-lactamase to said subject.

7. Use of an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase in the preparation of a medicament for use in combination with a β-lactamase inhibitor for treating a bacterial infection that includes bacteria comprising a serine β-lactamase and a metallo β-lactamase.

8. Use of a β-lactamase inhibitor in the preparation of a medicament for use in combination with an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase for treating a bacterial infection that includes bacteria comprising a serine β-lactamase and a metallo β-lactamase.

9. Use of a β-lactamase inhibitor in the preparation of a medicament for increasing the sensitivity of a bacterial infection to an antimicrobial β-lactam compound resistant to degradation by a metallo β-lactamase, wherein the bacterial infection includes bacteria comprising a serine β-lactamase and a metallo β-lactamase.

10. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the antimicrobial compound resistant to degradation by a metallo β-lactamase has a K_m for the metallo β-lactamase greater than about 100 μM.

11. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the antimicrobial compound resistant to degradation by a metallo β-lactamase has a K_m for the metallo β-lactamase greater than about 130 μM.

12. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the antimicrobial compound resistant to degradation by a metallo β-lactamase has a minimum inhibitory concentration for *E. coli* expressing the metallo β-lactamase less than about 250 μg/ml.

13. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the antimicrobial compound resistant to degradation by a metallo β-lactamase has a minimum inhibitory concentration for *E. coli* expressing the metallo β-lactamase less than about 0.05 μg/ml.

14. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the antimicrobial compound resistant to degradation by a metallo β-lactamase comprises biapenem.

15. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the antimicrobial compound resistant to degradation by a metallo β-lactamase comprises a monobactam.

16. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the antimicrobial compound resistant to degradation by a metallo β-lactamase is selected from the group consisting of Aztreonam, Tigemonam, Carumonam, SYN-2416, BAL30072, and Nocardicin A.

17. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the sensitivity to the antimicrobial compound resistant to degradation by a metallo β-lactamase of the bacteria contacted with the β-lactamase inhibitor increases at least about 8-fold compared to bacteria not contacted with the β-lactamase inhibitor.

18. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the sensitivity to the antimicrobial compound resistant to degradation by a metallo β-lactamase of

the bacteria contacted with the β-lactamase inhibitor increases at least about 4-fold compared to bacteria not contacted with the β-lactamase inhibitor.

19. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the sensitivity to the antimicrobial compound resistant to degradation by a metallo β-lactamase of the bacteria contacted with the β-lactamase inhibitor increases at least about 2-fold compared to bacteria not contacted with the β-lactamase inhibitor.

20. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the serine β-lactamase is selected from the group consisting of NMC-A, SME, KPC-2, OXA-48, and KPC-3.

21. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the serine β-lactamase comprises a KPC enzyme.

22. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the serine β-lactamase comprises KPC-2.

23. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the metallo β-lactamase comprises NDM-1.

24. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the metallo β-lactamase comprises IMP, VIM, SPM, and GIM.

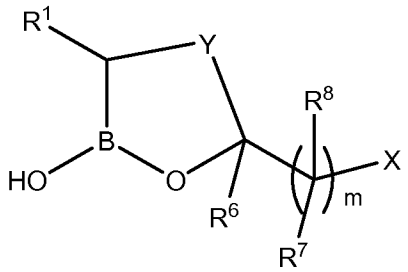
25. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the bacterial infection comprises a bacterium selected from the group consisting of *Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas acidovorans, Pseudomonas alcaligenes, Pseudomonas putida, Stenotrophomonas 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, and *Staphylococcus saccharolyticus*.

26. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein a mammal has said bacterial infection.

27. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein a human has said bacterial infection.

28. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises 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 $-C_{1\text{-}9}$alkyl, $-C_{2\text{-}9}$alkenyl, $-C_{2\text{-}9}$alkynyl, $-NR^9R^{10}$, $-C_{1\text{-}9}$alkylR^{11}, $-C_{2\text{-}9}$alkenylR^{11}, $-C_{2\text{-}9}$alkynylR^{11}, -carbocyclyl-R^{11}, $-CH(OH)C_{1\text{-}9}$alkylR^9, $-CH(OH)C_{2\text{-}9}$alkenylR^9, $-CH(OH)C_{2\text{-}9}$alkynylR^9, -CH(OH)carbocyclyl-R^9, $-C(=O)R^9$, $-C(=O)C_{1\text{-}9}$alkylR^9, $-C(=O)C_{2\text{-}9}$alkenylR^9, $-C(=O)C_{2\text{-}9}$alkynylR^9, $-C(=O)C_{2\text{-}9}$carbocyclyl-R^9, $-C(=O)NR^9R^{10}$, $-N(R^9)C(=O)R^9$, $-N(R^9)C(=O)NR^9R^{10}$, $-N(R^9)C(=O)OR^9$, $-N(R^9)C(=O)C(=NR^{10})R^9$, $-N(R^9)C(=O)C(=NOR^{10})R^9$, $-N(R^9)C(=O)C(=CR^9R^{10})R^9$, $-N(R^9)C(=O)C_{1\text{-}4}$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 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, or alternatively 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;

each R^7 is independently selected from a group consisting of H, –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, 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, or independently, 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, or independently a geminal R^7 and R^8 together form a –C_{2-9} alkenylenylCO_2R^9;

each R^8 is independently selected from a group consisting of H, –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, 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, or independently a geminal R^7 and R^8 together form a –C_{2-9} alkenylenylCO_2R^9;

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;

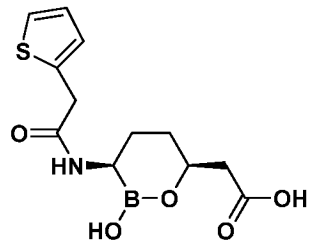
R^{12} is selected from a group consisting of H, C_{1-9}alkyl, $-(CH_2)_{0-3}-R_{11}$, $-C(R^{13})_2OC(O)C_{1-9}$alkyl, $-C(R^{13})_2OC(O)R^{11}$, $-C(R^{13})_2OC(O)OC_{1-9}$alkyl and $-C(R^{13})_2OC(O)OR^{11}$;

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

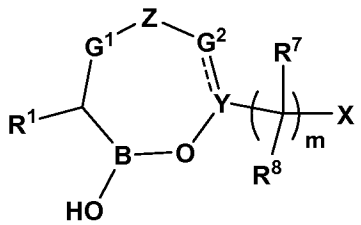
m is independently zero or an integer from 1 to 2,

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

29. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



30. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure of formula II:



II

or pharmaceutically acceptable salt thereof, wherein:

$R^{1\alpha}$ is selected from a group consisting of $-C_{1-9}$ alkyl, $-C_{2-9}$ alkenyl, $-C_{2-9}$ alkynyl, $-NR^{9\alpha}R^{10\alpha}$, $-C_{1-9}$ alkyl$R^{11\alpha}$, $-C_{2-9}$ alkenyl$R^{11\alpha}$, $-C_{2-9}$ alkynyl$R^{11\alpha}$, -carbocyclyl-$R^{11\alpha}$, $-CH(OH)C_{1-9}$alkyl$R^{9\alpha}$, $-CH(OH)C_{2-9}$alkenyl$R^{9\alpha}$, $-CH(OH)C_{2-9}$alkynyl$R^{9\alpha}$, -CH(OH)carbocyclyl-$R^{9\alpha}$, $-C(=O)R^{9\alpha}$, $-C(=O)C_{1-9}$alkyl$R^{9\alpha}$, $-C(=O)C_{2-9}$alkenyl$R^{9\alpha}$, $-C(=O)C_{2-9}$alkynyl$R^{9\alpha}$, $-C(=O)C_{2-9}$carbocyclyl-$R^{9\alpha}$, $-C(=O)NR^{9\alpha}R^{10\alpha}$, $-N(R^{9\alpha})C(=O)R^{9\alpha}$, $-N(R^{9\alpha})C(=O)NR^{9\alpha}R^{10\alpha}$, $-N(R^{9\alpha})C(=O)OR^{9\alpha}$, $-N(R^{9\alpha})C(=O)C(=NR^{10\alpha})R^{9\alpha}$, $-N(R^{9\alpha})C(=O)C(=CR^{9\alpha}R^{10\alpha})R^{9\alpha}$, $-N(R^{9\alpha})C(=O)C_{1-4}$alkyl$N(R^{9\alpha})C(=O)R^{9\alpha}$, –

$N(R^{9\alpha})C(=NR^{10\alpha})R^{9\alpha}$, $-C(=NR^{10\alpha})NR^{9\alpha}R^{10\alpha}$, $-N=C(R^{9\alpha})NR^{9\alpha}R^{10\alpha}$, $-N(R^{9\alpha})SO_2R^{9\alpha}$, $-N(R^{9\alpha})SO_2NR^{9\alpha}R^{10\alpha}$, $-N=CHR^{9\alpha}$, $-C(R^{9\alpha}R^{10\alpha})C(=O)NR^{9\alpha}R^{10\alpha}$, $-C(R^{9\alpha}R^{10\alpha})N(R^{9\alpha})C(=O)R^{9\alpha}$, $-C(R^{9\alpha}R^{10\alpha})OR^{9\alpha}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

$G^{1\alpha}$ is selected from a divalent group consisting of $-C(R^{a\alpha}R^{b\alpha})-$, $-C(=R^{a\prime\alpha})-$, $-C(R^{a\alpha}R^{b\alpha})C(R^{c\alpha}R^{d\alpha})-$, $-C(R^{a\alpha})=C(R^{c\alpha})-$, $-C(=O)C(R^{a\alpha}R^{b\alpha})-$, $-C(R^{a\alpha}R^{b\alpha})C(=O)-$, and a bond;

$G^{2\alpha}$ is selected from a divalent group consisting of $-C(R^{e\alpha}R^{f\alpha})-$, $-C(=R^{e\prime\alpha})-$, $=C(R^{e\alpha})-$, $-C(R^{e\alpha}R^{f\alpha})C(R^{g\alpha}R^{h\alpha})-$, $-C(R^{e\alpha}R^{f\alpha})C(R^{g\alpha}R^{h\alpha})C(R^{i\alpha}R^{j\alpha})-$, $-C(=O)-$, $-C(=O)C(R^{e\alpha}R^{f\alpha})-$, $-C(R^{e\alpha}R^{f\alpha})C(=O)-$, $-C(=O)C(R^{e\alpha}R^{f\alpha})C(R^{g\alpha}R^{h\alpha})-$, $-C(R^{e\alpha}R^{f\alpha})C(R^{g\alpha}R^{h\alpha})C(=O)-$, $-C(=O)C(R^{e\alpha}R^{f\alpha})C(R^{g\alpha}R^{h\alpha})C(R^{i\alpha}R^{j\alpha})-$, $-C(R^{e\alpha}R^{f\alpha})C(R^{g\alpha}R^{h\alpha})C(R^{i\alpha}R^{j\alpha})C(=O)-$, $-C(R^{e\alpha})=C(R^{g\alpha})-$,$-C(R^{e\alpha})=C(R^{g\alpha})C(R^{i\alpha}R^{j\alpha})-$ and $-C(R^{e\alpha}R^{f\alpha})C(R^{g\alpha})=C(R^{j\alpha})-$;

$R^{a\alpha}$, $R^{b\alpha}$, $R^{c\alpha}$, $R^{d\alpha}$, $R^{e\alpha}$, $R^{f\alpha}$, $R^{g\alpha}$, $R^{h\alpha}$, $R^{i\alpha}$, and $R^{j\alpha}$ are independently selected from a group consisting of H, Cl, F, CN, CF_3, $-R^{9\alpha}$, $-OR^{9\alpha}$, $NR^{9\alpha}R^{10\alpha}$, $-C(=O)NR^{9\alpha}R^{10\alpha}$, and $-C(=O)OR^{9\alpha}$, or independently: $R^{a\alpha}$ and $R^{c\alpha}$, $R^{e\alpha}$ and an $R^{7\alpha}$, $R^{k\alpha}$ and $R^{c\alpha}$, $R^{k\alpha}$ and $R^{e\alpha}$, $R^{e\alpha}$ and $R^{g\alpha}$, and $R^{g\alpha}$ and $R^{j\alpha}$ are taken together with the atoms to which they are attached and any intervening atoms to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl, or independently $R^{e\alpha}$ and $R^{f\alpha}$ are taken together with the atoms to which they are attached and any intervening atoms to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

$R^{a\prime\alpha}$ and $R^{e\prime\alpha}$ are $=CR^{9\alpha}R^{10\alpha}$ or independently $R^{a\prime\alpha}$ and $R^{k\alpha}$, or $R^{e\prime\alpha}$ and $R^{k\alpha}$, 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;

Z^{α} is selected from a divalent group consisting of $-C(R^{9\alpha}R^{10\alpha})-$, $-O-$, $-S-$, $-N(R^{9\alpha})-$, $-N[C(=O)R^{9\alpha}]-$, $-N[C(=O)NR^{9\alpha}R^{10\alpha}]-$, $-N[C(=O)OR^{9\alpha}]-$, $-N[C(=NR^{10\alpha})R^{9\alpha}]-$, $-N[SO_2R^{9\alpha}]-$, $-N[SO_2NR^{9\alpha}R^{10\alpha}]-$, $-N(R^{9\alpha})C(=O)-$, $-C(R^{9\alpha}R^{k\alpha})-$, $-C(=R^{k\alpha})-$, $-N(R^{k\alpha})-$, and a bond;

$R^{k\alpha}$ and $R^{c\alpha}$, $R^{k\alpha}$ and $R^{e\alpha}$, $R^{a\prime\alpha}$ and $R^{k\alpha}$, or $R^{e\prime\alpha}$ and $R^{k\alpha}$ are taken together with any intervening atoms to form a substituted or unsubstituted aryl, substituted or unsubstituted

heteroaryl, substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

Y^{α} is selected from a group consisting of N, $CR^{6\alpha}$, and C, with the proviso that when Z^{α} is a bond, -C($R^{9\alpha}R^{10\alpha}$)-, -C($R^{9\alpha}R^{k\alpha}$)-, or -C(=$R^{k\alpha}$)-, then Y^{α} is N;

