

COMPOUNDS AND METHODS FOR TREATING BACTERIAL INFECTIONS

RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/539,171, filed September 19, 2023, the entire contents of which are incorporated herein by reference.

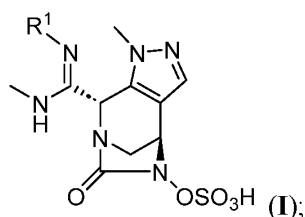
BACKGROUND

[0002] According to the Center for Disease Control and Prevention (CDC) an estimated 51,000 healthcare-associated *P. aeruginosa* infections occur each year in the United States alone with more than 6,000 (13%) of these infections being derived from multi-drug resistant strains. This has led to, on average, about 400 deaths per year. The European Center for Disease Control and Prevention has even higher values with an estimate in 2009 of approximately 800,000 extra hospital days and 10,000 extra deaths caused by resistant *P. aeruginosa* strains. Currently the multi-drug resistant rate is about 20% for *P. aeruginosa* and is expected to rise to about 30% by the year 2040.

[0003] Present treatments against *P. aeruginosa* include β -lactam antibiotics. Although some β -lactam antibiotics show promise *in vitro*, most, if not all, are plagued by high resistance in clinical settings. Due to the continued resistance and estimated increase for infection, the development of new antibacterials, particularly those which are not, or weakly, affected by the resistance mechanisms currently observed in the clinic, is an important medical need.

SUMMARY

[0004] Provided herein are antibacterial compounds which are useful for, among other uses, the treatment of bacterial infections. Such compounds are represented by Formula I,

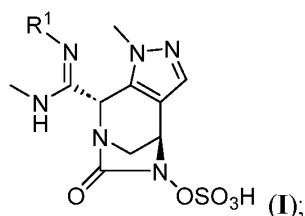


or pharmaceutically acceptable salts thereof, wherein R^1 is as defined herein. Also provided are pharmaceutical compositions comprising the compounds of Formula I.

DETAILED DESCRIPTION

1. General Description of Compounds

[0005] In certain embodiments, the present disclosure provides a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

$R^1 - OC(O)R^A$, and

R^A is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, and optionally substituted (C_1-C_{20}) alkyl, wherein said optionally substituted (C_1-C_{20}) alkyl may be interrupted with one or more heteroatoms selected from O, N, and S, and wherein two adjacent hydrogen atoms on the same carbon atom of one or more carbons on said (C_1-C_{20}) alkyl may be taken together to form $=O$.

2. Definitions

[0006] When used in connection to describe a chemical group that may have multiple points of attachment, a hyphen (-) designates the point of attachment of that group to the variable to which it is defined. For example, $-NR^dR^e$ means that the point of attachment for this group occurs on the nitrogen atom.

[0007] The terms “halo” and “halogen” as used herein refer to an atom selected from fluorine (fluoro, F), chlorine (chloro, Cl), bromine (bromo, Br), and iodine (iodo, I).

[0008] The term “alkyl” means saturated straight-chain or branched monovalent hydrocarbon radical. Unless otherwise specified, an alkyl group typically has 1-6 carbon atoms, *i.e.*, (C_1-C_6) alkyl. As used herein, a “ (C_1-C_6) alkyl” group means a radical having from 1 to 6 carbon atoms in a linear or branched arrangement.

[0009] “Alkoxy” means an alkyl radical attached through an oxygen linking atom, represented by $-O$ -alkyl. For example, “ (C_1-C_4) alkoxy” includes methoxy, ethoxy, propoxy, and butoxy.

[0010] Unless otherwise specified, the term “heteroaryl” refers to a 5- to 12-membered aromatic radical containing 1-4 heteroatoms selected from N, O, and S. In some instances, nitrogen atoms in a heteroaryl may be quaternized. A heteroaryl group may be mono- or bi-

cyclic. Monocyclic heteroaryl includes, for example, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, etc. Bi-cyclic heteroaryls include groups in which a monocyclic heteroaryl ring is fused to one or more aryl or heteroaryl rings. Nonlimiting examples include indolyl, benzooxazolyl, benzooxadiazolyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, quinazolinyl, quinoxalinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyridinyl, thienopyridinyl, thienopyrimidinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. It will be understood that when specified, optional substituents on a heteroaryl group may be present on any substitutable position and, include, *e.g.*, the position at which the heteroaryl is attached.

[0011] Unless otherwise specified, the term “heterocyclyl” means a 4- to 12-membered saturated or partially unsaturated heterocyclic ring containing 1 to 4 heteroatoms independently selected from N, O, and S. A heterocyclyl ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. A heterocyclyl group may be mono- or bicyclic. Examples of monocyclic saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, morpholinyl, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, dihydrooxadiazolyl, and dihydroisoxazolyl. Bi-cyclic heterocyclyl groups include, *e.g.*, unsaturated heterocyclic radicals fused to another unsaturated heterocyclic radical, cycloalkyl, aryl, or heteroaryl ring, such as for example, benzodioxolyl, dihydrobenzodioxinyl, dihydrobenzofuranyl, and the like. It will be understood that when specified, optional substituents on a heterocyclyl group may be present on any substitutable position and, include, *e.g.*, the position at which the heterocyclyl is attached.

[0012] The term “spiro” refers to two rings that shares one ring atom (*e.g.*, carbon).

[0013] The term “fused” refers to two rings that share two adjacent ring atoms with one another.

[0014] The term “bridged” refers to two rings that share three ring atoms with one another.

[0015] The term “aryl” refers to an aromatic carbocyclic single ring or two fused ring system containing 6 to 10 carbon atoms. Examples include phenyl, indanyl, tetrahydronaphthalene, and naphthyl. In one aspect, the aryl is phenyl.

[0016] The term “cycloalkyl” refers to a saturated cyclic aliphatic monocyclic or bicyclic ring system, as described herein, having from, unless otherwise specified, 3 to 10 carbon ring atoms. Monocyclic cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, and cyclooctyl. It will be understood that when specified, optional substituents on a cycloalkyl or cycloaliphatic group may be present on any substitutable position and, include, e.g., the position at which the cycloalkyl group is attached.

[0017] The term “optionally substituted” means that one or more hydrogens of the designated moiety may be replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group as valency permits. Optional substituents include, but are not limited to, one or more groups selected from cyano (–CN), halo, imino (=NH), nitro (–NO₂), oxo (=O), –C(O)Rⁱ, –C(O)ORⁱ, –C(O)NRⁱⁱRⁱⁱⁱ, –C(O)SRⁱ, –C(NRⁱ)NRⁱⁱRⁱⁱⁱ, –C(S)Rⁱ, –C(S)ORⁱ, –C(S)NRⁱⁱRⁱⁱⁱ, –ORⁱ, –OC(O)Rⁱ, –OC(O)ORⁱ, –OC(O)NRⁱⁱRⁱⁱⁱ, –OC(O)SRⁱ, –OC(NRⁱ)NRⁱⁱRⁱⁱⁱ, –OC(S)Rⁱ, –OC(S)ORⁱ, –OC(S)NRⁱⁱRⁱⁱⁱ, –OP(O)(ORⁱⁱ)ORⁱⁱⁱ, –OS(O)Rⁱ, –OS(O)₂Rⁱ, –OS(O)NRⁱⁱRⁱⁱⁱ, –OS(O)₂NRⁱⁱRⁱⁱⁱ, –NRⁱⁱRⁱⁱⁱ, –NRⁱC(O)R^{iv}, –NRⁱC(O)OR^{iv}, –NRⁱC(O)NRⁱⁱRⁱⁱⁱ, –NR^aC(O)SR^{iv}, –NRⁱC(NR^{iv})NRⁱⁱRⁱⁱⁱ, –NRⁱC(S)R^{iv}, –NRⁱC(S)OR^{iv}, –NRⁱC(S)NRⁱⁱRⁱⁱⁱ, –NRⁱS(O)R^{iv}, –NRⁱS(O)₂R^{iv}, –NRⁱS(O)NRⁱⁱRⁱⁱⁱ, –NRⁱS(O)₂NRⁱⁱR^{iv}, –SRⁱ, –S(O)Rⁱ, –S(O)₂Rⁱ, –S(O)NRⁱⁱR^{iv}, –S(O)₂NRⁱⁱR^{iv}, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein said alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are each further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a, wherein each Rⁱ, Rⁱⁱ, Rⁱⁱⁱ, and R^{iv} is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a or Rⁱⁱ and Rⁱⁱⁱ together with the N atom to which they are attached form heterocyclyl optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a, wherein each Q^a is independently selected from cyano, halo, imino, nitro, oxo, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, C₆₋₁₄ aryl, heteroaryl, heterocyclyl, –C(O)R^v, –C(O)OR^v, –C(O)NR^{vi}R^{vii}, –C(O)SR^v, –C(NR^v)NR^{vi}R^{vii}, –C(S)R^v, –C(S)OR^v, –C(S)NR^{vi}R^{vii}, –OR^v, –OC(O)R^v, –OC(O)OR^v, –OC(O)NR^{vi}R^{vii}, –OC(O)SR^v, –OC(NR^v)NR^{vi}R^{vii}, –OC(S)R^v, –OC(S)OR^v, –OC(S)NR^{vi}R^{vii}, –OP(O)(OR^v)OR^{vi}, –OS(O)R^v, –OS(O)₂R^v, –OS(O)NR^{vi}R^{vii}, –OS(O)₂NR^{vi}R^{vii}, –NR^{vi}R^{vii}, –NR^vC(O)R^{viii}, –NR^eC(O)OR^{vi}, –NR^vC(O)NR^{vi}R^{vii}, –NR^vC(O)SR^{vi}, –NR^vC(NR^{viii})NR^{vi}R^{vii}, –NR^vC(S)R^{viii}, –NR^vC(S)OR^{vi}, –NR^vC(S)NR^{vi}R^{vii}, –NR^vS(O)R^{viii}, –NR^vS(O)₂R^{viii}, –NR^vS(O)NR^{vi}R^{vii}, –

$\text{NR}^{\text{v}}\text{S}(\text{O})_2\text{NR}^{\text{vi}}\text{R}^{\text{vii}}$, $-\text{SR}^{\text{v}}$, $-\text{S}(\text{O})\text{R}^{\text{v}}$, $-\text{S}(\text{O})_2\text{R}^{\text{v}}$, $-\text{S}(\text{O})\text{NR}^{\text{vi}}\text{R}^{\text{vii}}$, and $-\text{S}(\text{O})_2\text{NR}^{\text{vi}}\text{R}^{\text{vii}}$, wherein each R^{v} , R^{vi} , R^{vii} , and R^{viii} is independently alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heterocyclyl; or (iii) R^{vi} and R^{viii} together with the N atom to which they are attached form heterocyclyl.

[0018] When a described compound is named or depicted by structure without indicating a particular geometric isomer form, it is to be understood that the name or structure encompasses one geometric isomer free of other geometric isomers, mixtures of geometric isomers, or mixtures of all geometric isomers.

[0019] Where the stereochemistry of a described compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure relative to all of the other stereoisomers. Percent by weight pure relative to all of the other stereoisomers is the ratio of the weight of one stereoisomer over the weight of the other stereoisomers.

[0020] Unless otherwise stated, all tautomeric forms of the compounds described herein are within the scope of the invention.

[0021] The compounds described herein may be present in the form of pharmaceutically acceptable salts. For use in medicines, the salts of the compounds of the invention refer to non-toxic “pharmaceutically acceptable salts.” Pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts such as e.g., ammonium salts, alkali metal salts (such as sodium and potassium salts), alkaline earth metal salts (such as magnesium and calcium salts), and ammonium salts (such as tetrabutylammonium, trimethylammonium, tributylammonium, triisopropylammonium, and N,N-diisopropylethylammonium).

[0022] The term “pharmaceutically acceptable carrier” refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions described herein include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0023] The terms “subject” and “patient” may be used interchangeably, and means a mammal in need of treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, pigs, horses, sheep, goats and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs and the like). Typically, the subject is a human in need of treatment.

[0024] The term “inhibit,” “inhibition” or “inhibiting” includes a decrease in the baseline activity of a biological activity or process.

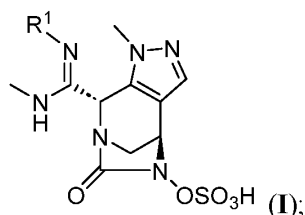
[0025] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed, *i.e.*, therapeutic treatment. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of exposure to a particular organism, or other susceptibility factors), *i.e.*, prophylactic treatment. Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[0026] The term “effective amount” or “therapeutically effective amount” includes an amount of the compound described herein that will elicit a biological or medical response of a subject, for example, the reduction or inhibition of enzyme or protein activity related to a bacterial infection, amelioration of symptoms of a bacterial infection, or the slowing or delaying of progression of a bacterial infection. In one aspect, a therapeutically effective amount refers to a dosage of from about 0.01 to about 100 mg/kg body weight/day.

[0027] The terms “administer,” “administering” or “administration” include any method of delivery of a pharmaceutical composition or agent into a subject's system or to a particular region in or on a subject. In certain embodiments of the invention, an agent is administered intravenously, intramuscularly, subcutaneously, intradermally, intranasally, orally, transcutaneously, or mucosally. In a preferred embodiment, an agent is administered intravenously. In another preferred embodiment, an agent is administered orally. Administering an agent can be performed by a number of people working in concert. Administering an agent includes, for example, prescribing an agent to be administered to a subject and/or providing instructions, directly or through another, to take a specific agent, either by self-delivery, *e.g.*, as by oral delivery, subcutaneous delivery, intravenous delivery through a central line, etc.; or for delivery by a trained professional, *e.g.*, intravenous delivery, intramuscular delivery, intratumoral delivery, etc.

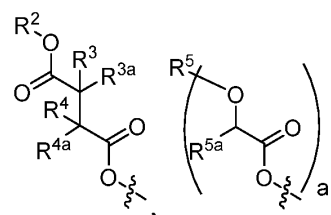
3. Description of Exemplary Compounds

[0028] In a first embodiment, the present disclosure provides a compound of Formula I:

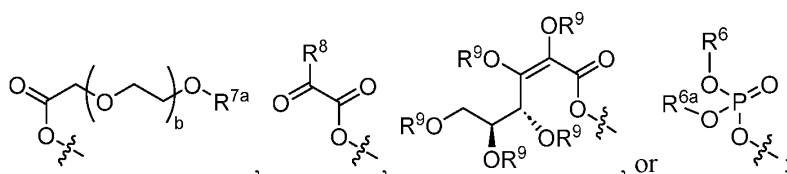


or a pharmaceutically acceptable salt thereof, wherein the variables are as described above.

[0029] In a second embodiment, in the compound of Formula I, or a pharmaceutically



acceptable salt thereof, R¹ is -OC(O)aryl, -OC(O)(C₁-C₆)alkyl,



R² is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, and optionally substituted (C₁-C₆)alkyl, wherein said optionally substituted (C₁-C₆)alkyl may be interrupted with one or more heteroatoms selected from O, N, and S;

R³, R^{3a}, R⁴, and R^{4a} are each independently selected from hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, OH, -OC(O)(C₁-C₆)alkyl, O(C₁-C₆)alkylO(C₁-C₆)alkyl, -O(C₁-C₆)alkylC(O)(C₁-C₆)alkyl, and -O(C₁-C₆)alkylC(O)(C₁-C₆)alkyl;

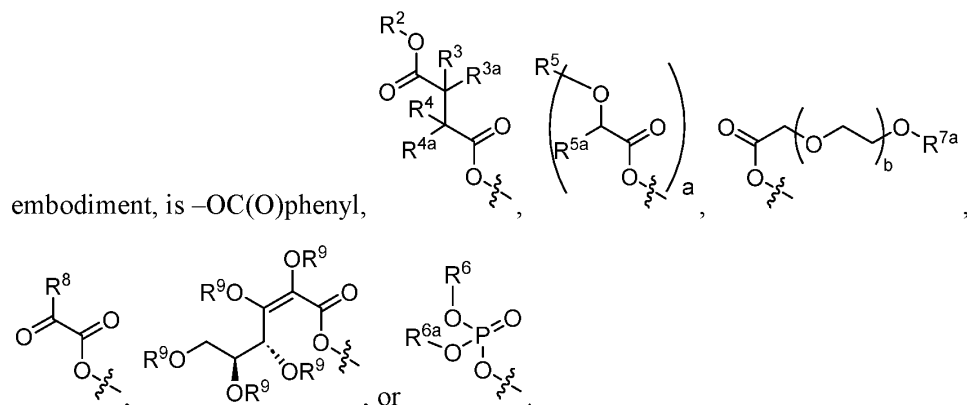
R⁵ is selected from hydrogen, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, optionally substituted (C₁-C₆)alkyl, -C(O)(C₁-C₂₀)alkyl, -C(O)aryl, -C(O)heterocyclyl, -C(O)heteroaryl, wherein each of said (C₁-C₂₀)alkyl, aryl, heterocyclyl, and heteroaryl on the -C(O) group are optionally substituted and wherein said (C₁-C₂₀)alkyl on the -C(O) group may be interrupted with one or more heteroatoms selected from O, N, and S, and wherein two adjacent hydrogen atoms on the same carbon atom of one or more carbons on said (C₁-C₂₀)alkyl may be taken together to form =O; R⁶ and R^{6a} are each independently hydrogen, aryl, or (C₁-C₆)alkyl;

R^{5a}, R⁷, R^{7a}, and R⁸ are each independently (C₁-C₆)alkyl;

R^6 and R^{6a} are each independently hydrogen, aryl, or (C₁-C₆)alkyl;

each R^9 is independently hydrogen or (C₁-C₆)alkyl; and

a and b are both integers ranging from 1 to 20. Alternatively, as part of a second



[0030] In a third embodiment, R^3 in the compound of Formula I, or a pharmaceutically acceptable salt thereof, is hydrogen or (C₁-C₄)alkyl (e.g., hydrogen or CH₃), wherein the remaining variables are as described above for Formula I or the second embodiment.

[0031] In a fourth embodiment, R^{3a} in the compound of Formula I, or a pharmaceutically acceptable salt thereof, is hydrogen or (C₁-C₄)alkyl (e.g., hydrogen or CH₃), wherein the remaining variables are as described above for Formula I or the second or third embodiments.

[0032] In a fifth embodiment, R^4 in the compound of Formula I, or a pharmaceutically acceptable salt thereof, is (C₁-C₄)alkyl (e.g., CH₃), wherein the remaining variables are as described above for Formula I or any one of the second to fourth embodiments.

[0033] In a sixth embodiment, R^{4a} in the compound of Formula I, or a pharmaceutically acceptable salt thereof, is (C₁-C₄)alkyl (e.g., CH₃), wherein the remaining variables are as described above for Formula I or any one of the second to fifth embodiment.

[0034] In a seventh embodiment, R^5 in the compound of Formula I, or a pharmaceutically acceptable salt thereof, is (C₁-C₄)alkyl, (C₁-C₄)alkyl(phenyl), or -C(O)(C₁-C₁₀)alkyl, wherein said (C₁-C₁₀)alkyl is interrupted with one or more O atoms, and wherein two adjacent hydrogen atoms on the same carbon atom of one or more carbons on said (C₁-C₁₀)alkyl are taken together to form =O, wherein the remaining variables are as described above for Formula I or any one of the second to sixth embodiments. Alternatively, as part of a seventh embodiment, R^5 in the compound of Formula I, or a pharmaceutically acceptable salt thereof, is (C₁-C₄)alkyl, (C₁-C₄)alkyl(phenyl), or -C(O)(C₁-C₁₀)alkyl, wherein said (C₁-C₁₀)alkyl is CH₃, CH₂(phenyl), or -C(O)(CH)CH₃OC(O)CHCH₃OC(O)CH₃, wherein the remaining

variables are as described above for Formula **I** or any one of the second to sixth embodiments.

[0035] In an eighth embodiment, R^{5a} in the compound of Formula **I**, or a pharmaceutically acceptable salt thereof, is (C₁-C₄)alkyl (e.g., CH₃), wherein the remaining variables are as described above for Formula **I** or any one of the second to seventh embodiments.

[0036] In a ninth embodiment, R^6 in the compound of Formula **I**, or a pharmaceutically acceptable salt thereof, is (C₁-C₄)alkyl (e.g., CH₂CH₃), wherein the remaining variables are as described above for Formula **I** or any one of the second to eighth embodiments.

[0037] In a tenth embodiment, R^{6a} in the compound of Formula **I**, or a pharmaceutically acceptable salt thereof, is (C₁-C₄)alkyl (e.g., CH₂CH₃), wherein the remaining variables are as described above for Formula **I** or any one of the second to ninth embodiments.

[0038] In an eleventh embodiment, R^7 in the compound of Formula **I**, or a pharmaceutically acceptable salt thereof, is (C₁-C₄)alkyl (e.g., CH₃), wherein the remaining variables are as described above for Formula **I** or any one of the second to tenth embodiments.