$R^{6\alpha}$ is selected from a group consisting of H, -C_{1-9}alkyl, -C_{2-9}alkenyl, -C_{2-9}alkynyl, carbocyclyl, -C_{1-9}alkyl$R^{11\alpha}$, -C_{2-9}alkenyl$R^{11\alpha}$, -C_{2-9}alkynyl$R^{11\alpha}$, carbocyclyl-$R^{11\alpha}$, -C(=O)$OR^{9\alpha}$ and -C_{1-9}alkyl$CO_2R^{9\alpha}$, -C_{2-9}alkenyl$CO_2R^{9\alpha}$, –C_{2-9}alkynyl$CO_2R^{9\alpha}$, and -carbocyclyl-$CO_2R^{9\alpha}$, or alternatively $R^{6\alpha}$ and an $R^{7\alpha}$ or $R^{6\alpha}$ and $R^{e\alpha}$ are taken together with the atoms to which they are attached and any intervening atoms to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl;

each $R^{7\alpha}$ is independently selected from a group consisting of H, halo , -C_{1-9}alkyl, -C_{2-9}alkenyl, -C_{2-9}alkynyl, –$NR^{9\alpha}R^{10\alpha}$, -$OR^{9\alpha}$, -C_{1-9}alkyl$CO_2R^{9\alpha}$, -C_{2-9}alkenyl$CO_2R^{9\alpha}$, –C_{2-9}alkynyl$CO_2R^{9\alpha}$, and -carbocyclyl-$CO_2R^{9\alpha}$, or independently, $R^{6\alpha}$ and an $R^{7\alpha}$ or an $R^{7\alpha}$ and an $R^{8\alpha}$ are taken together with the atoms to which they are attached and any intervening atoms to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl, or independently an $R^{7\alpha}$ and $R^{e\alpha}$ are are taken together with intervening atoms to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl;

each $R^{8\alpha}$ is independently selected from a group consisting of H, halo , -C_{1-9}alkyl, -C_{2-9}alkenyl, -C_{2-9}alkynyl, –$NR^{9\alpha}R^{10\alpha}$, -$OR^{9\alpha}$, -C_{1-9}alkyl$CO_2R^{9\alpha}$, -C_{1-9}alkyl$CO_2R^{9\alpha}$, -C_{2-9}alkenyl$CO_2R^{9\alpha}$, –C_{2-9}alkynyl$CO_2R^{9\alpha}$, and -carbocyclyl-$CO_2R^{9\alpha}$, or independently, and $R^{7\alpha}$ and an $R^{8\alpha}$ are taken together with the atoms to which they are attached to form a substituted or unsubstituted carbocyclyl or substituted or unsubstituted heterocyclyl, or independently, each $R^{8\alpha}$ attached to a ring atom forming part of the substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl is absent;

each $R^{9\alpha}$ 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}alkyl$R^{11\alpha}$, C_{2-9}alkenyl$R^{11\alpha}$, -C_{2-9}alkynyl$R^{11\alpha}$, -carbocyclyl-$R^{11\alpha}$, -C_{1-9}alkyl$CO_2R^{12\alpha}$, C_{2-9}alkenyl$CO_2R^{12\alpha}$, -C_{2-9}alkynyl$CO_2R^{12\alpha}$, -carbocyclyl-$CO_2R^{12\alpha}$, -C_{1-9}alkyl-N($R^{12\alpha}$)$OR^{12\alpha}$, C_{2-9}alkenyl-N($R^{12\alpha}$)$OR^{12\alpha}$, -C_{2-9}alkynyl-N($R^{12\alpha}$)$OR^{12\alpha}$, -carbocyclyl-N($R^{12\alpha}$)$OR^{12\alpha}$, -C_{1-9}alkyl-$OR^{12\alpha}$, C_{2-9}alkenyl-$OR^{12\alpha}$, -C_{2-9}alkynyl-$OR^{12\alpha}$, -carbocyclyl-$OR^{12\alpha}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, and substituted or unsubstituted heterocyclyl;

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

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

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

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

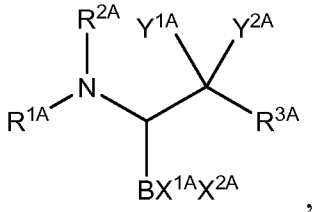
each X^{α} is independently selected from a group consisting of H, -$CO_2R^{12\alpha}$, and carboxylic acid isosteres;

m^{α} is independently zero or an integer from 1 to 2;

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; and

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

31. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure::



,

wherein, R^{1A} is -C(O)R^{4A}; -C(O)$NR^{4A}R^{5A}$; -C(O)OR^{4A}; -$S(O)_2R^{4A}$, -$C(=NR^{4A}R^{5A})R^{4A}$, -$C(=NR^{4A}R^{5A})NR^{4A}R^{5A}$, hydrogen, or is selected from the group consisting of: (a) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (b) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl,

heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (c) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido;

R^{2A} is hydrogen, or is selected from the group consisting of: (a) C_1-C_6 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_6 carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_7 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl,

sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

R^{3A} is an aryl or heteroaryl group substituted with from 1 to 4 substituents wherein one of the substituents is a hydroxyl or amino group located at the 2 position relative to the group containing Y^{1A} and Y^{2A}, and wherein the remaining substituents are selected from the group consisting of hydroxyl, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, amino, aminocarbonyl, carbonyl, aminosulfonyl, alkylaryl, aryl, aryloxy, carboxyl, cyano, guanidino, halogen, heteroaryl, heterocyclyl, sulfido, sulfonyl, sulfoxido, sulfonic acid, sulfate, and thiol;

R^{4A} is selected from the group consisting of: (a) C_1-C_{10} alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_{10} carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_{10} cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl,

heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

R^{5A} is hydrogen or is selected from the group consisting of: (a) C_1-C_6 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_{10} carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_7 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl,

alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

X^{1A} and X^{2A} are independently hydroxyl, halogen, $NR^{4A}R^{5A}$, C_1-C_6 alkoxy, or when taken together X^{1A} and X^{2A} form a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or when taken together X^{1A} and X^{2A} form a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or when taken together X^{1A} and X^{2A} form a cyclic boron amide-ester where said chain contains from 2-20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or X^{1A} and R^{1A} together form a cyclic ring where said ring contains 2 to 10 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, and X^{2A} is hydroxyl, halogen, $NR^{4A}R^{5A}$, C_1-C_6 alkoxy, or X^{1A} and R^{3A} together form a cyclic ring where said ring contains 3 to 10 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, and X^{2A} is hydroxyl, halogen, $NR^{4A}R^{5A}$, or C_1-C_6 alkoxy;

Y^{1A} and Y^{2A} are independently hydrogen, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, amino, aminosulfonyl, aminocarbonyl, carbonyl, alkylaryl, aryl, aryloxy, carboxyl, cyano, halogen, heteroaryl, heteroaryloxy, heterocyclyl, sulfido, sulfonyl, or sulfoxido, or taken together Y^{1A} and Y^{2A} form a cyclic structure containing from 3-12 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S;

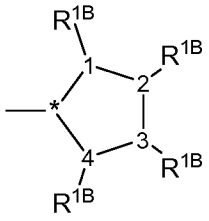
or a salt thereof;

provided that, when R^{1A} is $-C(O)R^{4A}$, R^{2A} is hydrogen, R^{3A} is a phenyl group having two substituents consisting of a hydroxyl at the 2-position and a carboxylic acid at the 3-position relative to the group containing Y^{1A} and Y^{2A}, X^{1A} and X^{2A} are hydroxyl or X^{1A} is hydroxyl and X^{2A} is replaced by the ortho-hydroxyl oxygen of R^{3A} such that a 6-membered ring is formed, and Y^{1A} and Y^{2A} are hydrogen, R^{4A} is not unsubstituted C_1 alkyl.

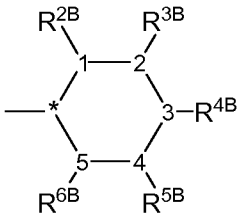
32. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:

$$(OH)_2—B—R^B$$

wherein, R^B is naphthalene, phenanthrene, or has one of the following formulas:



(2B)



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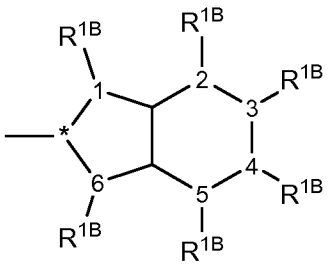

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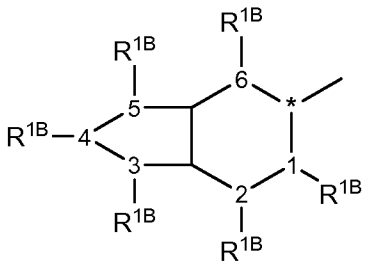

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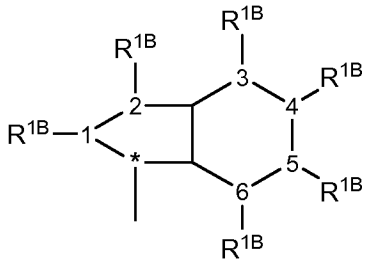

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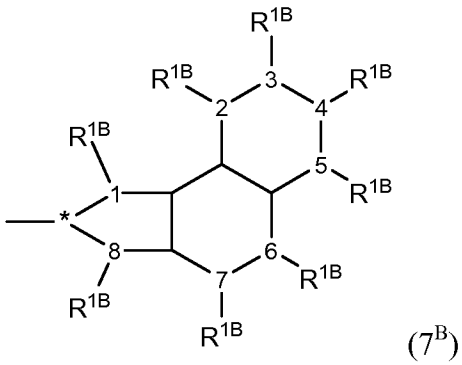

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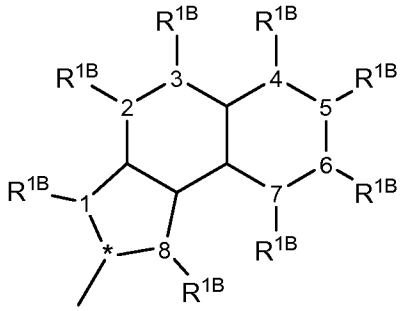

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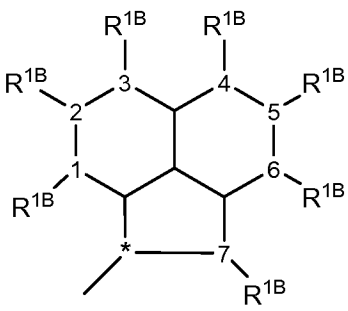

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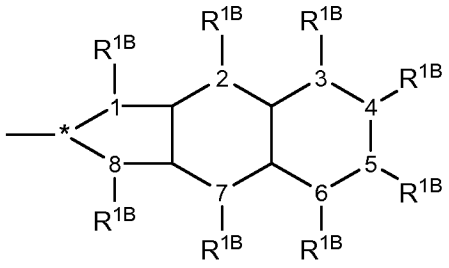
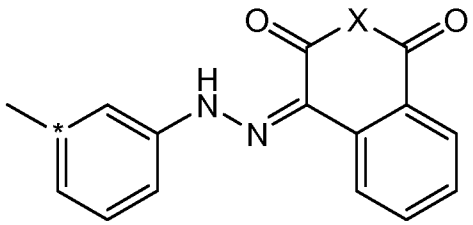
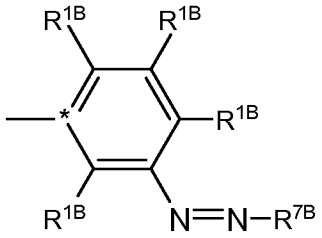


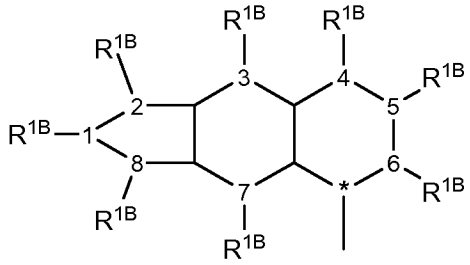
(10^B)



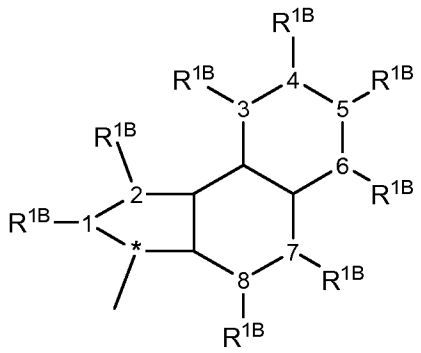
(11^B)



(12^B)



(13^B)



(14^B)

wherein, ring system (2^B), (3^B), (4^B), (5^B), (6^B), (7^B), (8^B), (9^B), (10^B), (13^B) or (14^B) is aromatic or nonaromatic;

the atom center * is (R) or (S) in the case of chiral compounds;

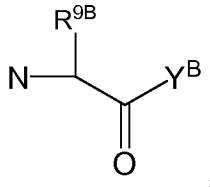
positions 1, 2, 3, 4, 5, 6, 7 and 8 each independently is C, N, O or S;

R^{1B} through R^{6B} each independently is a lone pair, H, $B(OH)_2$, a halogen atom, CF_3, CH_2 CF_3, CCl_3, CH_2 CCl_3, CBR^{3B}, CH_2 CBR^{3B}, NO_2, lower alkyl, CO_2H, CHCHCOOH, $CH_2CH_2CH_2$ COOH, SO_3H, PO_3H, OSO_3H, OPO_3H, OH, NH_2, $CONH_2$, $COCH_3$, OCH_3, or phenyl boronic acid, except that R^{2B}, R^{3B}, R^{4B}, R^{5B} and R^{6B} cannot all simultaneously be H, R^{2B} cannot be lower alkyl when R^{3B}, R^{4B}, R^{5B} and R^{6B} are H, R^{3B} cannot be NH_2, OH or lower alkyl when R^{2B}, R^{4B}, R^{5B} and R^{6B} are H, and R^{4B} cannot be lower alkyl when R^{2B}, R^{3B}, R^{5B} and R^{6B} are H;

R^{7B} is H, CF_3, CCl_3, CBR^{3B}, CH_2CF_3, CH_2CCl_3, CH_2CBR^{3B}, NO_2, $COCH_3$, OCH_3, lower alkyl, cyclic alkene, cyclic alkene substituted with one or more substituents R^{8B}, heterocyclic alkene, or heterocyclic alkene substituted with one or more substituents R^{8B};

each R^{8B} is independently H, $B(OH)_2$, a halogen atom, CF_3, CCl_3, CBR^{3B}, CH_2CF_3, CH_2CCl_3, CH_2CBR^{3B}, NO_2, lower alkyl, OH, NH_2, $N(CH_3)_2$, $N(CH_3)CH_2CH_3$, $NHCOCH_3$, COOH, CHCHCOOH, $CH_2CH_2CH_2COOH$, $COCH_3$, OCH_3, phenyl boronic acid, $CONH_2$, $CONHCH_2COOH$, $CONHCH_2CONH_2$, $CONHCH_2CONHCH_2R^{10B}$, SO_2NH_2, SO_2NHCH_2COOH, $SO_2NHCH_2CONH_2$, or $SO_2NHCH_2CONHCH_2R^{10B}$;

X is O, NH, NCH_3 or



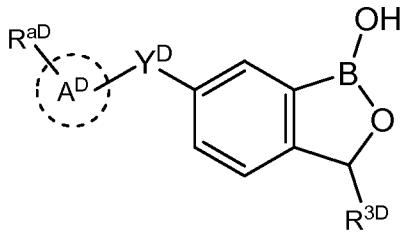
;

Y^B is OH, NH_2, NCH_3, $N(CH_3)_2$, $NHCOCH_3$ or $NHCOCH_2COOH$;

R^{9B} is H, a halogen atom, CF_3, CCl_3, CBR^{3B}, CH_2 CF_3, CH_2 CCl_3, CH_2CBR^{3B}, NO_2, CO_2H, CHCHCOOH, $CH_2CH_2CH_2COOH$, SO_3H, PO_3H, OSO_3 H, OPO_3H, OH, NH_2, $CONH_2$, $COCH_3$, OCH_3, phenyl boronic acid, lower alkyl, or a side chain of a standard amino acid; and

R^{10B} is a side chain of a standard amino acid.

33. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



,

wherein, A^D is a member selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

Y^D is a member selected from O and $-S(O)_2NH-$ wherein the sulfur in $-S(O)_2NH-$ is covalently attached to A^D;

R^{3D} is a member selected from H, cyano and substituted alkyl;

R^{aD} is a member selected from H, $-OR^{10D}$, $-NR^{10D}R^{11D}$, $-SR^{10D}$, $-S(O)R^{10D}$, $-S(O)_2R^{10D}$, $-S(O)_2NR^{10D}R^{11D}$, $-C(O)R^{10D}$, $--C(O)OR^{10D}$, $-C(O)NR^{10D}R^{11D}$, nitro, cyano, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,

substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

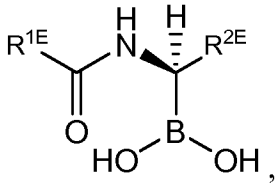
wherein, each R^{10D} and each R^{11D} is a member independently selected from H, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

with the proviso that R^{10D} and R^{11D}, together with the nitrogen to which they are attached, are optionally combined to form a 5- to 7-membered substituted or unsubstituted heterocycloalkyl ring;

with the proviso that when Y^D is O, R^{3D} is a member selected from cyano and substituted alkyl; with the proviso that when Y^D is $-S(O)_2NH-$, R^{3D} is H, and R^{aD} is not H or unsubstituted alkyl or halosubstituted alkyl,

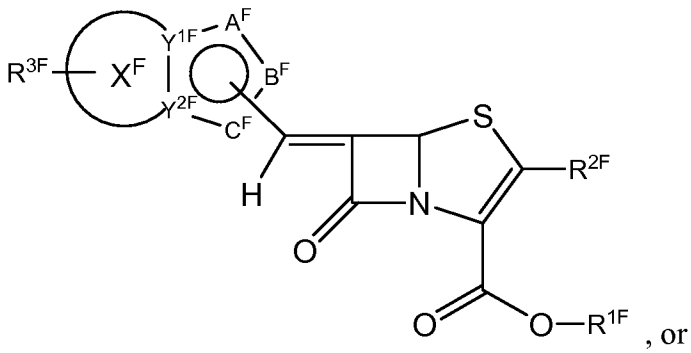
and salts thereof.

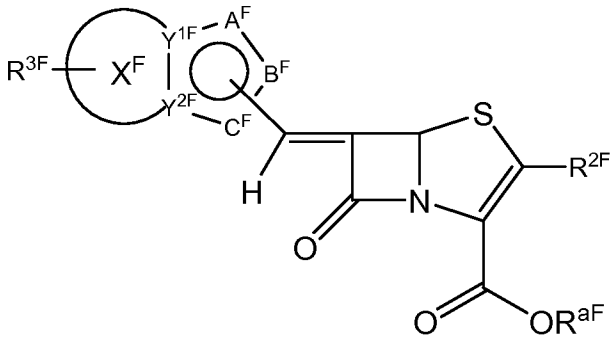
34. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, R^{1E} is a substituent selected from hydrogen, alkyl, alkenyl, cycloalkenyl, and heterocyclyl moieties, providing R^{1E} is not methyl and R^{1E} is not phenyl; and wherein R^{2E} is a substituent selected from heterocyclyl, cycloalkenyl, alkenyl and alkyl moieties.

35. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:





wherein, R^{1F} is the residue of a carboxy protecting group;

R^{aF} is hydrogen or a pharmaceutically-acceptable salt forming agent or a pharmaceutically-acceptable ester residue readily hydrolyzable *in vivo*;

R^{2F} is selected from the group consisting of: (a) Hydrogen, (b) straight or branched chain alkyl, (c) hydroxymethyl, (d) alkoxymethyl, (e) aminocarbonyloxymethyl, (f) aryl, (g) heteroaryl and (h) heterocyclyl;

heteroaryl means a 5- or 6-membered unsaturated aromatic ring containing from 1 to 4 of any one or more of the hetero atoms selected from O, S and N; heterocyclyl means a 5-membered saturated ring containing one hetero atom;

X^F is a bridged bicyclic ring system having optionally one or two hetero atoms selected from O, S and N; the ring X^F may be optionally substituted with R^{3F} wherein

R^{3F} is selected from (a) hydrogen, (b) alkyl, (c) hydroxy, (d) alkoxy, (e) hydroxymethyl, (f) alkoxymethyl, (g) halogen, (h) cyano, (i) carboxy, (j) alkoxycarbonyl, (k) amino, (l) aminoalkyl, (m) mono- or diallylamino, (n) mono- or dialkylaminoalkyl, (o) acylamino, (p) sulfonylamino, (q) substituted or unsubstituted amidino, (r) substituted or unsubstituted urea, (s) substituted or unsubstituted thiourea, (t) substituted or unsubstituted carboxamido, (u) substituted or unsubstituted thiocarboxamido, (v) substituted or unsubstituted aryl, (w) substituted or unsubstituted aralkyl, (x) substituted or unsubstituted heteroaryl, (y) substituted or unsubstituted heteroarylalkyl and (z) substituted or unsubstituted heterocyclylalkyl;

the heteroaryl groups mentioned in items (x) and (y) means a 5- or 6-membered unsaturated aromatic ring containing from 1 to 4 of any one or more of the hetero atoms selected from O, S and N, wherein the said heteroaryl groups could be bonded via carbon, or a nitrogen-containing heteroaryl group could be bonded via nitrogen;

the bridged bicyclic ring systems containing a NH ring atom may be optionally substituted on the said nitrogen by a substituent selected from: (a) alkyl, (b) alkenyl, (c) alkynyl, (d) cycloalkyl, (e) cycloalkylalkyl, (f) cycloalkenyl, (g) cycloalkenylalkyl, (h)

aryl, (i) arylalkyl, (j) heteroaryl, (k) heteroarylalkyl, (l) heterocyclyl, (m) heterocyclylalkyl (n) or a protecting group;

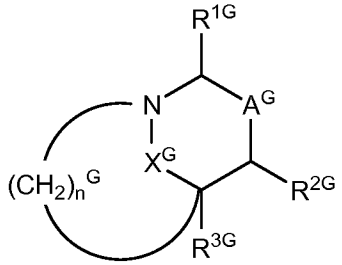
Y^{1F} and Y^{2F} may independently be C or N;

A^F, B^F or C^F form part of a heteroaryl ring where one of A^F, B^F or C^F is a carbon atom to which the remainder of the molecule is attached, and A^F, B^F and C^F are independently selected from CR^{4F}, O, N, S or NR^{5F};

R^{4F} is hydrogen; and

R^{5F} is selected from the group consisting of: (a) hydrogen, (b) straight or branched lower alkyl, (c) lower alkenyl, (d) lower alkynyl, (e) hydroxy alkyl, (f) alkoxy alkyl, (g) aminocarbonyloxy alkyl, (h) cyano alkyl, (i) aminoalkyl, (j) mono- or dialkylaminoalkyl, (k) alkoxycarbonylalkyl, (l) carboxyalkyl, (m) substituted or unsubstituted carboxamidoalkyl, (n) cycloalkylalkyl, (o) substituted or unsubstituted thiocarboxamidoalkyl, (p) substituted or unsubstituted amidinoalkyl, (q) substituted or unsubstituted guanidinoalkyl, (r) substituted or unsubstituted aminocarbonylaminoalkyl, (s) acylaminoalkyl, (t) aralkyl, (u) heteroarylalkyl and (v) heterocyclylalkyl.

36. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



,

wherein, R^{1G} is hydrogen, COOH, CN, $COOR^G$, $CONR^{6G}R^{7G}$, $(CH_2)_n{}^GR^{5G}$ or $C(=NR^{6G})NHR^{7G}$;

R^G is selected from the group consisting of alkyl containing 1 to 6 carbon atoms optionally substituted by a pyridyl or carbamoyl radical, -CH_2-alkenyl containing 3 to 9 carbon atoms, aryl containing 6 to 10 carbon atoms and aralkyl containing 7 to 11 carbon atoms, wherein the nucleus of said aryl or aralkyl is optionally substituted by OH, NH_2, NO_2, alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms or by one or more halogen atoms;

R^{6G} and R^{7G} are identical or different and are independently selected from the group consisting of hydrogen, alkyl containing 1 to 6 carbon atoms, aryl containing 6 to 10 carbon atoms and aralkyl containing 7 to 11 carbon atoms optionally substituted by a

carbamoyl, ureido or dimethylamino radical, and alkyl containing 1 to 6 carbon atoms substituted by a pyridyl radical;

n^{1G} is 1 or 2;

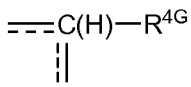
R^{5G} is selected from the group consisting of COOH, CN, OH, NH_2, CO-$NR^{6G}R^{7G}$, $COOR^G$, OR^G, OCHO, $OCOR^G$, $OCOOR^G$, $OCONHR^G$, $OCONH_2$, NHR^G, NHCOH, $NHCOR^G$, $NHSO_2R^G$, NH-$COOR^G$, NH-CO-NHR^G and $NHCONH_2$, wherein R^G, R^{6G} and R^{7G} are as defined above;

R^{2G} is hydrogen or $(CH_2)_n{}^{1G}{}_1R^{5G}$ wherein n^{1G} is 0, 1 or 2, and

R^{5G} is as defined above;

R^{3G} is hydrogen or alkyl containing 1 to 6 carbon atoms;

A^G is a bond between the two carbons which carry R^{1G} and R^{2G},



group wherein R^{4G} is hydrogen or $(CH_2)_n{}^{1G}{}_1R^{5G}$ and n^{1G} and R^{5G} are as defined above, and the dotted line is an optional bond with one of the two carbons which carry R^{1G} and R^{2G};

n^G is 1 or 2;

X^G is a divalent -C(O)-B^G- group linked to the nitrogen atom by the carbon atom wherein B^G is a divalent -O-$(CH_2)_n{}^{2G}$- group linked to the carbonyl by the oxygen atom, a divalent -NR^{8G}-$(CH_2)_n{}^{2G}$- or -NR^{8G}-O- group linked to the carbonyl by the nitrogen atom, n^{2G} is 0 or 1, and wherein B^G is -NR^{8G}-$(CH_2)_n{}^{2G}$-, R^{8G} is selected from the group consisting of hydrogen, OH, R^G, OR^G, Y^G, OY^G, Y^{1G}, OY^{1G}, Y^{2G}, OY^{2G}, Y^{3G}, $OCH_2CH_2SO_m{}^GR^G$, $OSiR^{aG}R^{bG}R^{cG}$ and $SiR^{aG}R^{bG}R^{cG}$ and wherein B^G is -NR^{8G}-O-, R^{8G} is selected from the group consisting of hydrogen, R, Y^G, Y^{1G}, Y^{2G}, Y^{3G} and $SiR^{aG}R^{bG}R^{cG}$, wherein R^{aG}, R^{bG} and R^{cG} is each independently a linear or branched alkyl containing 1 to 6 carbon atoms or aryl containing 6 to 10 carbon atoms, R^G is as defined above and m^G is 0, 1 or 2;

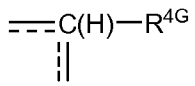
Y^G is selected from the group consisting of COH, COR^G, $COOR^G$, $CONH_2$, $CONHR^G$, CONHOH, $CONHSO_2R^G$, CH_2COOH, CH_2COOR^G, $CH_2CONHOH$, $CH_2CONHCN$, CH_2tetrazole, protected CH_2tetrazole, CH_2SO_3H, $CH_2SO_2R^G$, $CH_2PO(OR^G)_2$, $CH_2PO(OR^G)(OH)$, $CH_2PO(R^G)(OH)$ and $CH_2PO(OH)_2$;

Y^{1G} is selected from the group consisting of SO_2R^G, SO_2NHCOH, SO_2NHCOR^G, $SO_2NHCOOR^G$, $SO_2NHCONHR^G$, $SO_2NHCONH_2$ and SO_3H;

Y^{2G} is selected from the group consisting of $PO(OH)_2$, $PO(OR^G)_2$, $PO(OH)(OR^G)$ and $PO(OH)(R^G)$;

Y^{3G} is selected from the group consisting of tetrazole, tetrazole substituted by R^G, squarate, NH or NR^G-tetrazole, NH or NR^G-tetrazole substituted by R^G, $NHSO_2R^G$ and $NR^GSO_2R^G$ wherein R^G is as defined above; and

R^{1G}, R^{2G} and R^{3G} are not simultaneously hydrogen when n^G is 1, A^G is



,

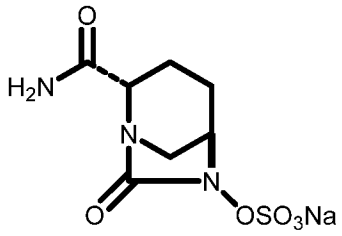
wherein R^{4G} is hydrogen and

X^G is $-C(O)-O-(CH_2)_n^{G2}$ wherein n^{G2} is 0 or 1, or

X^G is $-CO-NR^{8G}-(CH_2)_n^{G2}$ wherein n^{G2} is 1 and R^{8G} is isopropyl, or

X^G is $-CO-NR^{8G}-(CH_2)_n^{G2}$ wherein n^{G2} is 0 and R^{8G} is hydrogen or phenyl.

37. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



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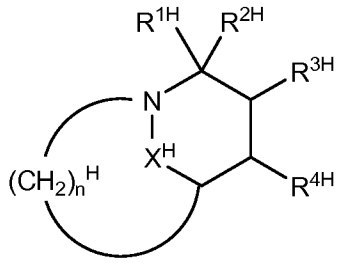
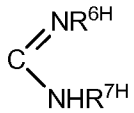
38. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



,

wherein, either:

a) R^{1H} is a radical selected from the group consisting of hydrogen, COOH, COOR, CN, $(CH_2)_n^{1H}R^{5H}$, $CONR^{6H}R^{7H}$ and



R^H is selected from the group consisting of an alkyl radical containing from 1 to 6 carbon atoms, optionally substituted with one or more halogen atoms or with a pyridyl radical; a $-CH_2$-alkenyl radical containing in total from 3 to 9 carbon atoms; a (poly)alkoxyalkyl group containing 1 to 4 oxygen atoms and 3 to 10 carbon atoms; an

aryl radical containing from 6 to 10 carbon atoms or an aralkyl radical containing from 7 to 11 carbon atoms, the nucleus of the aryl or aralkyl radical being optionally substituted with a radical selected from the group consisting of OH, NH_2, NO_2, alkyl containing from 1 to 6 carbon atoms, alkoxy containing from 1 to 6 carbon atoms and one or more halogen atoms;

R^{5H} is selected from the group consisting of COOH, CN, OH, NH_2, CO-N,

$R^{6H}R^{7H}$, $COOR^H$ and OR^H radicals, R^H being as defined above, R^{6H} and R^{7H} are individually selected from the group consisting of hydrogen, an alkyl radical containing from 1 to 6 carbon atoms, an alkoxy radical containing from 1 to 6 carbon atoms, an aryl radical containing from 6 to 10 carbon atoms, an aralkyl radical containing from 7 to 11 carbon atoms and an alkyl radical containing from 1 to 6 carbon atoms which is substituted with a pyridyl radical;

n^{1H} is equal to 1 or 2,

R^{3H} and R^{4H}, together with the carbons to which they are attached, form a phenyl or a 5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, which is substituted with one or more R^{1H} groups, R^{1H} being a radical selected from the group consisting of: $-(O)_a{}^H-(CH_2)_b{}^H-(O)_a{}^H-CONR^{6H}R^{7H}$, $-(O)_a{}^H-(CH_2)_b{}^H-OSO_3H$, $-(O)_a{}^H-(CH_2)_b{}^H-SO_3$, $-(O)_a{}^H-SO_2R^H$, $-(O)_a{}^H-SO_2-CHa^Hl_3$, $-(O)_a{}^H-(CH_2)_b{}^H-NR^{6H}R^{7H}$, $-(O)_a{}^H-(CH_2)_b{}^H-NH-COOR^H$, $-(CH_2)_b{}^H-COOH$, $-(CH_2)_b{}^H-COOR^H$, $-OR^{H"}$, OH, $-(CH_2)_b{}^H-$ phenyl, and $-(CH_2)_b{}^H-$5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur,

each of said phenyl and said heterocycle being optionally substituted with one or more substituents selected from halogen, alkyl containing from 1 to 6 carbon atoms, alkoxy containing from 1 to 6 carbon atoms and CF_3,

R^H, R^{6H} and R^{7H} being as defined above,

$R^{H"}$ being selected from alkyl radicals containing from 1 to 6 carbon atoms substituted with one or more radicals selected from hydroxy, protected hydroxy, oxo, halogen and cyano radicals,

a^H being equal to 0 or 1 and b being an integer from 0 to 6,

provided that, when $R^{1H}$is OH, R^{1H} is $CONR^{6H}R^{7H}$ in which one of R^{6H} and R^{7H} is an alkoxy containing from 1 to 6 carbon atoms; or

b) R^{4H} is hydrogen or $(CH_2)_n{}^{1H}{}_1$ R^{5H}, wherein $n^{1H}{}_1$, is 0, 1 or 2 and R^{5H} is as defined above,

and R^{1H} and R^{3H}, together with the carbons to which they are attached, form a substituted phenyl or heterocycle, as defined above;

and, in both cases a) and b),

R^{2H} is selected from the group consisting of hydrogen, halogen, R^H, $S(O)_{m^H}R^H$, OR^H, $NHCOR^H$, $NHCOOR^H$ and $NHSO_2R^H$, R being as defined above and m^H being 0, 1 or 2,

X^H is a divalent group -C(O)-B^H- linked to the nitrogen atom by the carbon atom,

B^H is a divalent group selected from 1) -O-$(CH_2)_{n"^H}$- linked to the carbonyl by the oxygen atom, 2) -NR^{8H}-$(CH_2)_{n"^H}$- and 3) -NR^{8H}-O- linked to the carbonyl by the nitrogen atom, $n"^H$ is 0 or 1 and R^{8H} is a radical selected from the group consisting of hydrogen, OH, R^H, OR^H, Y^H, OY^H, Y^{1H}, OY^{1H}, Y^{2H}, OY^{2H}, Y^{3H}, O-CH_2-CH_2-S(O-)m^H-R^H, $SiR^{aH}R^{bH}R^{cH}$ and $OSiR^{aH}R^{bH}R^{cH}$, wherein each of R^{aH}, R^{bH} and R^{cH} is a linear or branched alkyl containing from 1 to 6 carbon atoms or an aryl containing from 6 to 10 carbon atoms, and R^H and m^H are as defined above;

Y^H is selected from the group consisting of COH, COR^H, $COOR^H$, $CONH_2$, $CONHR^H$, CONHOH, $CONHSO_2R^H$, CH_2COOH, CH_2COOR^H, CHF-COOH, CHF-$COOR^H$, CF_2-COOH, CF_2-$COOR^H$, CN, CH_2CN, $CH_2CONHOH$, $CH_2CONHCN$, CH_2tetrazole, protected CH_2tetrazole, CH_2SO^{3H}, $CH_2SO_2R^H$, $CH_2PO(OR^H)_2$, $CH_2PO(OR^H)(OH)$, $CH_2PO(R^H)(OH)$ and $CH_2PO(OH)_2$;

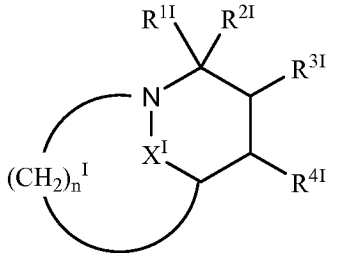
Y^{1H} is selected from the group consisting of SO_2R^H, SO_2NHCOH, SO_2NHCOR^H, $SO_2NHCOOR^H$, $SO_2NHCONHR^H$, $SO_2NHCONH_2$ and SO^{3H};

Y^{2H} is selected from the group consisting of $PO(OH)_2$, $PO(OR^H)_2$, $PO(OH)(OR^H)$ and $PO(OH)(R^H)$;

Y^{3H} is selected from the group consisting of tetrazole, tetrazole substituted with R^H, squarate, NH or NR^Htetrazole, NH or NR^Htetrazole substituted with R^H, $NHSO_2R^H$, $NR^HSO_2R^H$, CH_2tetrazole and CH_2tetrazole substituted with R^H, R^H being as defined above, and

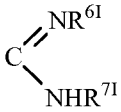
n^H is 1 or 2, or one of its salts with a base or an acid.

39. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, either:

a) R^{1I} is a radical selected from the group consisting of hydrogen, COOH, $COOR^I$, CN, $(CH_2)_{n'}{}^{I}R^{5I}$, $CONR^{6I}R^{7I}$ and



R^I is selected from the group consisting of an alkyl radical containing from 1 to 6 carbon atoms, optionally substituted with one or more halogen atoms or with a pyridyl radical; a $-CH_2$-alkenyl radical containing in total from 3 to 9 carbon atoms; a (poly)alkoxyalkyl group containing 1 to 4 oxygen atoms and 3 to 10 carbon atoms; an aryl radical containing from 6 to 10 carbon atoms or an aralkyl radical containing from 7 to 11 carbon atoms, the aryl or aralkyl radical being optionally substituted with a radical selected from the group consisting of OH, NH_2, NO_2, alkyl containing from 1 to 6 carbon atoms, alkoxy containing from 1 to 6 carbon atoms and one or more halogen atoms;

R^{5I} is selected from the group consisting of COOH, CN, OH, NH_2, $CO\text{-}NR^{6I}R^{7I}$, $COOR^I$ and OR^I radicals, R^I being as defined above,

R^{6I} and R^{7I} are individually selected from the group consisting of hydrogen, an alkyl radical containing from 1 to 6 carbon atoms, an alkoxy radical containing from 1 to 6 carbon atoms, an aryl radical containing from 6 to 10 carbon atoms, an aralkyl radical containing from 7 to 11 carbon atoms and an alkyl radical containing from 1 to 6 carbon atoms which is substituted with a pyridyl radical;

n'^I is equal to 1 or 2,

R^{3I} and R^{4I}, together with the carbons to which they are attached, form a phenyl or a 5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, which is substituted with one or more R'^I groups, R'^I being a radical selected from the group consisting of:

$-(O)_a{}^I\text{-}(CH_2)_b{}^I\text{-}(O)_a{}^ICONR^{6I}R^{7I}$, $-(O)_a{}^I\text{-}(CH_2)_b{}^I\text{-}OSO_3H$, $-(O)_a{}^I\text{-}(CH_2)_b{}^I\text{-}SO_3H$, $-(O)_a{}^I\text{-}SO_2R^I$, $-(O)_a{}^I\text{-}SO_2\text{-}CH_a{}^Il_3$, $-(O)_a{}^I\text{-}(CH_2)_b{}^I\text{-}NR^{6I}R^{7I}$, $-(O)_a{}^I\text{-}(CH_2)_b{}^I\text{-}NH\text{-}COOR^I$, $-(CH_2)_b{}^I\text{-}COOH$, $-(CH_2)_b{}^I\text{-}COOR^I$, $-OR''^I$, OH, $-(CH_2)_b{}^I$-phenyl, $-O\text{-}(CH_2)_2\text{-}O\text{-}CH_3$, $-O\text{-}CH_2$-(2,2-dimethyl-1,3-dioxolan-4-yl), -CO-NH phenyl,

-$(CH_2)_{b^I}$-5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, each of said phenyl and said heterocycle being optionally substituted with one or more substituents selected from halogen, alkyl containing from 1 to 6 carbon atoms, alkoxy containing from 1 to 6 carbon atoms and CF_3,

R^I, R^{6I} and R^{7I} being as defined above,

R''^I being selected from alkyl radicals containing from 1 to 6 carbon atoms substituted with one or more radicals selected from hydroxy, protected hydroxy, oxo, halogen and cyano radicals,

a^I being equal to 0 or 1 and b^I being an integer from 0 to 6,

provided that, when R'^I is OH, R^{1I} is $CONR^{6I}R^{7I}$ in which one of R^{6I} and R^{7I} is an alkoxy containing from 1 to 6 carbon atoms; or

b) R^{4I} is hydrogen or $(CH_2)_{n'^I_1}R^{5I}$, wherein n'^I_1, is 0, 1 or 2 and R^{5I} is as defined above,

and R^{1I} and R^{3I}, together with the carbons to which they are attached, form a substituted phenyl or heterocycle, as defined above;

and, in both cases a) and b), R^{2I} is selected from the group consisting of hydrogen, halogen, R^I, $S(O)_{m^I}R^I$, OR^I, $NHCOR^I$, $NHCOOR^I$ and $NHSO_2R^I$, R^I being as defined above and m^I being 0, 1 or 2,

X^I is a divalent group -C(O)-B^I- linked to the nitrogen atom by the carbon atom,

B^I is a divalent group selected from 1) $-NR^{8I}-(CH_2)_{n''^I}$-linked to the carbonyl by the nitrogen atom, n''^I is 0 and R^{8I} is a radical selected from the group consisting of hydrogen, OH, R^I, OR^I, Y^I, OY^I, Y^{1I}, OY^{1I}, Y^{2I}, OY^{2I}, Y^{3I}, $O\text{-}CH_2\text{-}CH_2\text{-}S(O\text{-})_{m^I}\text{-}R^I$, $SiR^{aI}R^{bI}R^{cI}$ and $OSiR^{aI}R^{bI}R^{cI}$, wherein each of R^{aI}, R^{bI} and R^{cI} is a linear or branched alkyl containing from 1 to 6 carbon atoms or an aryl containing from 6 to 10 carbon atoms, and R^I and m^I are as defined above;

Y^I is selected from the group consisting of COH, COR^I, $COOR^I$, $CONH_2$, $CONHR^I$, CONHOH, $CONHSO_2R^I$, CH_2COOH, CH_2COOR^I, CHF-COOH, CHF-$COOR^I$, CF_2-COOH, CF_2-$COOR^I$, CN, CH_2CN, $CH_2CONHOH$, $CH_2CONHCN$, CH_2tetrazole, protected CH_2tetrazole, CH_2SO_3H, $CH_2SO_2R^I$, $CH_2PO(OR^I)_2$, $CH_2PO(OR^I)(OH)$, $CH_2PO(R^I)(OH)$ and $CH_2PO(OH)_2$;

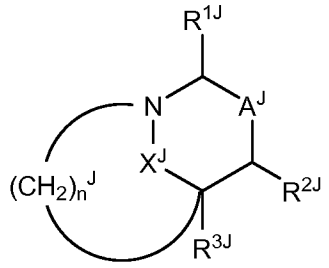
Y^{1I} is selected from the group consisting of SO_2R^I, SO_2NHCOH, SO_2NHCOR^I, $SO_2NHCOOR^I$, $SO_2NHCONHR^I$, $SO_2NHCONH_2$ and SO_3H;

Y^{2I} is selected from the group consisting of $PO(OH)_2$, $PO(OR^I)_2$, $PO(OH)(OR^I)$ and $PO(OH)(R^I)$;

Y^{3I} is selected from the group consisting of tetrazole, tetrazole substituted with R^I, squarate, NH or NR^Itetrazole, NH or NR^Itetrazole substituted with R^I, $NHSO_2R^I$, $NR^ISO_2R^I$, CH_2tetrazole and CH_2tetrazole substituted with R^I, R^I being as defined above,

and n^I is 1, or one of its salts with a base or an acid.

40. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



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wherein, R^{1J} is hydrogen, COOH, CN, $COOR^J$, $CONR^{6J}R^{7J}$, $(CH_2)_{n'}{}^JR^{5J}$ or $C(=NR^{6J})NHR^{7J}$;

R^J is selected from the group consisting of alkyl containing 1 to 6 carbon atoms optionally substituted by a pyridyl or carbamoyl radical, -CH_2-alkenyl containing 3 to 9 carbon atoms, aryl containing 6 to 10 carbon atoms and aralkyl containing 7 to 11 carbon atoms, wherein the nucleus of said aryl or aralkyl is optionally substituted by OH, NH_2, NO_2, alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms or by one or more halogen atoms;

R^{6J} and R^{7J} are identical or different and are independently selected from the group consisting of hydrogen, alkyl containing 1 to 6 carbon atoms, aryl containing 6 to 10 carbon atoms and aralkyl containing 7 to 11 carbon atoms optionally substituted by a carbamoyl, ureido or dimethylamino radical, and alkyl containing 1 to 6 carbon atoms substituted by a pyridyl radical;

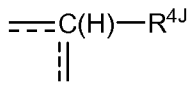
n'^J is 1 or 2;

R^{5J} is selected from the group consisting of COOH, CN, OH, NH_2, $CO\text{-}NR^{6J}R^{7J}$, $COOR^J$, OR^J, OCHO, $OCOR^J$, $OCOOR^J$, $OCONHR^J$, $OCONH_2$, NHR^J, NHCOH, $NHCOR^J$, $NHSO_2R^J$, $NH\text{-}COOR^J$, $NH\text{-}CO\text{-}NHR^J$ and $NHCONH_2$ wherein R^J, R^{6J} and R^{7J} are as defined above;

R^{2J} is hydrogen or $(CH_2)_{n'}{}^J{}_1R^{5J}$ wherein $n'^J{}_1$ is 0, 1 or 2, and R^{5J} is as defined above;

R^{3J} is hydrogen or alkyl containing 1 to 6 carbon atoms;

A^J is a



group wherein R^{4J} is hydrogen or $(CH_2)_{n'J_1}R^{5J}$ and n'^J_1 and R^{5J} are as defined above, and the dotted line is an optional bond with one of the two carbons which carry R^{1J} and R^{2J};

n^J is 1;

X^J is a divalent -C(O)-B^J- group linked to the nitrogen atom by the carbon atom wherein B^J is a divalent -O-$(CH_2)_{n''^J}$- group linked to the carbonyl by the oxygen atom, a divalent -NR^{8J}-$(CH_2)_{n''^J}$- or -NR^{8J}-O- group linked to the carbonyl by the nitrogen atom, n''^J is 0, and wherein B^J is -NR^{8J}-$(CH_2)_{n''^J}$-, R^{8J} is selected from the group consisting of hydrogen, OH, R^J, OR^J, Y^J, OY^J, Y^{1J}, OY^{1J}, Y^{2J}, OY^{2J}, Y^{3J}, $OCH_2CH_2SO_{m^J}R^J$, $OSiR^{aJ}R^{bJ}R^{cJ}$ and $SiR^{aJ}R^{bJ}R^{cJ}$ and wherein B^J is -NR^{8J}-O-, R^{8J} is selected from the group consisting of hydrogen, R, Y^J, Y^{1J}, Y^{2J}, Y^{3J} and $SiR^{aJ}R^{bJ}R^{cJ}$, wherein R^{aJ}, R^{bJ} and R^{cJ} is each independently a linear or branched alkyl containing 1 to 6 carbon atoms or aryl containing 6 to 10 carbon atoms, R^J is as defined above and m^J is 0, 1 or 2;