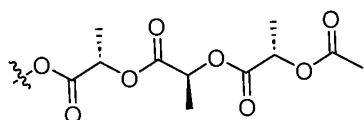
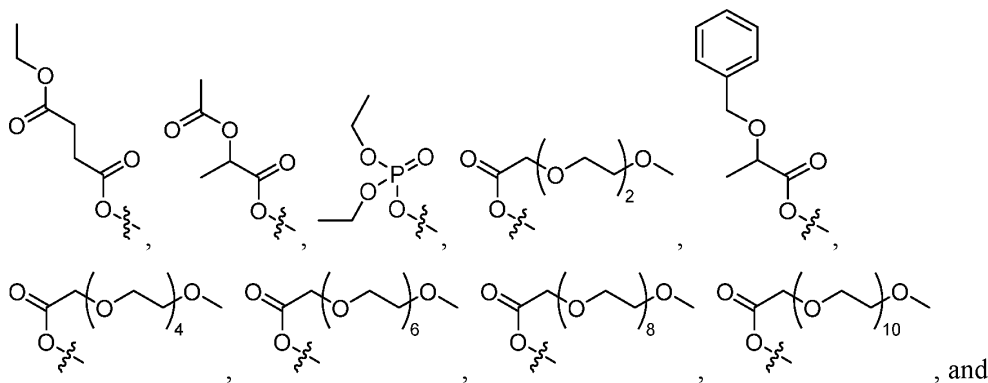
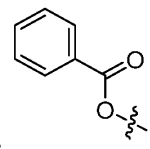
[0039] In a twelfth embodiment, R^{7a} in the compound of Formula **I**, or a pharmaceutically acceptable salt thereof, is (C₁-C₄)alkyl (e.g., CH₃), wherein the remaining variables are as described above for Formula **I** or any one of the second to eleventh embodiments.

[0040] In a thirteenth embodiment, a in the compound of Formula **I**, or a pharmaceutically acceptable salt thereof, is 1, wherein the remaining variables are as described above for Formula **I** or any one of the second to twelfth embodiments.

[0041] In a fourteenth embodiment, b in the compound of Formula **I**, or a pharmaceutically acceptable salt thereof, is an integer from 2 to 10 (e.g., 2, 4, 6, 8, or 10), wherein the remaining variables are as described above for Formula **I** or any one of the second to thirteenth embodiments. Alternatively, as part of a fourteenth embodiment, b in the compound of Formula **I**, or a pharmaceutically acceptable salt thereof, is 2, wherein the remaining variables are as described above for Formula **I** or any one of the second to thirteenth embodiments.

[0042] In a fifteenth embodiment, R^1 in the compound of Formula I, or a

pharmaceutically acceptable salt thereof, is selected from $-\text{OC}(\text{O})\text{C}(\text{CH}_3)_3$,

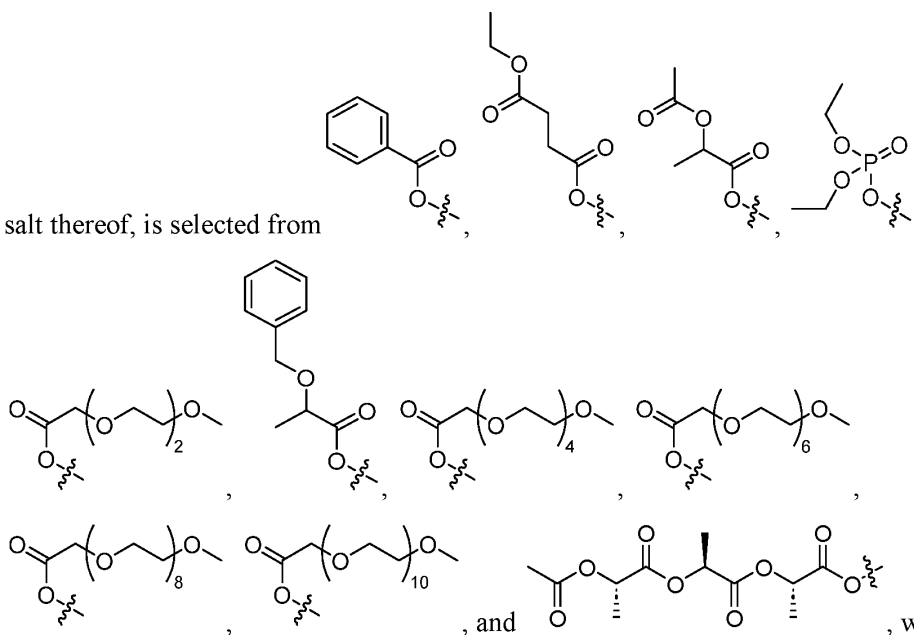


, wherein the remaining variables are as described above for

Formula I or any one of the second to fourteenth embodiments. Alternatively, as part of a

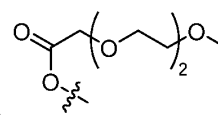
thirteenth embodiment, R^1 in the compound of Formula I, or a pharmaceutically acceptable

salt thereof, is selected from



remaining variables are as described above for Formula I or any one of the second to

fourteenth embodiments. In another alternative, as part of a thirteenth embodiment, R^1 in the



compound of Formula I, or a pharmaceutically acceptable salt thereof, is wherein the remaining variables are as described above for Formula I or any one of the second to fourteenth embodiments.

[0043] Specific examples of compounds are provided in the EXEMPLIFICATION. Pharmaceutically acceptable salts as well as the neutral forms of these compounds are included herein.

4. Uses, Formulation and Administration

[0044] The compounds described herein can be used to treat bacterial infections caused by one or more species of Gram-negative, or atypical bacteria. Gram-negative bacteria include, but are not limited, to *Haemophilus influenzae*, *Acinetobacter baumannii*, *Burkholderia* spp., *Citrobacter* spp., *Escherichia coli*, *Enterobacter* spp., *Pseudomonas aeruginosa*, *Klebsiella* spp., *Stenotrophomonas maltophilia*, *Francisella tularensis*, *Yersinia* spp., *Salmonella* spp., *Shigella* spp., *Legionella* spp. and *Neisseria gonorrhoeae*. Atypical bacteria include, but are not limited to, *Mycoplasma pneumoniae*, *Chlamydomphila pneumoniae*, and *Legionella pneumophila*.

[0045] In some aspects, the bacteria are resistant to one or more antibacterials other than the compounds described herein. The language “resistance” and “antibacterial resistance” refers to bacteria that are able to survive exposure to one or more antibacterials. In one aspect, the compounds described herein can be used to treat bacterial infections caused by Gram-negative bacteria or resistant Gram-negative bacteria. In another aspect, the compounds described herein can be used to treat bacterial infections caused by *Enterobacteriaceae* such as *E. coli*, *K. pneumoniae*, and *Acinetobacter* spp. In yet a further aspect, the compounds described herein can be used to treat bacterial infections caused by *P. aeruginosa*, *A. baumannii*, or *Enterobacteriaceae*, as well as antibacterial-resistant forms. In yet a further aspect, the compounds described herein can be used to treat bacterial infections caused by *P. aeruginosa*, as well as antibacterial-resistant forms. For example, resistance mechanisms in Gram-negative bacteria include, but are not limited to, extended-spectrum β -lactamase expression, metallo- β -lactamase expression, carbapenemase expression, DNA gyrase mutation, porin mutation, efflux system overexpression, lipopolysaccharide modification, and 16S rRNA methylase expression.

[0046] In one aspect, the bacterial infection treated by the present compounds is caused by a Gram-negative bacteria. In another aspect, the bacterial infection treated by the present

compounds is caused by *P. aeruginosa*, *A. baumannii*, *E. coli*, or *K. pneumoniae* and other *Enterobacteriaceae*. In a further aspect, the bacterial infection treated by the present compounds is caused by *P. aeruginosa*. In another aspect, the bacterial infection treated by the present compounds is caused by an antibacterial-resistant Gram-negative bacteria. In yet another aspect, the bacterial infection treated by the present compounds is caused by an antibacterial-resistant strain of *P. aeruginosa*. In yet another aspect, the bacterial infection treated by the present compounds is caused by *Enterobacteriaceae*. In yet another aspect, the bacterial infection treated by the present compounds is caused by *E. coli*, *K. pneumoniae*, or *Acinetobacter* spp. In yet another aspect, the bacterial infection treated by the present compounds is caused by a pathogen selected from *Burkholderia* spp., *B. anthracis*, *Y. pestis*, and *F. tularensis*.

[0047] Bacterial infections treated by the present compounds include, but are not limited to, respiratory (e.g., pneumonia), blood stream (e.g., bacteremia), heart (e.g., endocarditis), CNS (e.g., meningitis, brain abscess), ear (e.g., otitis externa), eye (e.g., bacterial keratitis, endophthalmitis), GI tract (diarrhea, enteritis, enterocolitis), urinary tract, skin, intraabdominal, nosocomial and wound/burn infections.

[0048] In one aspect, the compounds described herein inhibit penicillin-binding protein 3 (PBP3). Thus, in one aspect, the present disclosure provides a method of inhibiting bacterial PBP3, comprising administering to a subject in need thereof one or more of the compounds described herein, or a pharmaceutically acceptable salt thereof.

[0049] In another aspect, the compounds described herein inhibit penicillin-binding protein 1 (e.g., PBP1a and/or PBP1b). Thus, in one aspect, the present disclosure provides a method of inhibiting bacterial PBP1, comprising administering to a subject in need thereof one or more of the compounds described herein, or a pharmaceutically acceptable salt thereof. In another aspect, the present disclosure provides a method of inhibiting bacterial PBP1 (e.g., PBP1a and/or PBP1b) and bacterial PBP3, comprising administering to a subject in need thereof one or more of the compounds described herein, or a pharmaceutically acceptable salt thereof.

[0050] In yet another aspect, the compounds described herein are not specific inhibitors of penicillinbinding protein 2 (PBP2).

[0051] According to other aspect, the present disclosure provides pharmaceutically acceptable compositions comprising a compound described herein; and a pharmaceutically acceptable carrier. These compositions can be used to treat one or more of the bacterial infections described above, as well as inhibit PBP3.

[0052] Compositions described herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Liquid dosage forms, injectable preparations, solid dispersion forms, and dosage forms for topical or transdermal administration of a compound are included herein.

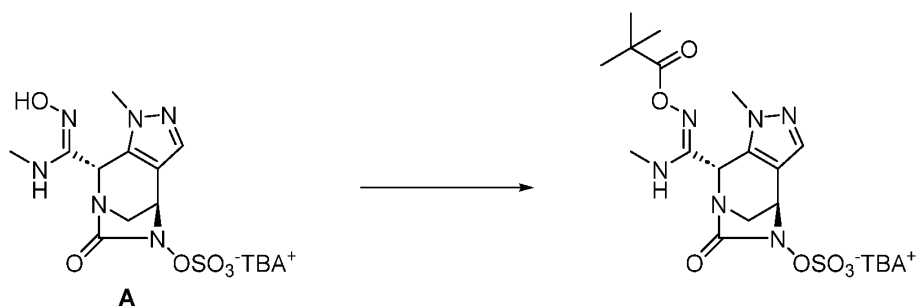
[0053] The amount of provided compounds that may be combined with carrier materials to produce a composition in a single dosage form will vary depending upon the patient to be treated and the particular mode of administration.

[0054] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, the judgment of the treating physician, and the severity of the particular disease being treated. The amount of a provided compound in the composition will also depend upon the particular compound in the composition.

EXEMPLIFICATION

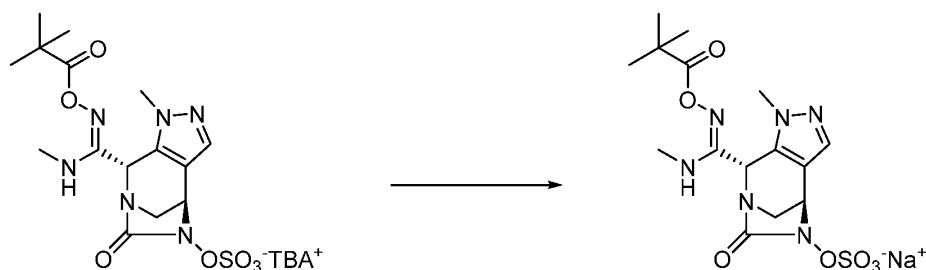
[0055] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds herein, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

[0056] [(1R,7S)-7-[(Z)-N'-hydroxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt (**A**) can be prepared according to the procedures described in PCT/US2018/031593.



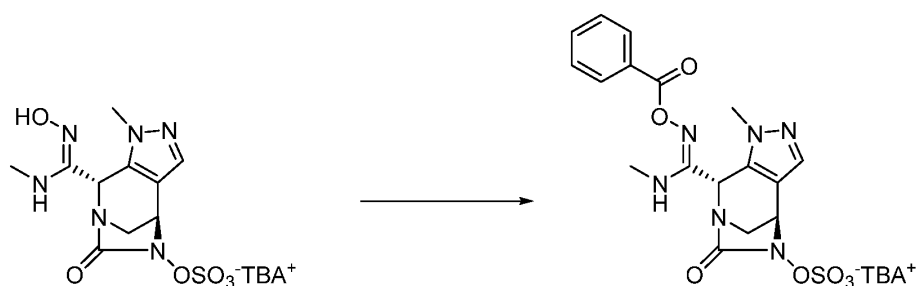
[0057] Intermediate 1: [(1R,7S)-7-[(Z)-N'-(2,2-dimethylpropanoyloxy)-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt

[0058] To a solution of [(1R,7S)-7-[(Z)-N'-hydroxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt (200 mg, 0.34 mmol) and triethylamine (0.05 mL, 0.34 mmol) in DCM (3.4 mL) at 0 °C was added 2,2-dimethylpropanoyl chloride (0.04 mL, 0.34 mmol). The reaction mixture was warmed to room temperature, stirred for 15 minutes, then concentrated and purified by silica gel chromatography (0%-100% acetone/DCM) to afford title compound as a white solid, 195 mg (85%). LCMS: m/z 431 [M+H]⁺, 429 [M-H]⁻ for C₁₅H₂₂N₆O₇S



[0059] Example 1: [(1R,7S)-7-[(Z)-N'-(2,2-dimethylpropanoyloxy)-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate sodium salt

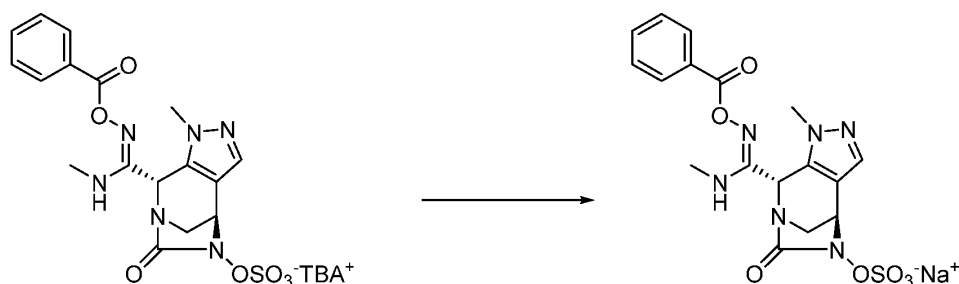
[0060] Dowex® 50WX8 100-200 (25 g) was prepared by stirring in 2N NaOH (50 mL) for 1 hour. The resin was then loaded into a column and washed with water until eluent was neutral pH. The column was then washed with 1:1 water:acetone and water. [(1R,7S)-7-[(Z)-N'-(2,2-dimethylpropanoyloxy)-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt (193.2 mg, 0.29 mmol) was dissolved in water with a small amount of acetone and loaded onto the column. The title compound was eluted with water, frozen and lyophilized to afford a white solid, 113.9 mg (88%). LCMS: m/z 431 [M+H]⁺, 429 [M-H]⁻ for C₁₅H₂₂N₆O₇S. ¹H NMR: (300 MHz, DMSO): 1.20 (s, 9H), 3.03 (d, J = 5.1 Hz, 3H), 3.33 (m, 2H), 3.69 (s, 3H), 4.70 (s, 1H), 5.64 (s, 1H), 6.40 (m, 1H), 7.32 (s, 1H).



[0061] **Intermediate 2: [(1R,7S)-7-[(Z)-N'-benzoyloxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0.2,6]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt**

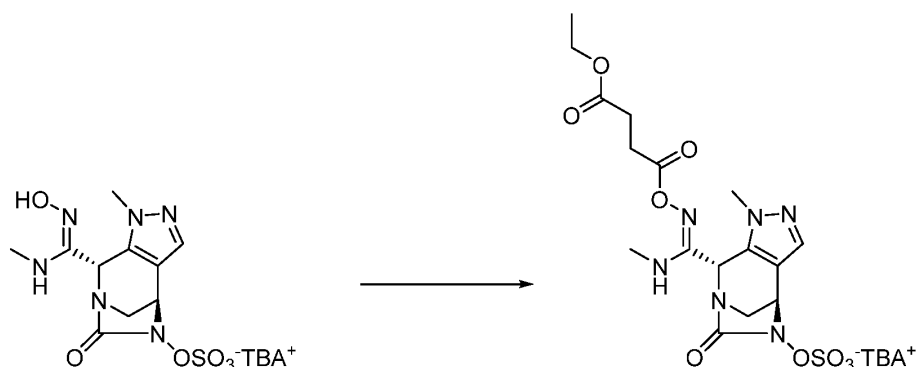
[0062] The title compound was prepared according to the procedure for Intermediate 1 using benzoyl chloride. The compound was obtained as a white solid, 188.9 mg (80%).

LCMS: m/z 451 $[M+H]^+$, 449 $[M-H]^-$ for $C_{17}H_{18}N_6O_7S$



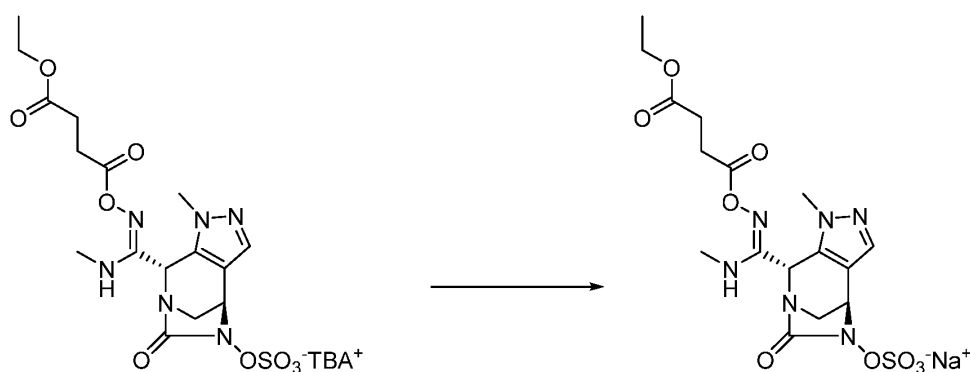
[0063] **Example 2: [(1R,7S)-7-[(Z)-N'-benzoyloxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0.2,6]undeca-2(6),3-dien-10-yl] sulfate sodium salt**

[0064] The title compound was prepared from Intermediate 2 according to the procedure for Example 1 to afford a white solid, 119.1 mg (92%). LCMS: m/z 451 $[M+H]^+$, 449 $[M-H]^-$ for $C_{17}H_{18}N_6O_7S$. 1H NMR: (300 MHz, DMSO): 3.05 (d, $J = 4.8$ Hz, 3H), 3.41 (m, 2H), 3.75 (s, 3H), 4.73 (m, 1H), 5.71 (s, 1H), 6.98 (m, 1H), 7.35 (s, 1H), 7.53 (m, 2H), 7.65 (m, 1H), 8.19 (m, 2H).



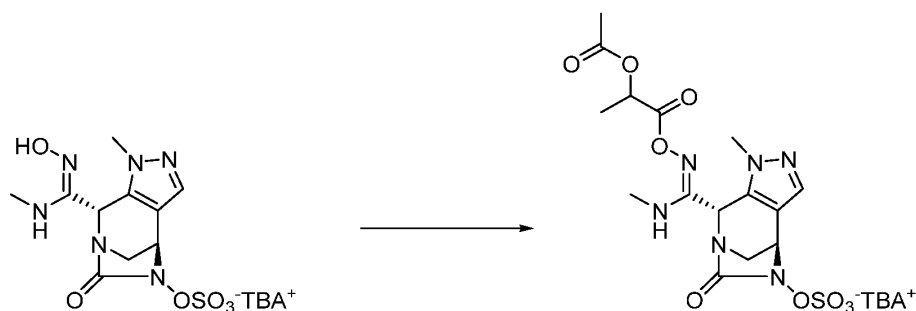
[0065] Intermedaite 3: [(1R,7S)-7-[(Z)-N'-(4-ethoxy-4-oxo-butanoyl)oxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt

[0066] The title compound was prepared according to the procedure for Intermediate 1 using ethyl 4-chloro-4-oxo-butanoate. The compound was obtained as a white solid, 212.2 mg (87%). LCMS: m/z 475 [M+H]⁺, 473 [M-H]⁻ for C₁₆H₂₂N₆O₉S



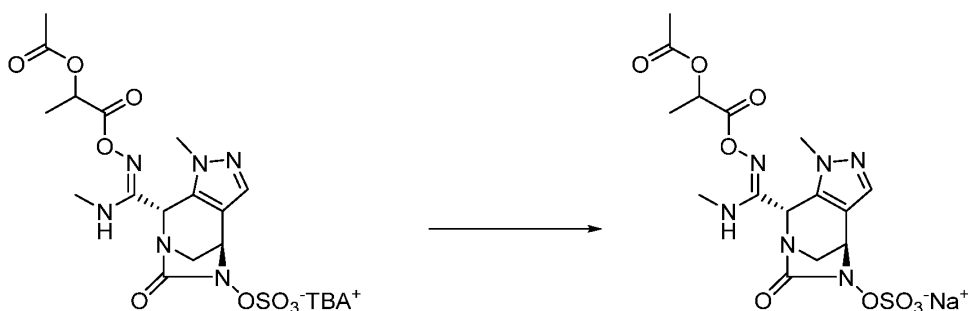
[0067] Example 3: [(1R,7S)-7-[(Z)-N'-(4-ethoxy-4-oxo-butanoyl)oxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate sodium salt

[0068] The title compound was prepared from Intermediate 3 according to the procedure for Example 1 to afford a white solid, 126.1 mg (86%). LCMS: m/z 475 [M+H]⁺, 473 [M-H]⁻ for C₁₆H₂₂N₆O₉S. ¹H NMR: (300 MHz, DMSO): 1.18 (t, J = 7.2 Hz, 3H), 2.62 (m, 4H), 3.01 (d, J = 4.8 Hz, 3H), 3.33 (m, 2H), 3.66 (s, 3H), 4.06 q, J = 7.2 Hz, 2H), 4.70 (m, 1H), 5.64 (s, 1H), 6.85 (m, 1H), 7.32 (s, 1H).