Y^J is selected from the group consisting of COH, COR^J, $COOR^J$, $CONH_2$, $CONHR^J$, CONHOH, $CONHSO_2R^J$, CH_2COOH, CH_2COOR^J, $CH_2CONHOH$, $CH_2CONHCN$, CH_2tetrazole, protected CH_2tetrazole, CH_2SO_3H, $CH_2SO_2R^J$, $CH_2PO(OR^J)_2$, $CH_2PO(OR^J)(OH)$, $CH_2PO(R^J)(OH)$ and $CH_2PO(OH)_2$;

$Y_1{}^J$ is selected from the group consisting of SO_2R^J, SO_2NHCOH, SO_2NHCOR^J, $SO_2NHCOOR^J$, $SO_2NHCONHR^J$, $SO_2NHCONH_2$ and SO_3H;

$Y_2{}^J$ is selected from the group consisting of $PO(OH)_2$, $PO(OR^J)_2$, $PO(OH)(OR^J)$ and $PO(OH)(R^J)$;

$Y_3{}^J$ is selected from the group consisting of tetrazole, tetrazole substituted by R^J, squarate, NH or NR^J-tetrazole, NH or NR^J-tetrazole substituted by R^J, $NHSO_2R^J$ and $NRSO_2R^J$ wherein R^J is as defined above; and

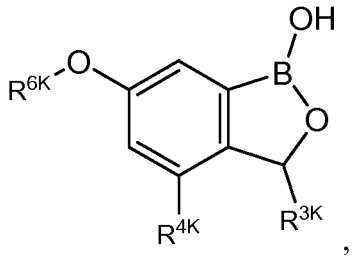
R^{1J}, R^{2J} and R^{3J} are not simultaneously hydrogen when n^J is 1,

R^{4J} is hydrogen and

X^J is -C(O)-O-$(CH_2)_{n''^J}$ wherein n''^J is 0, or

X^J is -CO-NR^{8J}-$(CH_2)_{n''^J}$ wherein n''^J is 0 and R^{8J} is hydrogen or phenyl.

41. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, R^{3K} is $-(CH_2)_m{}^K C(O)OR^{3aK}$,

m^K is an integer selected from 1, 2, 3, 4, 5, or 6;

R^{3aK} is selected from the group consisting of H, unsubstituted alkyl, and phenyl substituted alkyl;

R^{4K} is selected from the group consisting of unsubstituted alkyl, $-OR^{4bK}$, $-(CH_2)_n{}^K$-O-$(CH_2)p^KCH_3$, and halogen

n^K is an integer selected from 1, 2, 3, 4, 5, or 6;

p^K is an integer selected from 0, 1, 2, 3, 4, 5, or 6;

R^{4bK} is H or substituted or unsubstituted alkyl;

R^{6K} is selected from the group consisting of H, substituted or unsubstituted alkyl, $-C(O)OR^{6aK}$, $-C(O)NR^{6aK}R^{6bK}$, $-S(O_2)R^{6cK}$, and A^K;

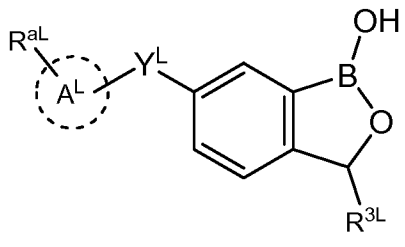
R^{6aK} is H or unsubstituted alkyl;

R^{6bK} is H or unsubstituted alkyl;

R^{6cK} is selected from the group consisting of unsubstituted alkyl, NH_2 and heteroaryl, optionally substituted with unsubstituted alkyl A is selected from the group consisting of substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

or a salt, hydrate or solvate thereof.

42. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, A^L is a member selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

Y^L is a member selected from O and $-S(O)_2NH-$

wherein the sulfur in $-S(O)_2NH-$ is covalently attached to A^L;

R^{3L} is a member selected from H, cyano and substituted alkyl;

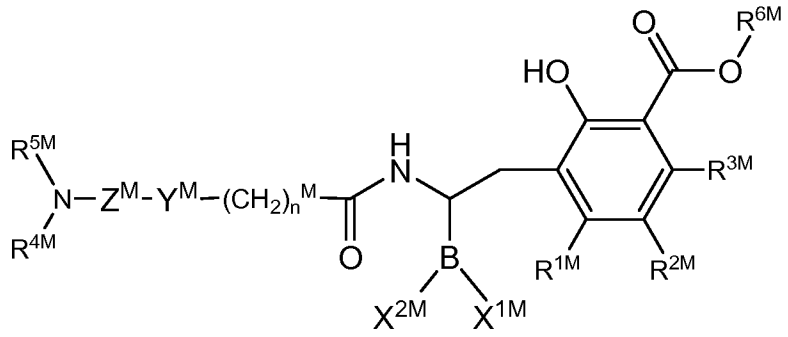
R^{aL} is a member selected from H, $-OR^{10L}$, $-NR^{10L}R^{11L}$, $-SR^{10L}$, $-S(O)R^{10L}$, $-S(O)_2R^{10L}$, $-S(O)_2NR^{10L}R^{11L}$, $-C(O)R^{10L}$, $-C(O)OR^{10L}$, $-C(O)NR^{10L}R^{11L}$, nitro, cyano, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

each R^{10L} and each R^{11L} is a member independently selected from H, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

with the proviso that R^{10L} and R^{11L}, together with the nitrogen to which they are attached, are optionally combined to form a 5- to 7- membered substituted or unsubstituted heterocycloalkyl ring; with the proviso that when Y^L is O, R^L is a member selected from cyano and substituted alkyl;

with the proviso that when Y^L is $-S(O)_2NH-$, R^{3L} is H, and R^{aL} is not H or unsubstituted alkyl or halosubstituted alkyl and salts thereof.

43. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



,

wherein, R^{1M}, R^{2M}, and R^{3M} are independently hydrogen, or selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, optionally substituted: C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 alkenyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocyclyl, amino, sulfide, and sulfone;

n^M is O, 1, or 2;

Y^M is selected from the group consisting of: (a) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy,

heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino, imino, amidino, sulfido, and sulfoxido, (b) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino, imino, amidino, sulfido, and sulfoxido, and (c) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, imino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said imino group, amidino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said amidino group, sulfido, and sulfoxido;

R^{4M} is hydrogen, or selected from the group consisting of: (a) C_1-C_5 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: alkyl, alkenyl, alky ny I_1 cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_5 carbons comprise part of said oxyimino group, imino wherein any of the C_1-C_5 carbons comprise part of said imino group, amidino wherein any of the C_1-C_5 carbons comprise part of said amidino group, sulfido, and sulfoxido, (b) C_3-C_6 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, imino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said imino group, amidino wherein any of the carbons of the cycloalkyl group

other than the one attached to the rest of the molecule comprise part of said amidino group, sulfide and sulfoxido, (c) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, alkenyf, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino, imino, amidino, sulfido, and sulfoxido, and (d) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, imino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said imino group, amidino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said amidino group, sulfido, and sulfoxido;

R^{5M} is a lone pair of electrons, hydrogen, or selected from the group consisting of: (a) C_1-C_5 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_5 carbons comprise part of said oxyimino group, imino wherein any of the C_1-C_5 carbons comprise part of said imino group, amidino wherein any of the C_1-C_5 carbons comprise part of said amidino group, sulfido, and sulfoxido, (b) C_3-C_6 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, imino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said imino group, amidino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise

part of said amidino group, sulfido, and sulfoxido, (c) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino, imino, amidino, sulfido, and sulfoxido, and (d) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, oxo, optionally substituted: heteroaryl, heterocyclyl, alkoxy, cycloalkoxy, heterocyclyloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, imino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said imino group, amidino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said amidino group, sulfido, and sulfoxido;

or R^{4M} and Y^{M} together form a ring of between 5 and 7 atoms where said ring is optionally fused or spiro in relation to the ring system of Y^{M}, said ring optionally being partially saturated or aromatic and optionally containing 1-2 additional heteroatoms selected from the group consisting of N, O, S, and a combination thereof;

or R^{4M} and R^{5M} together form a ring of between 3 and 7 atoms where said ring is optionally substituted, said ring optionally being saturated, partially unsaturated or aromatic and optionally containing 1-2 additional heteroatoms selected from the group consisting of N, O, S, and a combination thereof;

R^{6M} is hydrogen or an ester prodrug of the carboxylic acid;

Z^{M} is a bond;

or Z^{M} is optionally substituted: C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 sulfido, C_3-C_6 cycloalkyl, C_3-C_6 heterocyclyl where the bond to Y is through a carbon atom of said heterocyclyl ring, heteroaryl where the bond to Y is through a carbon atom of said heteraryl ring, oxyimino, imino, or amidino where the carbon of said oxyimino, imino, or amidino group is attached to Y;

or Z^{M} and Y^{M} together form a ring of 5-7 atoms where said ring is optionally fused or spiro in relation to the ring system of Y^{M}, said ring optionally being partially saturated or aromatic and optionally containing 1-3 heteroatoms selected from the group consisting of N, O, S, and a combination thereof;

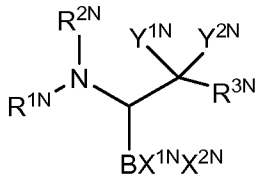
or Z^M and R^{4M} together form a ring of 4-7 atoms where said ring optionally is saturated, partially unsaturated, or aromatic and optionally contains 1-2 additional heteroatoms selected from the group consisting of N, O, S, and a combination thereof;

X^{1M} and X^{2M} are independently hydroxyl, halogen, $NR^{4M}R^{5M}$, C_1-C_6 alkoxy, or when taken together X^{1M} and X^{2M} form a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms selected from the group consisting of N, O, S, and a combination thereof, or when taken together X^{1M} and X^{2M} form a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms selected from the group consisting of N, O, S, and a combination thereof, or when taken together X^{1M} and X^{2M} form a cyclic boron amide-ester where said chain contains from 2-20 carbon atoms and, optionally, 1-3 heteroatoms selected from the group consisting of N, O, S, and a combination thereof, or X^{1M} is hydroxyl and X^{2M} is replaced by the ortho-hydroxyl oxygen of the phenyl ring such that a 6-membered ring is formed;

or a salt thereof;

provided that when R^{1M}, R^{2M}, R^{3M}, R^{4M}, R^{5M} and R^{6M} are hydrogen, X^{1M} and X^{2M} are hydroxyl, n^M is 0, Y^M is phenyl, and Z^M is CH_2 then Z^M cannot be at the meta-position of the phenyl ring relative to the rest of the molecule.

44. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, R^{1N} is $-C(O)R^{4N}$; $-C(O)NR^{4N}R^{5N}$; $-C(O)OR^{4N}$; $-S(O)_2R^{4N}$, $-C(=NR^{4N}R^{5N})R^{4N}$, $-C(=N\ R^{4N}R^{5N})\ N\ R^{4N}R^{5N}$, hydrogen, or is selected from the group consisting of: (a) aryl group substituted with from O to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (b) heteroaryl group substituted with from O to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl,

heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (c) heterocyclic group substituted with from O to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido;

R^{2N} is hydrogen, or is selected from the group consisting of: (a) C_1-C_6 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_6 carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_7 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido,

and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

R^{3N} is an aryl or heteroaryl group substituted with from 1 to 4 substituents selected from the group consisting of hydroxyl, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, amino, aminocarbonyl, carbonyl, aminosulfonyl, alkylaryl, aryl, aryloxy, carboxyl, cyano, guanidino, halogen, heteroaryl, heterocyclyl , sulfido, sulfonyl, sulfoxido, sulfonic acid, sulfate, and thiol, provided that, when one of the substituents is a carboxylic acid group located at the 3-position relative to the group containing Y^{1N} and Y^{2N}, one of the remaining substituents is not a hydroxyl or amino group located at the 2- or 6-position relative to the group containing Y^{1N} and Y^{2N};

R^{4N} is selected from the group consisting of: (a) C_1-C_{10} alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_{10} carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_{10} cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl,

arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

R^{5N} is hydrogen or is selected from the group consisting of: (a) C_1-C_6 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_{10} carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_7 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl,

arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

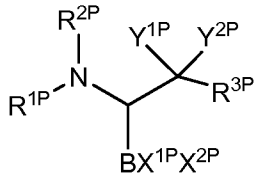
X^{1N} and X^{2N} are independently hydroxyl, halogen, $NR^{4N}R^{5N}$, C_1-C_6 alkoxy, or when taken together X^{1N} and X^{2N} form a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or when taken together X^{1N} and X^{2N} form a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or when taken together X^{1N} and X^{2N} form a cyclic boron amide-ester where said chain contains from 2-20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or X^{1N} and $R^{1N}N$ together form a cyclic ring where said ring contains 2 to 10 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, and X^{2N} is hydroxyl, halogen, $NR^{4N}R^{5N}$, C_1-C_6 alkoxy, or X^{1N} and R^{3N} together form a cyclic ring where said ring contains 2 to 10 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, and X^{2N} is hydroxyl, halogen, $NR^{4N}R^{5N}$, or C_1-C_6 alkoxy;

Y^{1N} and Y^{2N} are independently hydrogen, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, amino, aminosulfonyl, aminocarbonyl, carbonyl, alkylaryl, aryl, aryloxy, carboxyl, cyano, halogen, heteroaryl, heteroaryloxy, heterocyclyl, sulfido, sulfonyl, or sulfoxido, or taken together Y^{1N} and Y^{2N} form a cyclic structure containing from 3-12 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S;

or a salt thereof;

provided that, when $R^{1N}N$ is $-C(O)R^{4N}$, $R^{2N}N$ is hydrogen, R^{3N} is a phenyl group having one substitution consisting of a carboxylic acid group located at the 3-position relative to the group containing Y^{1N} and Y^{2N}, X^{1N} and X^{2N} are hydroxyl, and Y^{1N} and Y^{2N} are hydrogen, R^{4N} is not unsubstituted C_1 alkyl or C_1 alkyl having one substitution consisting of a phenyl group.

45. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, R^{1P} is $-C(O)R^{4P}$; $-C(O)NR^{4P}R^{5P}$; $-C(O)OR^{4P}$; $-S(O)_2R^{4P}$, $-C(=NR^{4P}R^{5P})R^{4P}$, $-C(=NR^{4P}R^{5P})NR^{4P}R^{5P}$, hydrogen, or is selected from the group consisting of: (a) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (b) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (c) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido;

R^{2P} hydrogen, or is selected from the group consisting of: (a) C_1-C_6 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy,

aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_6 carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_7 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxide), and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

R^{3P} is an aryl or heteroaryl group substituted with from 1 to 4 substituents wherein one of the substituents is a hydroxyl or amino group located at the 2 position relative to the group containing Y^{1P} and Y^{2P}, and wherein the remaining substituents are selected from the group consisting of hydroxyl, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, amino, aminocarbonyl, carbonyl, aminosulfonyl, alkylaryl, aryl, aryloxy,

carboxyl, cyano, guanidino, halogen, heteroaryl, heterocyclyl , sulfido, sulfonyl, sulfoxido, sulfonic acid, sulfate, and thiol;

R^{4P} is selected from the group consisting of: (a) C_1-C_{10} alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_{10} carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_{10} cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the

heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

R^{5P} is hydrogen or is selected from the group consisting of: (a) C_1-C_6 alkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the C_1-C_{10} carbons comprise part of said oxyimino group, sulfido, and sulfoxido, (b) C_3-C_7 cycloalkyl any carbon of which can be substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the cycloalkyl group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido, (c) aryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, (d) heteroaryl group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, sulfido, and sulfoxido, and (e) heterocyclic group substituted with from 0 to 3 substituents selected from the group consisting of hydroxyl, halogen, carboxyl, cyano, thiol, sulfonic acid, sulfate, optionally substituted: alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, alkylheteroaryl, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amino, carbonyl, aminocarbonyl, oxycarbonyl, aminosulfonyl, sulfonyl, guanidino, oxyimino wherein any of the carbons of the

heterocyclic group other than the one attached to the rest of the molecule comprise part of said oxyimino group, sulfido, and sulfoxido;

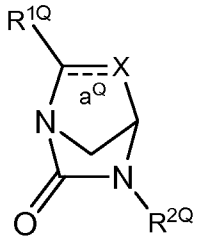
X^{1P} and X^{2P} are independently hydroxyl, halogen, $NR^{4P}R^{5P}$, C_1-C_6 alkoxy, or when taken together X^{1P} and X^{2P} form a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or when taken together X^{1P} and X^{2P} form a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or when taken together X^{1P} and X^{2P} form a cyclic boron amide-ester where said chain contains from 2-20 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, or X^{1P} and R^{1P} together form a cyclic ring where said ring contains 2 to 10 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, and X^{2P} is hydroxyl, halogen, $NR^{4P}R^{5P}$, C_1-C_6 alkoxy, or X^{1P} and R^{3P} together form a cyclic ring where said ring contains 3 to 10 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S, and X^{2P} is hydroxyl, halogen, $NR^{4P}R^{5P}$, or C_1-C_6 alkoxy;

Y^{1P} and Y^{2P} are independently hydrogen, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, amino, aminosulfonyl, aminocarbonyl, carbonyl, alkylaryl, aryl, aryloxy, carboxyl, cyano, halogen, heteroaryl, heteroaryloxy, heterocyclyl, sulfido, sulfonyl, or sulfoxido, or taken together Y^{1P} and Y^{2P} form a cyclic structure containing from 3-12 carbon atoms and, optionally, 1-3 heteroatoms which can be O, N, or S;

or a salt thereof;

provided that, when R^{1P} is $-C(O)R^{4P}$, R^{2P} is hydrogen, R^{3P} is a phenyl group having two substituents consisting of a hydroxyl at the 2-position and a carboxylic acid at the 3-position relative to the group containing Y^{1P} and Y^{2P}, X^{1P} and X^{2P} are hydroxyl or X^{1P} is hydroxyl and X^{2P} is replaced by the ortho-hydroxyl oxygen of R^{3P} such that a 6-membered ring is formed, and Y^{1P} and Y^{2P} are hydrogen, R^{4P} is not unsubstituted C_1 alkyl.

46. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



or a pharmaceutically acceptable salt thereof, wherein the bond identified as a^Q is a single bond or a double bond;

when bond a^Q is a single bond, X is CH_2, CH_2CH_2, $CH_2CH_2CH_2$, CH-CH_5, CH_2-CH-CH, or CH=CH-CH_2;

when bond a^Q is a double bond, X is CH, CH-CH_2, or CH-CH=CH;

R^{1Q} is $C(O)N(R^{3Q})R^{4Q}$, $C(O)OR^{3Q}$, or $C(O)OR^{5Q}$;

R^{2Q} is SO_3M^Q, OSO_3M^Q, SO_2NH_2, PO_3M^Q, OPO_3M^Q, $CH_2CO_2M^Q$, $CF_2CO_2M^Q$, or CF_3;

M^Q is H or a pharmaceutically acceptable cation;

R^{3Q} is (1) C 1-8 alkyl substituted with a total of from 1 to 4 substituents selected from the group consisting of zero to 2 $N(R^{AQ})R^{BQ}$, zero to 2 R^{CQ}, and zero to 1 of $AryA^Q$, $HetA^Q$, or $HetB^Q$, (2) $CycA^Q$, (3) $HetA^Q$, (4) $AryA^Q$, (5) $HetB^Q$, or (6) $AryB^Q$;

R^{4Q} is H or C 1-8 alkyl optionally substituted with $N(R^{AQ})R^{BQ}$;

or alternatively, when R^{1Q} is $C(O)N(R^{3Q})R^{4Q}$, R^{3Q} and R^{4Q} together with the N atom to which they are both attached form a 4- to 9-membered, saturated monocyclic ring optionally containing 1 heteroatom in addition to the nitrogen attached to R^{3Q} and R^{4Q} selected from N, O, and S, where the S is optionally oxidized to S(O) or $S(O)_2$; wherein the monocyclic ring is optionally fused to, bridged with, or spiro to a 4- to 7-membered, saturated heterocyclic ring containing from 1 to 3 heteroatoms independently selected from N, O and S, where the S is optionally oxidized to S(O) or $S(O)_2$, to form a bicyclic ring system, wherein the monocyclic ring or the bicyclic ring system so formed is optionally substituted with 1 or 2 substituents each of which is independently: (1) C_{1-6} alkyl, (2) C_{1-6} fluoroalkyl, (3) $(CH_2)_{1-2}G$, wherein G is OH, O-C_{1-6} alkyl, O-C_{1-6} fluoroalkyl, $N(R^{AQ})R^{BQ}$, $C(O)N(R^{AQ})R^{BQ}$, $C(O)R^{AQ}$, CO_2R^{AQ}, or SO_2R^{AQ}, (4) O-C_{1-6} alkyl, (5) O-C_{1-6} fluoroalkyl, (6) OH, (7) oxo, (8) halogen, (9) $N(R^{AQ})R^{BQ}$, (10) $C(O)N(R^{AQ})R^{BQ}$, (11) $C(O)R^{AQ}$, (12) C(O)-C_{1-6} fluoroalkyl, (13) $C(O)OR^{AQ}$, or (14) $S(O)_2R^{AQ}$;

R^{5Q} is C_{1-8} alkyl substituted with 1 or 2 substituents each of which is independently $N(R^{AQ})C(O)$-$AryA^Q$;

$CycA^Q$ is C_{4-9} cycloalkyl which is optionally substituted with a total of from 1 to 4 substituents selected from zero to 2 $(CH_2)_n{}^QN(R^{AQ})R^{BQ}$ and zero to 2 $(CH_2)_n{}^QR^{CQ}$;

$HetA^Q$ is a 4- to 9-membered saturated or mono-unsaturated heterocyclic ring containing from 1 to 3 heteroatoms independently selected from N, O and S, wherein any ring S is optionally oxidized to S(O) or S $(O)_2$ and either 1 or 2 ring carbons are optionally oxidized to C(O); wherein the ring is optionally fused with a C_{3-7} cycloalkyl; and wherein the optionally fused, saturated or mono-unsaturated heterocyclic ring is

optionally substituted with a total of from 1 to 4 substituents selected from zero to 2 $(CH_2)_n{}^QN(R^{AQ})R^{BQ}$ and zero to 2 $(CH_2)_n{}^QR^{CQ}$;

$AryA^Q$ is phenyl which is optionally substituted with a total of from 1 to 4 substituents selected from zero to 2 $(CH_2)_n{}^QN(R^{AQ})R^{BQ}$ and zero to 2 $(CH_2)_n{}^QR^{CQ}$;

$HetB^Q$ is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms selected from 1 to 3 N atoms, zero or 1 O atom, and zero or 1 S atom; wherein the heteroaromatic ring is optionally fused with a 5- to 7-membered, saturated heterocyclic ring containing 1 or 2 heteroatoms independently selected from N, O and S, wherein any ring S is optionally oxidized to S(O) or $S(O)_2$ and either 1 or 2 non-fused ring carbons are optionally oxidized to C(O); and wherein the optionally fused heteroaromatic ring is optionally substituted with a total of from 1 to 4 substituents selected from zero to 2 $(CH_2)_n{}^QN(R^{AQ})R^{BQ}$ and zero to 2 $(CH_2)_n{}^QR^{CQ}$;

$AryB^Q$ is a bicyclic ring system which is phenyl fused with a 5- to 7-membered saturated heterocyclic ring containing from 1 to 3 heteroatoms independently selected from N, O and S, wherein any ring S is optionally oxidized to S(O) or $S(O)_2$, and wherein the bicyclic ring system is optionally substituted with a total of from 1 to 4 substituents selected from zero to 2 2 $(CH_2)_n{}^QN(R^{AQ})R^{BQ}$ and zero to 2 $(CH_2)_n{}^QR^{CQ}$;

each n^Q is independently an integer which is 0, 1, 2, or 3;

each R^{AQ} is independently H or C_{1-8} alkyl;

each R^{BQ} is independently H or C_{1-8} alkyl;

each R^{CQ} is independently C_{1-6} alkyl, OH, O-C_{1-8} alkyl, OC(O)-C_{1-8} alkyl, $C(=NH)NH_2$, NH-$C(=NH)NH_2$, halogen, CN, $C(O)R^{AQ}$, $C(O)OR^{AQ}$, $C(O)N(R^{AQ})R^{BQ}$, SO_2R^{AQ}, $SO_2N(R^{AQ})R^{BQ}$, pyridyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl; and

provided that:

(A) when R^{1Q} is $C(O)OR^{3Q}$ and R^{3Q} is $AryA^Q$, then $AryA^Q$ is not (i) unsubstituted phenyl, (ii) phenyl substituted with NH_2, (iii) phenyl substituted with OH, (iii) phenyl substituted with O-C_{1-6} alkyl, (iv) phenyl substituted with one or more halogens, or (v) phenyl substituted with C_{1-6} alkyl;

(B) when R^{1Q} is $C(O)OR^{3Q}$ and R^{3Q} is C_{1-6} alkyl substituted with $HetB^Q$, then $HetB^Q$ is not pyridyl;

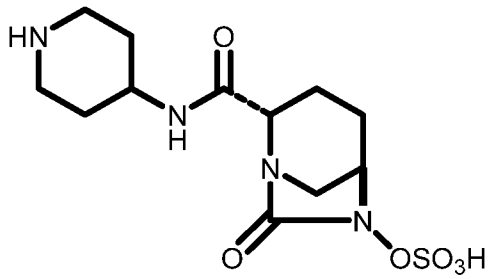
(C) when R^{1Q} is $C(O)OR^{3Q}$ and R^{3Q} is CH_2-$AryA^Q$ or CH_2CH_2-$AryA^Q$, then $AryA^Q$ is not (i) unsubstituted phenyl, (ii) phenyl substituted with NH_2, OH, O-C_{1-6} alkyl, or C_{1-6} alkyl, or (iii) phenyl substituted with one or more halogens;

(D) when R^{1Q} is $C(O)N(R^{3Q})R^{4Q}$, R^{3Q} is $AryA^Q$, CH_2-$AryA^Q$ or CH_2CH_2-$AryA^Q$, and R^{4Q} is H or C_{1-6} alkyl, then $AryA^Q$ is not unsubstituted phenyl, phenyl substituted with $N(CH_3)_2$, or phenyl substituted with $C(O)NH_2$;

(E) when R^{1Q} is $C(O)N(R^{3Q})R^{4Q}$, R^{3Q} is C_{1-6} alkyl substituted with $HetB^Q$, and R^{4Q} is H or C_{1-6} alkyl then $HetB^Q$ is not pyridyl; and

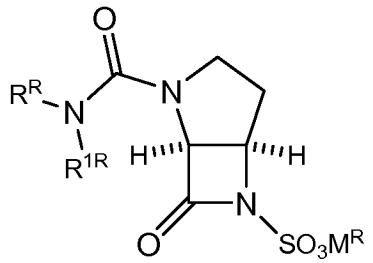
(F) when R^{1Q} is $C(O)OR^{3Q}$ and R^{3Q} is C_{1-6} alkyl substituted with R^{CQ}, then R^{CQ} is not $C(O)NH_2$.

47. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



MK-7655

48. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



or a pro-drug or pharmaceutically acceptable salt thereof,

wherein, R^R represents a 7-, 8-, or 9-membered saturated or unsaturated ring optionally containing from 1 to 3 heteroatoms independently selected from N, O and S, wherein the ring is optionally substituted with one or more R^{aR} groups;

R^{1R} represents hydrogen or methyl;

each R^{aR} independently represents hydrogen, C_{1-6} alkyl, halo, $-(CH_2)_n{}^RCN$, $-(CH2)_n{}^RNO_2$, $-(CH_2)_n{}^ROR^{bR}$, $-(CH_2)_n{}^RSR^{bR}$, $-(CH_2)_n{}^RN(R^{bR})_2$, $-(CH_2)_n{}^RC(O)N(R^{bR})_2$, $-(CH_2)_n{}^RSO_2N(R^{bR})_2$, $-(CH_2)_n{}^RCO_2R^{bR}$, $-(CH_2)nC(O)R^{bR}$, $-(CH_2)_n{}^ROC(O)R^{bR}$, $-(CH_2)_n{}^RNHC(O)R^{bR}$, $-(CH_2)_n{}^RNHC(O)_2R^{bR}$, $-(CH_2)_n{}^RNHSO_2R^{bR}$, $-(CH_2)_n{}^RC(=NH)NH_2$, or $-(CH_2)_n{}^RC(=NH)H$; or two R^{aR} groups on the same ring carbon atom are optionally taken together to form oxo; or two R^{aR} groups on the same ring sulfur atom are

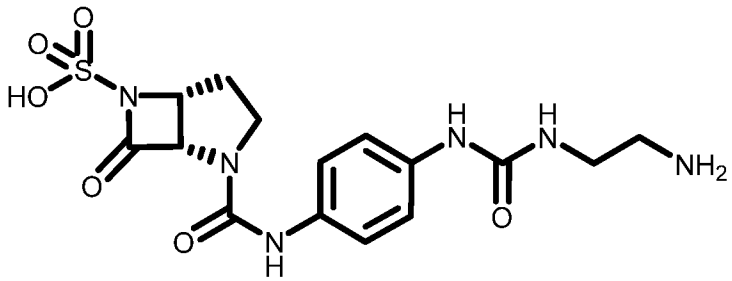
optionally taken together with the sulfur to represent SO; or four R^{aR} groups on the same ring sulfur atom are optionally taken together with the sulfur to represent SO_2;

each n^R is independently 0, 1, 2, 3, or 4;

each R^{bR} independently represents hydrogen or C_{1-4} alkyl; and

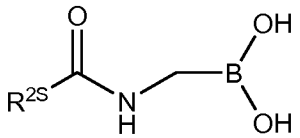
M^R represents hydrogen or a pharmaceutically acceptable cation or, when the compound contains an internal base which is capable of being protonated by a sulfonic acid, M^R is optionally a negative charge.

49. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:

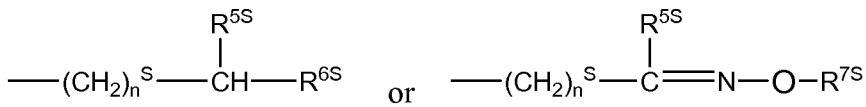


BAL-29880

50. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, R^{2S} is H, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkyl-cycloalkyl, heteroalkyl-cycloalkyl, alkyl-heterocycloalkyl, heteroalkyl-heterocycloalkyl, alkenyl, heteroalkenyl, cyclic alkene, heterocyclic alkene, alkyl-cyclic alkene, heteroalkyl-cyclic alkene, cyclic alkene-alkyl, cyclic alkene-heteroalkyl, alkyl-heterocyclic alkene, heterocyclic alkene-alkyl, heterocyclic alkene-heteroalkyl, heteroalkyl-heterocyclic alkene, alkyl-O-cyclic alkene, alkyl-O-heterocyclic alkene, alkyl-S-cyclic alkene, alkyl-S-heterocyclic alkene, or



each R^{2S} may be unsubstituted or substituted with one or more R^{3S} groups;

each R^{3S} is independently alkyl, heteroalkyl, cyclic alkene, cyclic alkene substituted with one or more R^{4S} groups, heterocyclic alkene, heterocyclic alkene substituted with one or more R^{4S} groups, halogen, $-NH_2$, =NH, =N, =N-OH, =O, -OH, -

O-C(O)H, -O-alkyl,-COOH, -$(CH_2)_m^S$-COOH, =CH-$(CH_2)_m^S$-COOH, -CN, =N-O-CH_3, =N-O-$C(CH_3)_2$-COOH, =N-O-$C(CH_3)_2$-C(O)-O-alkyl, -$(CH_2)_m^S$-NH_2, =C(COOH)-C(O)-NH_2, -C(O)-O-alkyl, -C(O)-O-cyclic alkene, -S-alkyl, -SO_3H, or -SO_2-CH_3;

each R^{4S} is independently alkyl, halogen, =NH, -NH_2,-$(CH_2)_m^S$-NH_2, =O, -OH, -$(CH_2)_m^S$-OH, -COOH, -$(CH_2)_m^S$-COOH, -C(=O)NH_2, -SO_3H, or -SO_2-CH_3;

R^{5S} is cyclic alkene or heterocyclic alkene, each of which may be unsubstituted or substituted with one or more R^{4S} groups;

R^{6S} is alkyl or heteroalkyl, each of which may be unsubstituted or substituted with one or more R^{4S} groups;

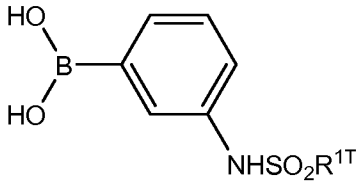
R^{7S} is H or R^{7S} is alkyl or heteroalkyl, each of which may be unsubstituted or substituted with one or more R^{4S} groups;

m^S is 1-4; and

n^S is 0-2;

or a pharmaceutically-acceptable salt thereof.

51. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, R^{1T} is N-lower alkyl, a cyclic alkene or a heterocyclic alkene, wherein the cyclic alkene and heterocyclic alkene may be substituted with one or more substituents R^{2T}; and

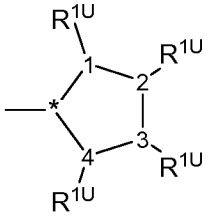
each R^{2T} is independently H, a halogen atom, lower, alkyl, lower alkyl substituted with one or more halogen atoms, NH_2, NO, NO_2, N-lower alkyl, N-lower alkyl substituted with one or more halogen atoms, OH, O-lower alkyl, O-lower alkyl substituted with one more halogen atoms, CO-lower alkyl, CO-lower alkyl substituted with one or more halogen atoms, COOH, lower alkyl-COOH, COO-lower alkyl, $CONH_2$, CON-lower alkyl, SO_3H, SO_2NH_2, SO_2N-lower alkyl, or $B(OH)_2$, except that R^{2T} cannot be N-lower alkyl when R^{1T} is naphthalene;

or a pharmaceutically-acceptable salt thereof.

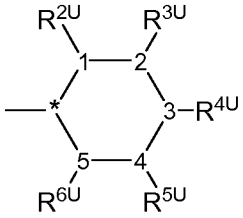
52. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:

$$\mathbf{(OH)_2\ B - R^U}$$

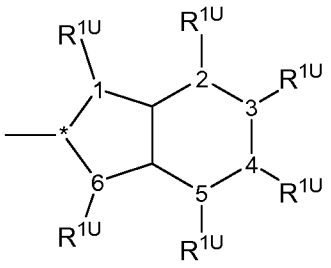
wherein, R^U is naphthalene, phenanthrene, or has one of the following formulas:



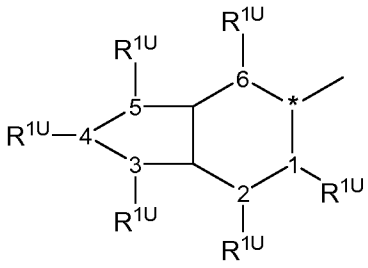
(2)



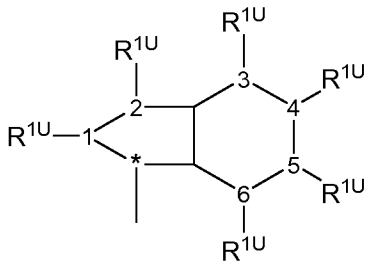
(3)



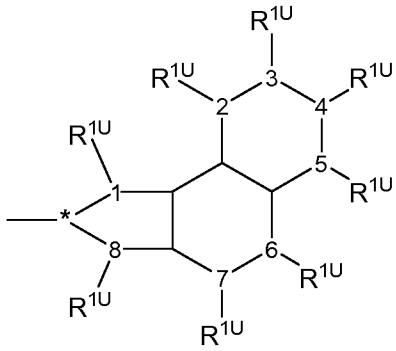
(4)



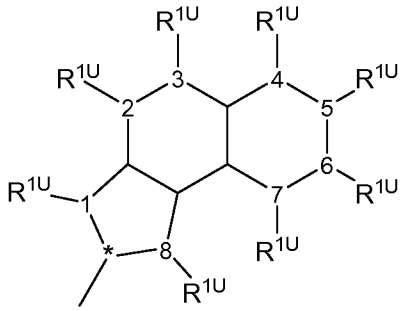
(5)



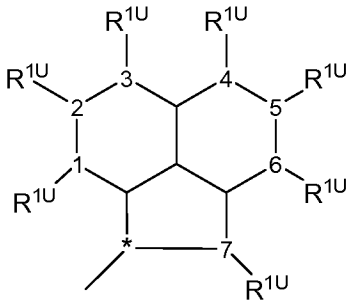
(6)



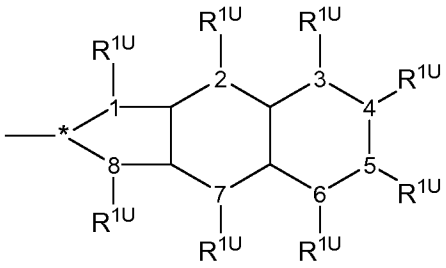
(7)



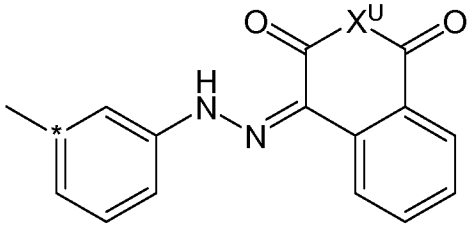
(8)



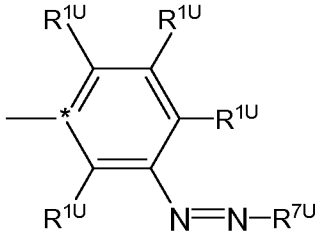
(9)



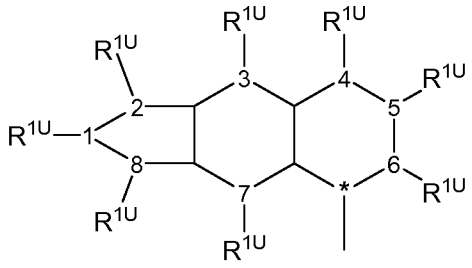
(10)



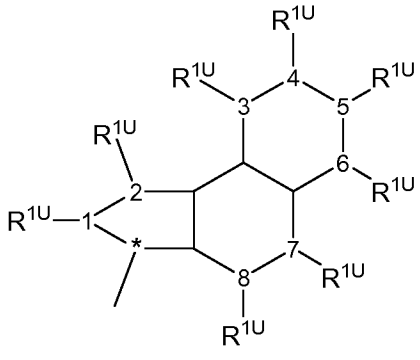
(11)



(12)



(13)



(14)

wherein, ring system (2), (3), (4), (5), (6), (7), (8), (9) or (10) is aromatic or nonaromatic;

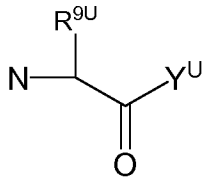
the atom center * is (R) or (S) in the case of chiral compounds; positions 1, 2, 3, 4, 5, 6, 7 or 8 each independently is C, N, O or S;

R^{1U} through R^{6U} each independently is a lone pair, H, $B(OH)_2$, a halogen atom, CF_3, CH_2CF_3, CCl_3, CH_2CCl_3, CBR^{3U}, CH_2CBR^{3U}, NO_2, lower alkyl, CO_2H, CHCHCOOH, CH2CH_2CH_2COOH, SO_3H, PO_3H, OSO_3H, OPO_3H, OH, NH_2, $CONH_2$, $COCH_3$, OCH_3, or phenyl boronic acid, except that R^{2U}, R^{3U}, R^{4U}, R^{5U} and R^{6U} cannot all simultaneously be H, R^{2U} cannot be lower alkyl when R^{3U}, R^{4U}, R^{5U} and R^{6U} are H, R^{3U} cannot be NH_2, OH or lower alkyl when R^{2U}, R^{4U}, R^{5U} and R^{6U} are H, and R^{4U} cannot be lower alkyl when R^{2U}, R^{3U}, R^{5U} and R^{6U} are H;

R^{7U} is a lone pair of electrons, H, $B(OH)_2$, a halogen atom, CF_3, CCl_3, CBR^{3U}, CH_2CF_3, CH_2CCl_3, CH_2CBR^{3U}, NO_2, $CONH_2$, $COCH_3$, OCH_3, lower alkyl, aryl, aryl substituted with one or more substituents R^{8U}, heteroaryl, or heteroaryl substituted with one or more substituents R^{8U};

each R^{8U} is independently a lone pair, H, $B(OH)_2$, a halogen atom, CF_3, CCl_3, CBR^{3U}, CH_2CF_3, CH_2CCl_3, CH_2CBR^{3U}, NO_2, lower alkyl, O, N, S, OH, NH_2, $N(CH_3)_2$, $N(CH_3)CH_2CH_3$, $NCOCH_3$, COOH, CHCHCOOH, $CH_2CH_2CH_2COOH$, $CONH_2$, $COCH_3$, OCH_3, OCl or phenyl boronic acid;

X^U is O, NH, NCH_3 or

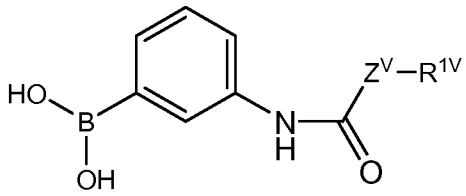


Y^U is OH, NH_2, NCH_3, $N(CH_3)_2$, $NHCOCH_3$ or $NHCOCH_2COOH$; and

R^{9U} is a lone pair of electrons, H, B $(OH)_2$, a halogen atom, CF_3, CCl_3, CBR^{3U}, CH_2CF_3, CH_2CCl_3, CH_2CBR^{3U}, NO_2, CO_2H, CHCHCOOH, $CH_2CH_2CH_2COOH$, SO_3H, PO_3H, OSO_3H, OPO_3H, OH, NH_2, $CONH_2$, $COCH_3$, OCH_3, phenyl boronic acid, lower alkyl, or a side chain of a standard amino acid;

or a pharmaceutically-acceptable salt thereof.

53. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



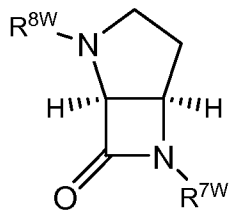
wherein, R^{1V} is lower alkyl, lower alkyl substituted with one or more halogen atoms, a cyclic alkene, or a heterocylic alkene, wherein the cyclic alkene or heterocyclic alkene may be substituted with one or more substituents R^{2V};

each R^{2V} is independently H, a halogen atom, lower alkyl, lower alkyl substituted with one or more halogen atoms, NH_2, NO, NO_2, CN, N-lower alkyl, N-lower alkyl substituted with one or more halogen atoms, OH, O-lower alkyl, O-lower alkyl substituted with one or more halogen atoms, CO-lower alkyl, CO-lower alkyl substituted with one or more halogen atoms, COOH, lower alkyl-COOH, $CONH_2$, CON-lower alkyl, SO_3H, SO_2NH_2, or SO_2N-lower alkyl; and

Z^V is a bond, O, S, lower alkyl radical, or lower heteroalkyl radical;

or a pharmaceutically-acceptable salt thereof.

54. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, R^{7W} signifies SO_3H, OSO_3H or $OCR^{jW}R^{jW'}COOH$,

wherein R^{jW} and $R^{j'W}$ are independently selected from hydrogen; alkyl; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen; benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen; alkylamino and alkoxyalkyl;

R^{8W} is alkoxycarbonylamino, the acyl residue of an α or β-amino acid, or a residue of the formula Q^W-$(X^W)_r{}^W$-Y^W-, wherein Q^W is a 3-6 membered .ring which optionally contains nitrogen, sulphur and/or oxygen and which is optionally fused to a phenyl ring or to a 5-6 membered heterocyclic ring and which is optionally substituted with 1 to 4 substituents selected from alkyl, allyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino, carboxamide which may be substituted, carboxylic acid, carbonylalkoxy, aminocarbonyl, alkylaminocarbonyl , halogen, ha1ogenomethyl, dihalogenomethyl, trihalogenomethyl, sulfamide, substituted sulfamide with substituents selected from alkyl, allyl, phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl , amino, alkylamino and halogen and benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, halogen and benzyl, urea which may be substituted with alkyl, aminoalkyl or alkylhydroxyl and carbamate which may be substituted with alkyl, aminoalkyl or alkylhydroxyl,

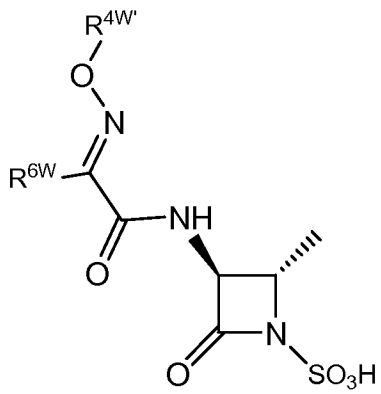
X^W signifies a linear spacer of from 1 to 6 atoms length and containing carbon, nitrogen, oxygen and/or sulphur atoms, of which up to 2 atoms can be nitrogen atoms and 1 atom can be oxygen or sulphur,

r^W is an integer of from 0 to 1; and

Y^W is selected from -CO-, -CS-, -NHCO- and -SO_2-;

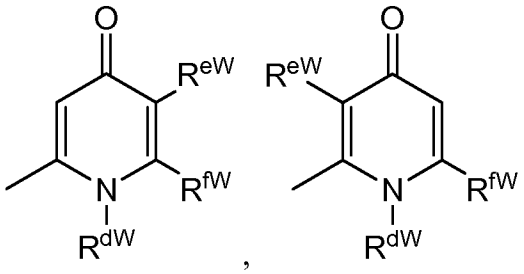
or a pharmaceutically acceptable salt thereof.

55. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, $R^{4W'}$ signifies hydrogen, alkyl, $C(R^{xW'})(R^{yW'})Z^{W'}$,

wherein $R^{xW'}$ and $R^{yW'}$ are independently selected from hydrogen, alkyl and (C_3-C_6) cycloalkyl; and $Z^{W'}$ signifies COOH or a group of one of the following two formulae

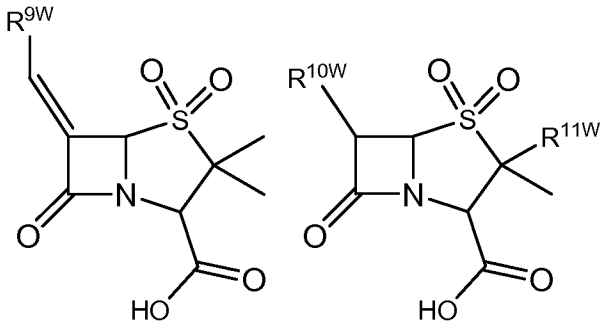


wherein, R^{dW} is hydrogen; amino; monoalkylamino ; alkyl; alkoxycarbony; benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen, diphenylmethyl; trityl; or ORg whereby R^{gW} is hydrogen, alkyl, benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino and halogen; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino and halogen;

R^{eW} and R^{fW} are independently selected from hydrogen; alkyl; benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino and halogen; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino and halogen; OR^{gW} whereby R^{gW} is hydrogen, alkyl, benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino and halogen; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino and halogen; diphenylmethyl; trityl or alkoxycarbonyl; or, when R^{eW} and R^{fW} are vicinal substituents, R^{eW} and R^{fW} taken together may also be -O-CH=CH-CH_2-, -O-CH_2-CH_2-O-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -CH=CH-CH=CH- or -CH=C(OH)-C(OH)=CH-;

$R^{6W'}$ signifies phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen; or a 5-6 membered heteroaromatic ring which may be substituted with amino, alkyl amino, carbonylamino or halogen.

56. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



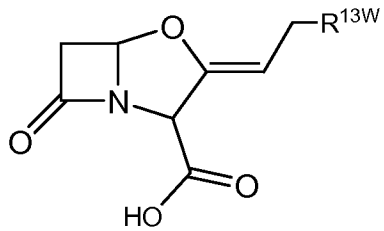
wherein, R^{9W} signifies COOH or a 5-6 membered monocyclic or polycyclic heteroaromatic group;

R^{10W} signifies hydrogen or halogen;

R^{11W} signifies CH_2R^{12W}; $CH{=}CHR^{12W}$ wherein R^{12W} is hydrogen, halogen, cyano, carboxylic acid, carboxamide which may be substituted, alkoxycarbonyl or a 5-6 membered heteroaromatic ring which is optionally substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl , amino, alkylamino, dialkylamino and halogen; or which is optionally fused with a 5-6 membered heteroaromatic ring; $CH{=}NR^{12W'}$ wherein $R^{12W'}$ is amino, alkylamino, dialkylamino, aminocarbonyl , hydroxy, alkylhydroxy,

or a pharmaceutically acceptable salt thereof.

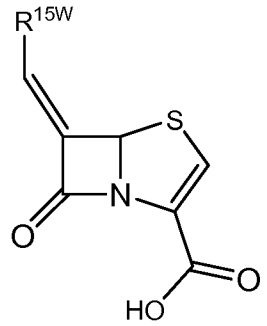
57. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, R^{13W} signifies OR^{14W}; $S(O)_n{}^WR^{14W}$ or a 5-6 membered heteroaromatic ring which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen; whereby n^W = 0, 1 or 2, and R^{14W} is hydrogen, alkyl, (C_2-C_7) alkene, (C_2-C_7) alkyne or a 5-6 membered heteroaromatic ring which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen,

or a pharmaceutically acceptable salt thereof.

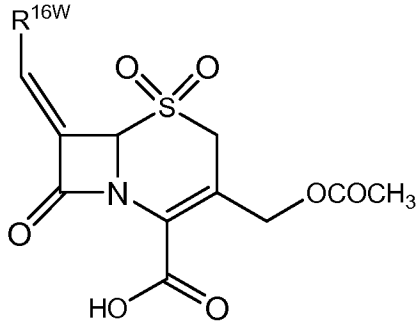
58. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, R^{15W} signifies a 5-6 membered heteroaromatic ring which maybe substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl , amino, alkylamino, dialkylamino and halogen; or which is optionally fused with a 5-6 membered heteroaromatic ring and/or which is optionally bound to the exo-methylene group over a -CH=CH- spacer being preferably in the (E) -configuration,

or a pharmaceutically acceptable salt thereof.

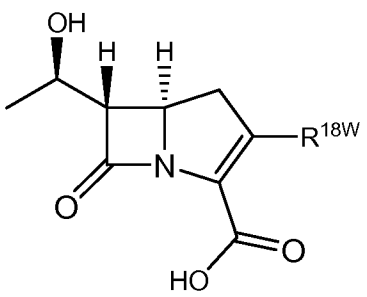
59. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



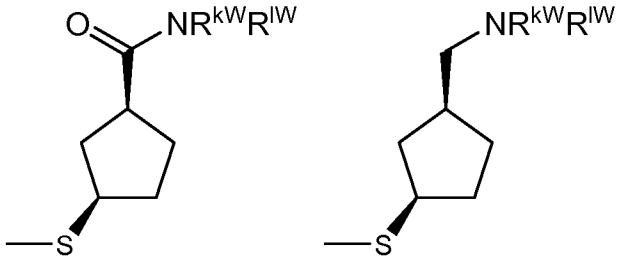
wherein, R^{16W} signifies $COOR^{17W}$, whereby R^{17W} signifies hydrogen or alkyl; or a 5-6 membered heteroaromatic ring which is optionally fused with a 5-6 membered heteroaromatic ring being optionally substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl , amino, alkylamino, dialkylamino , halogen; and/or being optionally bound to the exo-methylene group over a -CH=CH- spacer being preferably in the (E)-configuration,

or a pharmaceutically acceptable salt thereof.

60. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:

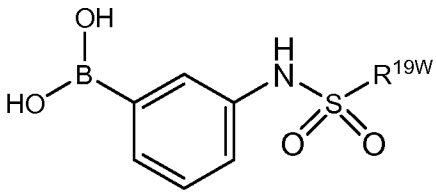


wherein, R^{18W} signifies -S-alkyl , -S-(CH_2) 2-NH-CH=NH or a group of one of the following two formulae



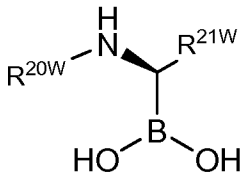
wherein R^{kW} and R^{lW} are individually selected from hydrogen, alkyl, 2-, 3-, 4-carboxyphenyl and sulfamoyl, or a pharmaceutically acceptable salt thereof.

61. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein R^{19W} signifies a 5-6 membered heteroaromatic ring which may be substituted with amino, alkylamino, dialkylamino or alkylsulfoxide, or a pharmaceutically acceptable salt thereof.

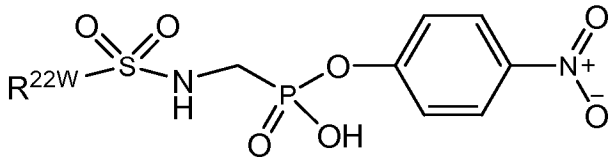
62. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, R^{20W} and R^{21W} are independently selected from a 5-6 membered heteroaromatic ring; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkyl- hydroxyl, amino, alkylamino, dialkylamino and halogen and benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen,

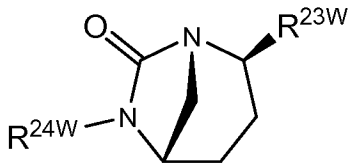
or a pharmaceutically acceptable salt thereof.

63. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, R^{22W} is selected from a 5-6 membered heteroaromatic ring which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen and which is optionally fused with a 5-6 membered heteroaromatic ring; phenyl which may be substituted with 1 to 5 substituents selected from al- kyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen; and benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkylhydroxyl, amino, alkylamino, dialkylamino and halogen.

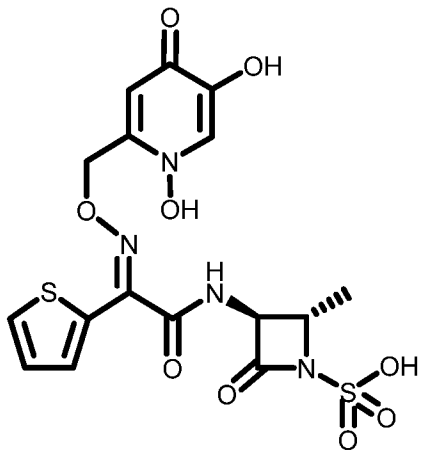
64. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



wherein, R^{23W} signifies hydrogen, carboxylic acid, alkoxycarbonyl or carboxamide which may be substituted, and

R^{24W} signifies SO_3H, OSO_3H or $OCR^{jW}R^{jW'}COOH$, wherein R^{jW} and $R^{jW'}$ are independently selected from hydrogen, alkyl, phenyl which may be substituted, benzyl which may be substituted, aminoalkyl and alkoxy.

65. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



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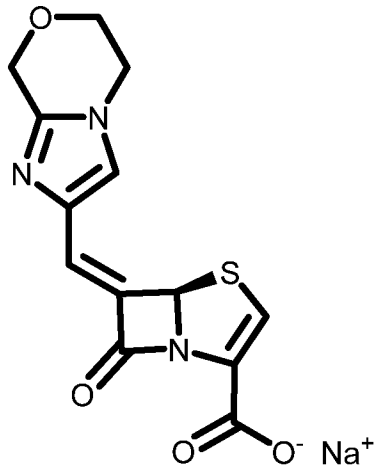
66. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



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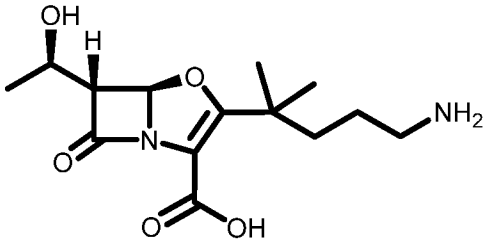
67. The method of any one of claims 1-6 or use of any one of claims 7-9, wherein the β-lactamase inhibitor comprises a compound having the structure:



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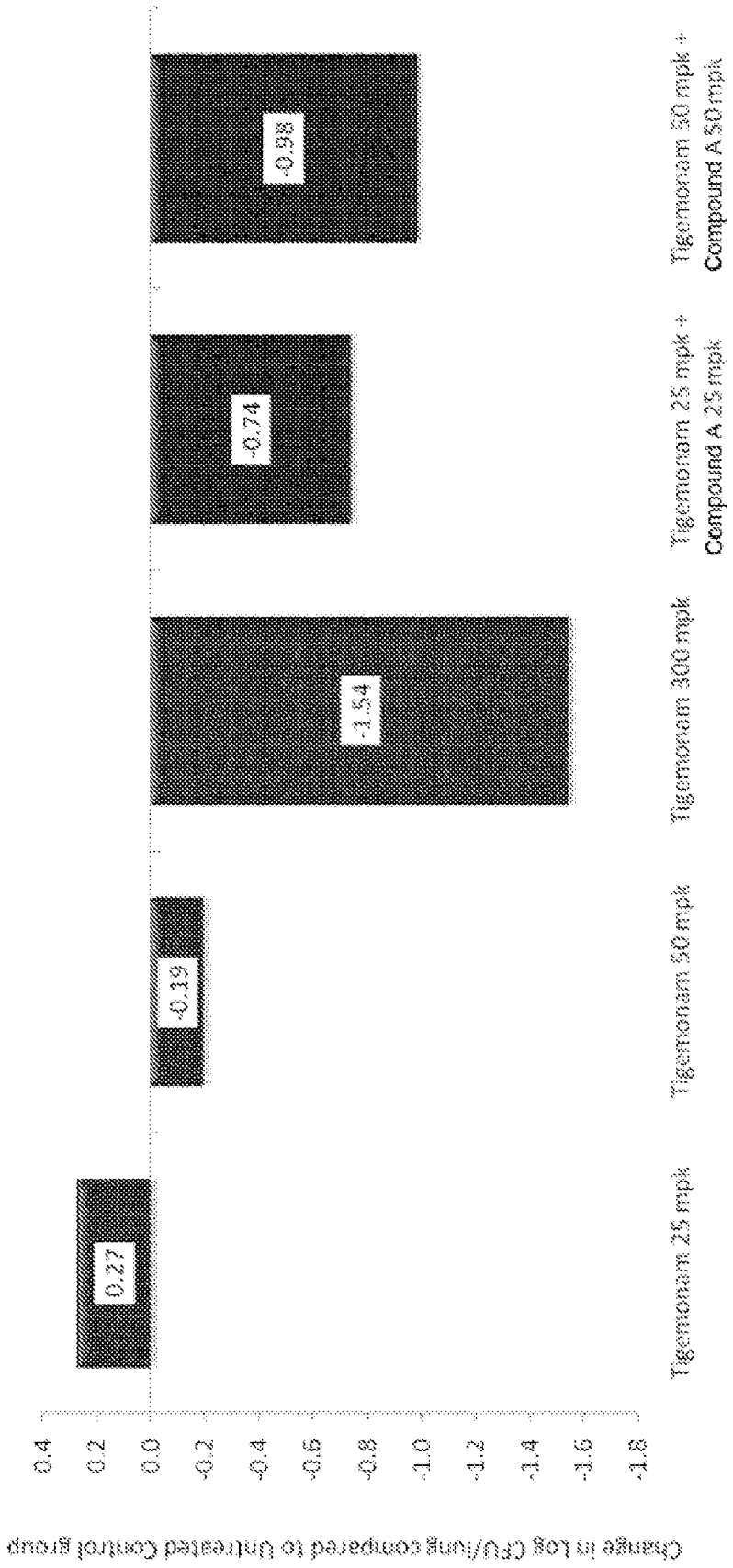
Change in log CFU/lung compared to Untreated Control group
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
0.27
-0.19
-1.54
-0.74
-0.98
Tigemonam 25 mpk
Tigemonam 50 mpk
Tigemonam 300 mpk
Tigemonam 25 mpk + Compound A 25 mpk
Tigemonam 50 mpk + Compound A 50 mpk

Figure 1