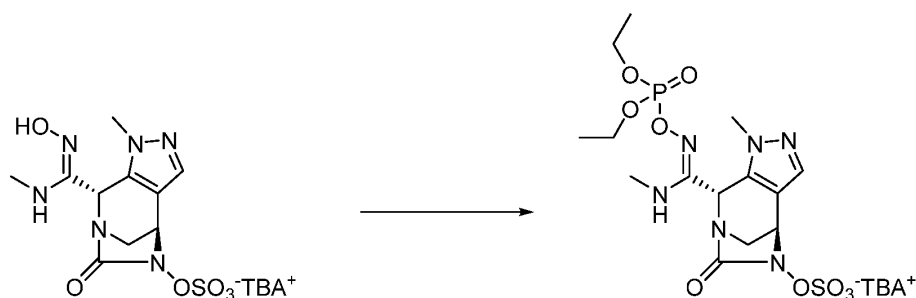
[0069] Intermediate 4: [(1R,7S)-7-[(Z)-N'-(2-acetoxypropanoyloxy)-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt

[0070] The title compound was prepared according to the procedure for Intermediate 1 using (2-chloro-1-methyl-2-oxo-ethyl) acetate. The compound was obtained as a white solid, 177.1 mg (75%). LCMS: m/z 461 $[M+H]^+$, 459 $[M-H]^-$ for $C_{15}H_{20}N_6O_9S$



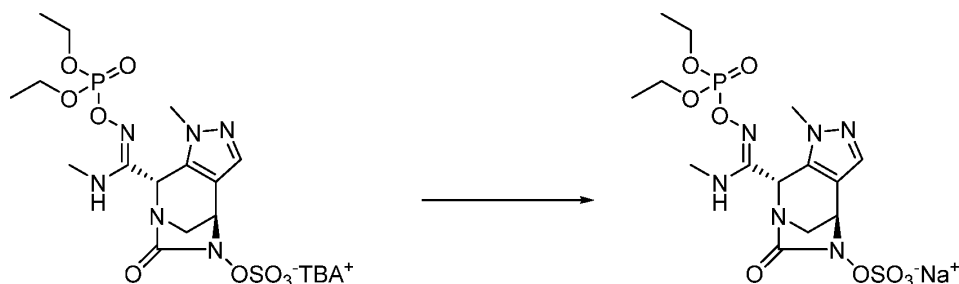
[0071] Example 4: [(1R,7S)-7-[(Z)-N'-(2-acetoxypropanoyloxy)-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0]undeca-2(6),3-dien-10-yl] sulfate sodium salt

[0072] The title compound was prepared from Intermediate 4 according to the procedure for Example 1 to afford a white solid, 114.4 mg (85%). LCMS: m/z 461 $[M+H]^+$, 459 $[M-H]^-$ for $C_{15}H_{20}N_6O_9S$. 1H NMR: (300 MHz, DMSO): 1.42 (d, $J = 6.9$ Hz, 3H), 2.07 (s, 3H), 3.03 (d, $J = 4.8$ Hz, 3H), 3.34 (m, 2H), 3.67 (s, 3H), 4.70 (m, 1H), 5.15 (q, $J = 6.9$ Hz, 1H), 5.67 (m, 1H), 6.90 (m, 1H), 7.35 (s, 1H).



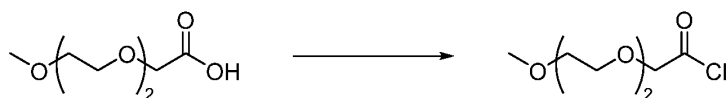
[0073] **Intermediate 5: [(1R,7S)-7-[(Z)-N'-diethoxyphosphoryloxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt**

[0074] The title compound was prepared according to the procedure for Intermediate 1 using 1-[chloro(ethoxy)phosphoryl]oxyethane. The compound was obtained as white solid, 178 mg (72%). LCMS: m/z 483 [M+H]⁺, 481 [M-H]⁻ for C₁₄H₂₃N₆O₉PS.



[0075] **Example 5: [(1R,7S)-7-[(Z)-N'-diethoxyphosphoryloxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate sodium salt**

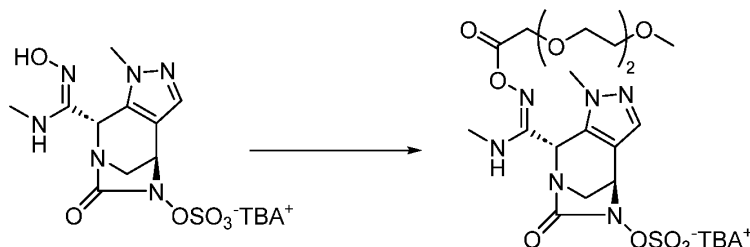
[0076] The title compound was prepared from Intermediate 5 according to the procedure for Example 1 to afford a white solid, 33.1 mg (27%). LCMS: m/z 483 [M+H]⁺, 481 [M-H]⁻ for C₁₄H₂₃N₆O₉PS. ¹H NMR: (300 MHz, DMSO): 1.23 (t, J = 7.2 Hz, 3H), 3.01 (d, J = 5.1 Hz, 3H), 3.36 (m, 2H), 3.64 (s, 3H), 3.93 (m, 4H), 4.71 (m, 1H), 5.66 (s, 1H), 6.89 (m, 1H), 7.33 (s, 1H).



[0077] **Intermediate 6: 2-[2-(2-methoxyethoxy)ethoxy]acetyl chloride**

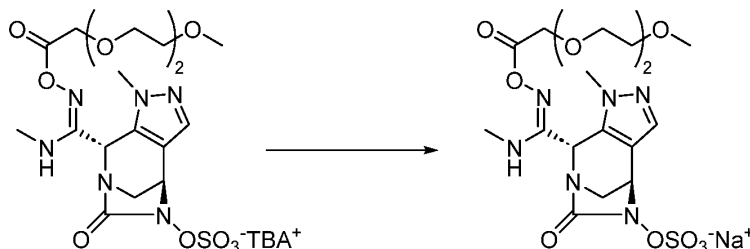
[0078] To a solution of 2-[2-(2-methoxyethoxy)ethoxy]acetic acid (1000 mg, 5.61 mmol) in toluene (0.56 mL) was added oxalyl chloride (0.77 mL, 8.98 mmol) dropwise. The reaction mixture was heated at 65 °C for 4 hours then concentrated to remove solvent and excess

reagent. The resulting yellow oil was dried at 40 °C under vacuum overnight, 1103 mg (100%).



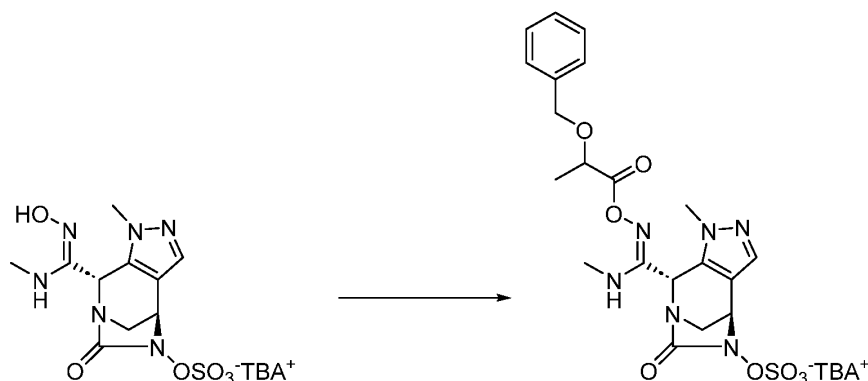
[0079] **Intermediate 7: [(1R,7S)-7-[(Z)-N'-[2-[2-(2-methoxyethoxy)ethoxy]acetyl]oxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0.2,6]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt**

[0080] The title compound was prepared according to the procedure for Intermediate 1 using 2-[2-(2-methoxyethoxy)ethoxy]acetyl chloride (Intermediate 6). The compound was obtained as white solid, 194.4 mg (76%). LCMS: m/z 507 $[M+H]^+$, 505 $[M-H]^-$ for $C_{17}H_{26}N_6O_{10}S$.



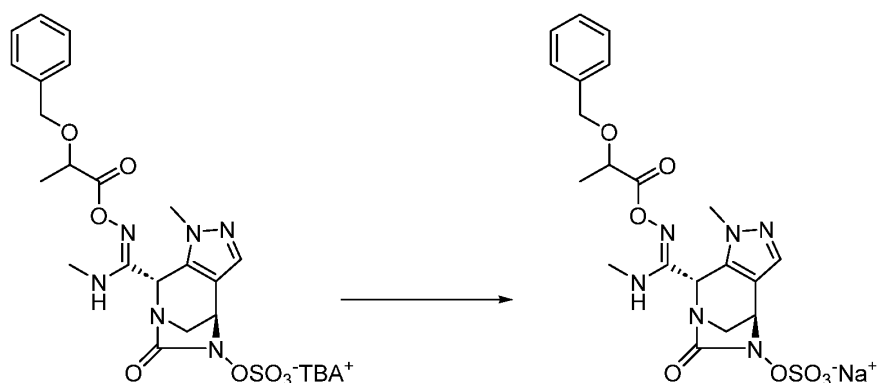
[0081] **Example 6: [(1R,7S)-7-[(Z)-N'-[2-[2-(2-methoxyethoxy)ethoxy]acetyl]oxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0.2,6]undeca-2(6),3-dien-10-yl] sulfate sodium salt**

[0082] The title compound was prepared from Intermediate 7 according to the procedure for Example 1 with additional purification by ISCO (C18Aq column, 0%-50% acetonitrile/water) to afford a white solid, 72.8 mg (51%). LCMS: m/z 507 $[M+H]^+$, 505 $[M-H]^-$ for $C_{17}H_{26}N_6O_{10}S$. 1H NMR: (300 MHz, DMSO): 3.01 (d, $J = 4.8$ Hz, 3H), 3.24 (s, 3H), 3.36 (m, 2H), 3.43 (m, 2H), 3.51 (m, 4H), 3.59 (m, 2H), 3.67 (s, 3H), 4.19 (s, 2H), 4.71 (m, 1H), 6.91 (m, 1H), 7.34 (s, 1H).



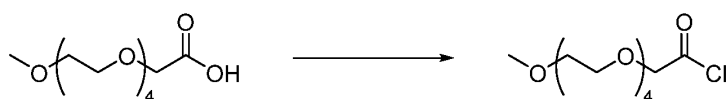
[0083] Intermediate 8: [(1R,7S)-7-[(Z)-N'-(2-benzyloxypropanoyloxy)-N-methyl-carbamimidovyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt

[0084] The title compound was prepared according to the procedure for Intermediate 1 using 2-benzyloxypropanoyl chloride. The compound was obtained as white solid, 205.3 mg (80%). LCMS: m/z 509 [M+H]⁺, 507 [M-H]⁻ for C₂₀H₂₄N₆O₈S.



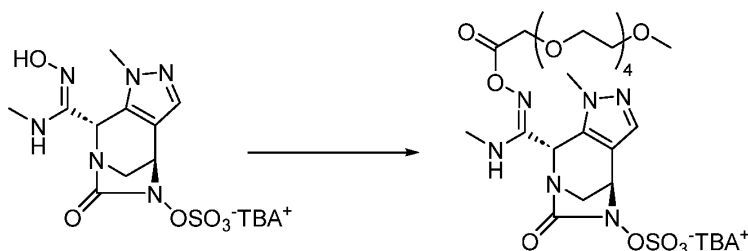
[0085] Example 7: [(1R,7S)-7-[(Z)-N'-(2-benzyloxypropanoyloxy)-N-methyl-carbamimidovyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate sodium salt

[0086] The title compound was prepared from Intermediate 8 according to the procedure for Example 1 to afford a white solid, 116.3 mg (80%). LCMS: m/z 509 [M+H]⁺, 507 [M-H]⁻ for C₂₀H₂₄N₆O₈S. ¹H NMR: (300 MHz, DMSO): 1.38 (d, J = 6.9 Hz, 3H), 3.02 (d, J = 4.8 Hz, 3H), 3.37 (m, 2H), 3.67 (s, 3H), 4.21 (q, J = 6.9 Hz, 1H), 4.49 (q, J = 12 Hz, 2H), 4.72 (m, 1H), 5.67 (s, 1H), 6.81 (m, 1H), 7.29 (m, 6H).



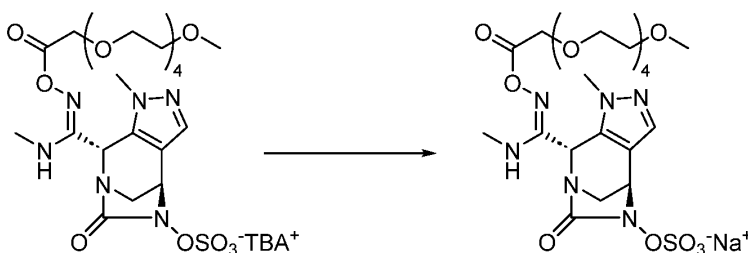
[0087] Intermediate 9: 2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]acetyl chloride

[0088] The title compound was prepared according to the procedure for Intermediate 6 using 2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]acetic acid (500 mg, 1.88 mmol) and drying for 2 hours under vacuum. The compound was obtained as a yellow oil, 534 mg (100%).



[0089] Intermediate 10: [(1R,7S)-7-[(Z)-N'-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]acetyl]oxy-N-methyl-carbamimidovyl]-5-methyl-9-oxo-4,5,8,10-tetraazatricyclo[6.2.1.0]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt

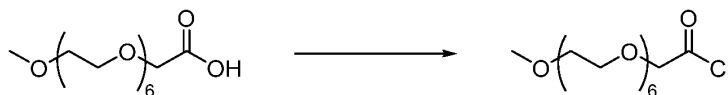
[0090] The title compound was prepared according to the procedure for Intermediate 1 using 2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]acetyl chloride (121.1 mg, 0.43 mmol) (Intermediate 9). The compound was obtained as white solid, 264 mg (74%). LCMS: m/z 595 [M+H]⁺, 593 [M-H]⁻ for C₂₁H₃₄N₆O₁₂S.



[0091] Example 8: (4R,8S)-8-((Z)-N'-((2,5,8,11,14-pentaoxahexadecan-16-oyl)oxy)-N-methylcarbamimidovyl)-1-methyl-6-oxo-4,8-dihydro-1H-4,7-methanopyrazolo[3,4-e][1,3]diazepin-5(6H)-yl hydrogen sulfate sodium salt

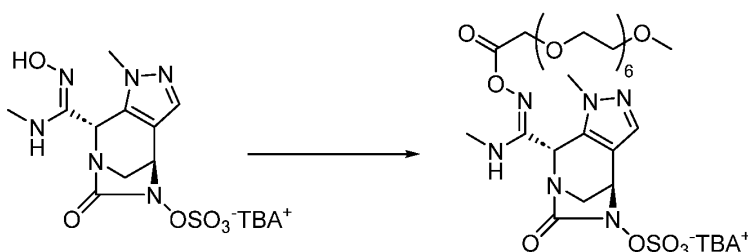
[0092] The title compound was prepared from Intermediate 10 according to the procedure for Example 1 with additional purification by ISCO (C18Aq column, 0%-50% acetonitrile/water) to afford a white solid, 116.4 mg (60%). LCMS: m/z 595 [M+H]⁺, 593 [M-H]⁻ for C₂₁H₃₄N₆O₁₂S. ¹H NMR: (300 MHz, DMSO) 3.01 (d, J = 4.8 Hz, 3H), 3.24 (s,

3H), 3.36 (m, 2H), 3.43 (m, 2H), 3.51 (m, 13H), 3.59 (m, 2H), 3.67 (s, 3H), 4.19 (s, 2H), 4.71 (m, 1H), 5.64 (s, 1H), 6.91 (m, 1H), 7.34 (s, 1H).



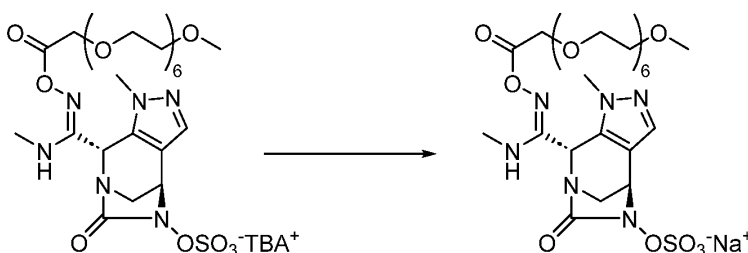
[0093] Intermediate 11: 2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acetyl chloride

[0094] The title compound was prepared according to the procedure for Intermediate 6 using 2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acetic acid (500 mg, 1.41 mmol) and drying for 2 hours under vacuum. The compound was obtained as a yellow oil, 526 mg (100%).



[0095] Intermediate 12: [(1R,7S)-7-[(Z)-N'-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acetyl]oxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt

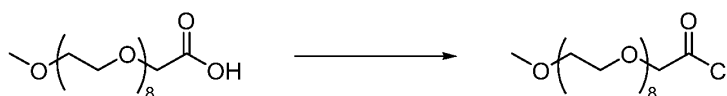
[0096] The title compound was prepared according to the procedure for Intermediate 1 using 2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acetyl chloride (158.58 mg, 0.43 mmol) (Intermediate 11). The compound was obtained as white solid, 277 mg (71%). LCMS: m/z 683 [M+H]⁺, 681 [M-H]⁻ for C₂₅H₄₂N₆O₁₄S.



[0097] Example 9: [(1R,7S)-7-[(Z)-N'-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acetyl]oxy-N-methyl-

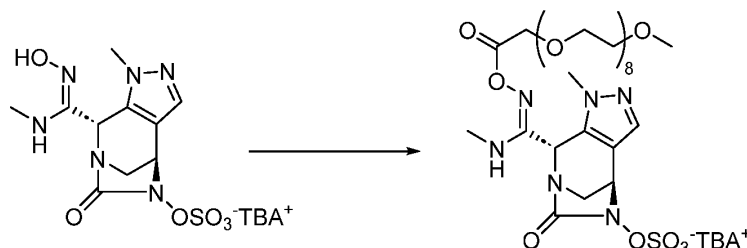
carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate sodium salt

[0098] The title compound was prepared from Intermediate 12 according to the procedure for Example 1 with additional purification by ISCO (C18Aq column, 0%-50% acetonitrile/water) to afford a white solid, 137.8 mg (65%). LCMS: m/z 683 [M+H]⁺, 681 [M-H]⁻ for C₂₅H₄₂N₆O₁₄S. ¹H NMR: (300 MHz, DMSO) 3.01 (d, J = 4.8 Hz, 3H), 3.24 (s, 3H), 3.36 (m, 2H), 3.43 (m, 2H), 3.51 (m, 2H), 3.59 (m, 2H), 3.67 (s, 3H), 4.19 (s, 2H), 4.71 (m, 1H), 5.64 (s, 1H), 6.90 (m, 1H), 7.34 (s, 1H).



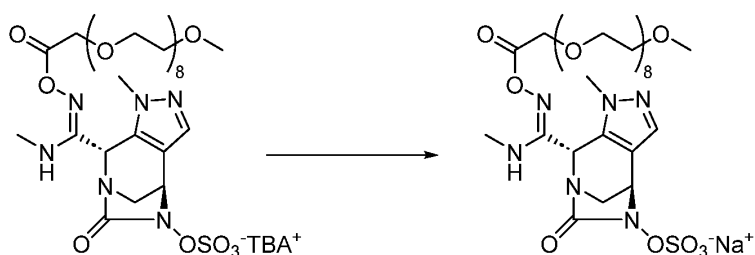
Intermediate 13: 2-[2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acetyl chloride

[00100] The title compound was prepared according to the procedure for Intermediate 6 using 2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acetic acid (500 mg, 1.13 mmol) and drying for 2 hours under vacuum. The compound was obtained as a yellow oil, 521 mg (100%).



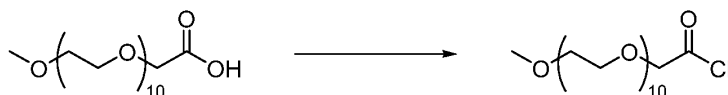
Intermediate 14: [(1R,7S)-7-[(Z)-N'-[2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acetyl]oxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt

[00102] The title compound was prepared according to the procedure for Intermediate 1 using 2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acetyl chloride (196.05 mg, 0.43 mmol) (Intermediate 13). The compound was obtained as white solid, 251.5 mg (57%). LCMS: m/z 771 [M+H]⁺, 769 [M-H]⁻ for C₂₉H₅₀N₆O₁₆S.



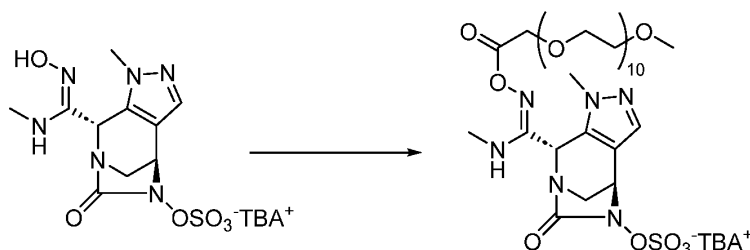
[00103] Example 10: (4R,8S)-8-((Z)-N'-((2,5,8,11,14,17,20,23,26-nonaaoctacosan-28-oyl)oxy)-N-methylcarbamimidoyl)-1-methyl-6-oxo-4,8-dihydro-1H-4,7-methanopyrazolo[3,4-e][1,3]diazepin-5(6H)-yl hydrogen sulfate sodium salt

[00104] The title compound was prepared from Intermediate 14 according to the procedure for Example 1 with additional purification by ISCO (C18Aq column, 0%-50% acetonitrile/water) to afford a white solid, 63.9 mg (32%). LCMS: m/z 771 [M+H]⁺, 769 [M-H]⁻ for C₂₉H₅₀N₆O₁₆S. ¹H NMR: (300 MHz, DMSO) 3.01 (d, J = 4.8 Hz, 3H), 3.24 (s, 3H), 3.36 (m, 2H), 3.43 (m, 2H), 3.51 (m, 29H), 3.59 (m, 2H), 3.67 (s, 3H), 4.19 (s, 2H), 4.71 (m, 1H), 5.64 (s, 1H), 6.91 (m, 1H), 7.34 (s, 1H).



[00105] Intermediate 15: 2-[2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acetyl chloride

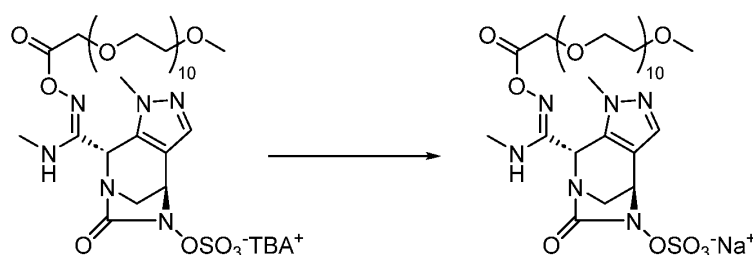
[00106] The title compound was prepared according to the procedure for Intermediate 6 using 2-[2-[2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acetic acid (500 mg, 0.94 mmol) and drying for 2 hours under vacuum. The compound was obtained as a yellow oil, 517 mg (100%).



[00107] Intermediate 16: [(1R,7S)-7-[(Z)-N'-(2-[2-[2-[2-[2-[2-[2-[2-[2-[2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acety

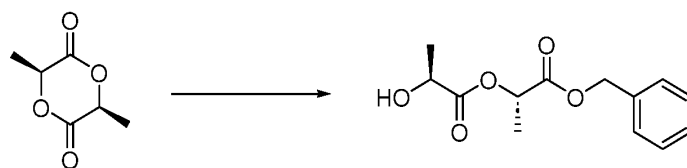
lloxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0^{2,6}undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt

[00108] The title compound was prepared according to the procedure for Intermediate 1 using 2-[2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]acetyl chloride (233.53 mg, 0.43 mmol) (Intermediate 15). The compound was obtained as a colorless oil, 322.6 mg (69%). LCMS: m/z 859 [M+H]⁺, 857 [M-H]⁻ for C₃₃H₅₈N₆O₁₈S.



[00109] Example 11: (4R,8S)-8-((Z)-N'-((2,5,8,11,14,17,20,23,26,29,32-undeca-oxatetriacontan-34-oyl)oxy)-N-methylcarbamimidoyl)-1-methyl-6-oxo-4,8-dihydro-1H-4,7-methanopyrazolo[3,4-c][1,3]diazepin-5(6H)-yl hydrogen sulfate sodium salt

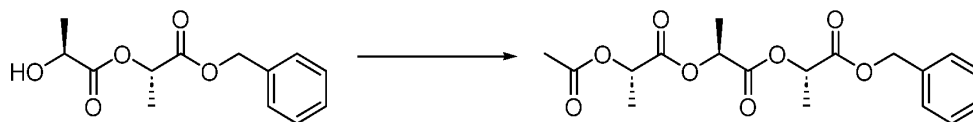
[00110] The title compound was prepared from Intermediate 16 according to the procedure for Example 1 with additional purification by ISCO (C18Aq column, 0%-50% acetonitrile/water) to afford a white solid, 164.7 mg (64%). LCMS: m/z 859 [M+H]⁺, 857 [M-H]⁻ for C₃₃H₅₈N₆O₁₈S. ¹H NMR: (300 MHz, DMSO) 3.01 (d, J = 4.8 Hz, 3H), 3.24 (s, 3H), 3.36 (m, 2H), 3.43 (m, 2H), 3.51 (m, 37H), 3.59 (m, 2H), 3.67 (s, 3H), 4.19 (s, 2H), 4.71 (m, 1H), 5.64 (s, 1H), 6.91 (m, 1H), 7.34 (s, 1H).



[00111] Intermediate 17: [(1S)-2-benzyloxy-1-methyl-2-oxo-ethyl] (2S)-2-hydroxypropanoate

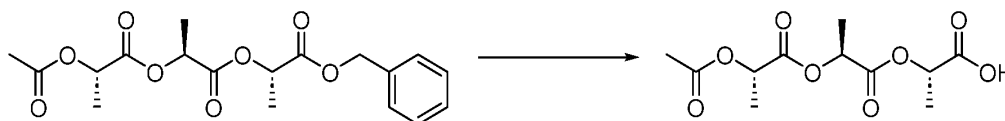
[00112] To a solution of (3S,6S)-3,6-dimethyl-1,4-dioxane-2,5-dione (500 mg, 3.47 mmol) and phenylmethanol (0.32 mL, 3.12 mmol) in toluene at room temperature was added camphor sulfonic acid (80.59 mg, 0.35 mmol). The reaction mixture was heated to 80 C for 2 hours then cooled to room temperature. The reaction mixture was diluted with ethyl acetate

and washed with 1:1 brine:water. The organics were dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0%-5% methanol/DCM) afforded desired product as a colorless liquid, 685 mg (78%). LCMS: m/z 253 $[M+H]^+$ for $C_{13}H_{16}O_5$.



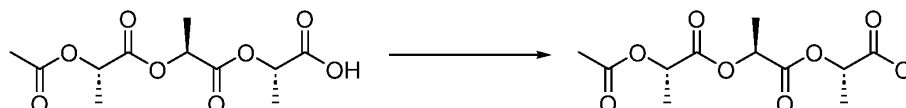
[00113] Intermediate 18: [(1S)-2-[(1S)-2-benzyloxy-1-methyl-2-oxo-ethoxy]-1-methyl-2-oxo-ethyl] (2S)-2-acetoxypropanoate

[00114] To a solution of [(1S)-2-benzyloxy-1-methyl-2-oxo-ethyl] (2S)-2-hydroxypropanoate (400 mg, 1.59 mmol) (Intermediate 17) and triethylamine (0.22 mL, 1.59 mmol) in DCM (6 mL) at 0 °C was added [(1S)-2-chloro-1-methyl-2-oxo-ethyl] acetate (238.74 mg, 1.59 mmol). The reaction mixture was warmed to room temperature, stirred for 1 hour and concentrated. C18Aq ISCO (100% water to 100% acetonitrile/water) afforded product as a colorless oil, 276.8 mg (48%). LCMS: m/z 367 $[M+H]^+$ for $C_{18}H_{22}O_8$.



[00115] Intermediate 19: (2S)-2-[(2S)-2-[(2S)-2-acetoxypropanoyl]oxypropanoyl]oxypropanoic acid

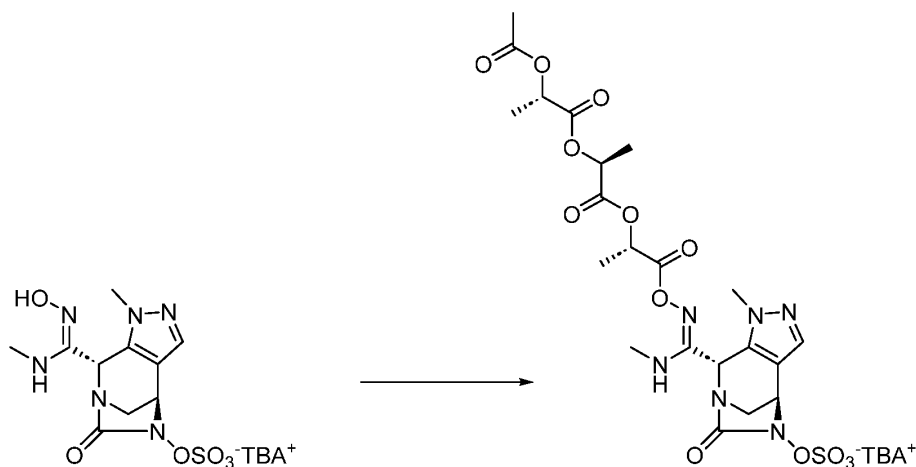
[00116] A solution of (2S)-2-[(2S)-2-[(2S)-2-acetoxypropanoyl]oxypropanoyl]oxypropanoic acid (191.1 mg, 0.69 mmol) (Intermediate 18) in methanol (4 mL) was degassed with nitrogen and Pd/C (80.4 mg, 0.08 mmol) was added. The mixture was degassed again and placed under hydrogen balloon for 1 hour. The reaction mixture was flushed with nitrogen, filtered through a 0.45 μ filter and concentrated to afford a colorless oil, 191.1 mg (92%). LCMS: m/z 277 $[M+H]^+$ for $C_{11}H_{16}O_8$.



[00117] Intermediate 20: [(1S)-2-[(1S)-2-chloro-1-methyl-2-oxo-ethoxy]-1-methyl-2-oxo-ethyl] (2S)-2-acetoxypropanoate

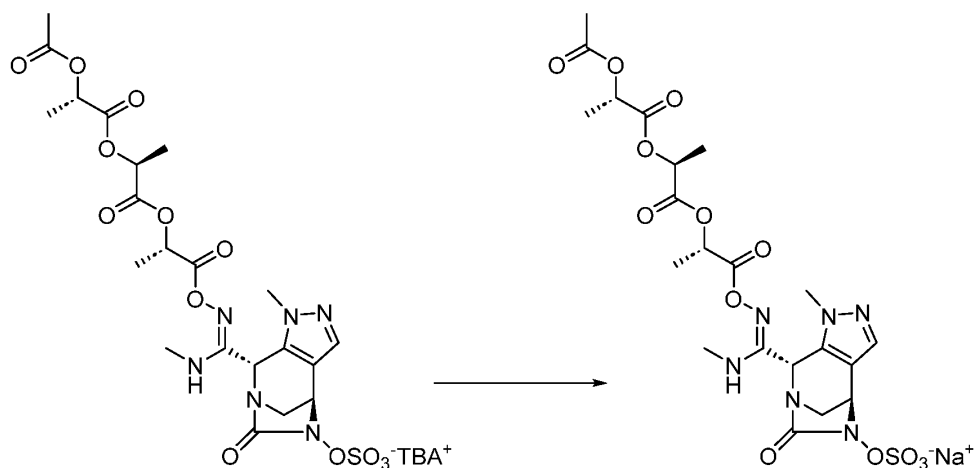
[00118] The title compound was prepared according to the procedure for Intermediate 6 using (2S)-2-[(2S)-2-[(2S)-2-acetoxypropanoyl]oxypropanoyl]oxypropanoic acid (191.1 mg,

0.69 mmol) (Intermediate 19) and drying for 2 hours under vacuum. The compound was obtained as a yellow oil, 174.8 mg (86%).



[00119] Intermediate 21: [(1R,7S)-7-[(Z)-N'-[(2S)-2-[(2S)-2-[(2S)-2-acetoxypropanoyl]oxypropanoyl]oxypropanoyl]oxy-N-methyl-carbamimidoyl]-5-methyl-9-oxo-4,5,8,10-tetrazatricyclo[6.2.1.0]undeca-2(6),3-dien-10-yl] sulfate tetrabutylammonium salt

[00120] The title compound was prepared according to the procedure for Intermediate 1 using [(1S)-2-[(1S)-2-chloro-1-methyl-2-oxo-ethoxy]-1-methyl-2-oxo-ethyl] (2S)-2-acetoxypropanoate (125.34 mg, 0.43 mmol) (Intermediate 20). The compound was obtained as a white solid, 329.9 mg (92%). LCMS: m/z 605 $[M+H]^+$, 603 $[M-H]^-$ for $C_{21}H_{28}N_6O_{13}S$.



[00121] Example 12: (7S,10S,Z)-7-methyl-3-((4R,8S)-1-methyl-6-oxo-5-(sulfooxy)-4,5,6,8-tetrahydro-1H-4,7-methanopyrazolo[3,4-e][1,3]diazepin-8-yl)-6,9-dioxo-5,8-dioxa-2,4-diazaundec-3-en-10-yl (2S)-2-acetoxypropanoate sodium salt

[00122] The title compound was prepared from Intermediate 21 according to the procedure for Example 1 with additional purification by ISCO (C18Aq column, 0%-50% acetonitrile/water) to afford a white solid, 159.3 mg (65%). LCMS: m/z 605 [M+H]⁺, 603 [M-H]⁻ for C₂₁H₂₈N₆O₁₃S. ¹H NMR: (300 MHz, DMSO) 1.38 (m, 9H), 1.99 (m, 3H), 2.96 (d, J=4.8 Hz, 3H), 3.22 (m, 2H), 3.59 (s, 3H), 4.63 (m, 1H), 5.09 (m, 3H), 5.60 (s, 1H), 6.82 (m, 1H), 7.25 (m, 1H).

[00123] **Microbiological testing.** The minimal inhibitory concentrations (MICs) of Comparator A and Example 6 against the *Klebsiella pneumoniae* isolate ARC2356 were determined according to Clinical and Laboratory Standards Institute (CLSI) guideline M07-A10 (*Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* 11th edn (Clinical and Laboratory Standards Institute, 2018)). The results are summarized in Table 1.

Table 1. MIC Summary of Comparator A and Example 6 vs. *K. pneumoniae* ARC2356

Strain	MIC (μg/mL)	
	Comparator A	Example 6
<i>K. pneumoniae</i> ARC2356	0.25	4

[00124] **Animal Welfare Statement:** All *in vivo* procedures were completed in compliance with the Animal Welfare Act Regulations (9 CFR 3) under Entasis reviewed IACUC protocols and under the supervision of a site attending veterinarian.

[00125] **Neutropenic Murine Lung Model.** *In vivo* neutropenic infection models in the mouse were conducted as previously described (2,3). All procedures were performed to Entasis approved IACUC policies and guidelines as well as OLAW standards. Briefly, Female CD-1 mice (20-22 gm, Charles River Laboratories) were acclimated for 5 days prior to start of study. Animals were housed 3 per cage with free access to food and water. Mice were rendered neutropenic via two doses of cyclophosphamide on days -4 and -1 with 150 mg/kg and 100 mg/kg delivered intraperitoneally in a dose volume of 10 mL/kg, respectively.

[00126] The *K. pneumoniae* isolate ARC2356 was prepared for infection from an overnight plate culture. A portion of the plate was resuspended in sterile saline and adjusted to an OD of 0.1 at 625 nm. The adjusted bacterial suspension was further diluted to target an

infecting inoculum of approximately 5.0×10^5 CFU/mouse. Mice were anesthetized with isoflurane and infected by intratracheal injection of 50 μ L of the prepared inoculum. Infected the animals were returned to cages to recover from the anesthesia. The actual inoculum size was 8.0×10^5 CFU/mouse lung. Plate counts of the inoculum were performed to confirm inoculum concentration and treatment was initiated 2 hours after bacterial challenge.

[00127] Comparator A, Example 6, and the positive control, levofloxacin were formulated in water for injection (WFI) and dosed via subcutaneous administration. A vehicle (no treatment) control was included as a dose arm. Levofloxacin was dosed at 160 mg/kg q24h. All dose concentrations were adjusted to deliver targeted mg/kg doses within a dose volume of 10 mL/kg. Comparator A was administered at doses of 10 and 50 mg/kg q3h and Example 6 was administered at Comparator A equivalent doses of 10 and 50 mg/kg q3h. Formulation potency was verified by LC/MS/MS. Comparator A and Example 6 were administered via q3h dose intervals in order to achieve targeted unbound exposures. At 24 hours post initiation of therapy, animals were euthanized and lungs were aseptically collected and homogenized. Bacterial colony enumeration of tissue homogenate was performed by serial dilution on TSA plates which were incubated overnight at 35°C prior to colony (CFU) counting. Efficacy was measured as the change in $\log_{10}$ CFU/g of lung following 24 hours of treatment. The results of the study are summarized in Table 2.

Table 2. Summary of Murine Lung Infection Model vs. *K. pneumoniae* ARC2356

Group ID	Dose (mg/kg)	route/ regimen	Average $\log_{10}$ CFU/ g of lung	St. Dev.	Change in $\log_{10}$ CFU/ g of lung from	
					2-hour controls (pre-dose)	26-hour controls
T=2 hr	n/a	n/a	6.00	0.32		-1.45
26 hr. Inf. Vehicle Control	n/a	n/a	7.45	0.79	1.45	
Comparator A	10	SC/Q3 hr	4.14	0.26	-1.86	-3.31
	50	SC/Q3 hr	2.64	0.21	-3.36	-4.81
Example 6	10	SC/Q3 hr	4.25	0.27	-1.75	-3.20
	50	SC/Q3 hr	2.83	0.24	-3.17	-4.62
Levofloxacin	160	SC/Q24 hr	2.24	0.05	-3.76	-5.21

[00128] Near equivalent reduction in CFU burden was observed with Comparator A and Example 6 dose arms administered subcutaneously at 10 and 50 mg/kg q3h. These data

suggest that once Example 6 is administered, the compound is efficiently hydrolyzed to Comparator A resulting in identical efficacy as observed with dosing of Comparator A itself.

[00129] Murine Pharmacokinetics

[00130] Satellite groups of infected animals were used for pharmacokinetic analysis of Comparator A and Example 6 following subcutaneous administration. Absolute dose levels of 10, 50, and 250 mg/kg were evaluated. Three animals were utilized per blood sampling timepoint with three timepoints per animal- two submandibular bleeds and one terminal bleed taken via cardiac puncture. Blood samples (50 μ L) were collected into K₂EDTA microtainer tubes and process for plasma. Resulting plasma was diluted 1:1 with a solution of SigmaFast protease inhibitor (10 mg/mL in water), prior to storage at -70°C. Timepoints were taken at 0.25, 0.5, 1, 2, 4, and 6 hours post-dose.

[00131] Bioanalytical Assay

[00132] Calibration standards and quality control samples were prepared by serial dilution in 1:1 (by volume) blank mouse plasma:SigmaFast protease inhibitor solution. The SigmaFast was made by dissolving one tablet in 10 ml of deionized water (10 mg/mL). An aliquot (50 μ l) of each standard along with plasma samples (diluted separately) were transferred to a 96-well plate and treated with 200 μ l of crash solution to precipitate the protein. The crash solution consisted of 100% acetonitrile containing 0.1% formic acid and 250 ng/mL of carbutamide (Millipore-Sigma) as an internal standard. The plates were then vortexed and centrifuged, and the supernatant was transferred for LC/MS/MS analysis. Instrument conditions for LC/MS/MS analysis are summarized in Table 3.

Table 3. LC-MS/MS conditions for the determination of Comparator A and Example 6 in treated mouse plasma

Instrument	Shimadzu UPLC - QTrap 6500 LC/MS/MS Mass Spectrometer		
Column	Atlantis T3, 5 μ , 50 x 3.0mm		
Column Temperature	35°C		
Sample Temperature	15°C		
Flow rate	1.200 mL/min		
Gradient	Time (min)	%B	Curve
	Initial	1.0	
	0.3	1.0	6
	1.3	98	6
	1.75	98	6
	1.76	1.0	6
	2.00	Stop	

Divert Valve	0.30 min to Mass Spec 1.80 min to waste		
Mobile Phase A	0.1% formic acid in water		
Mobile Phase B	0.1% formic acid in Acetonitrile		
MRM	Source Type Turbo Spray Polarity: Negative Resolution Q1: Unit Resolution Q3: Unit DP -55.00 IS: -4500.00 TEM: 650.00 GS1: 70.00 GS2: 60.00 CAD: Medium		
Injection volume	0.5 µL		

MRM Transitions:

Compound ID	Q1	Q3	DP	CE	CXP
Comparator A	344.786	96.90	-55	-26	-13
Example 6	504.958	95.900	-15	-86	-15
Carbutamide (IS)	270.00	171.00	-55	-25	-10

[00133] Protein Binding

[00134] Plasma protein binding was determined for Comparator A by rapid equilibrium dialysis. Plasma was freshly prepared from mouse blood samples drawn into tubes containing K₂EDTA (anticoagulant). Plasma was prepared using a tabletop centrifuge and spun per instruction of the tube manufacturer and specifications (Beckton Dickinson) and placed on ice before use. Pooled plasma samples were centrifuged at 2,000 rpm (approximately 1,400g) for 15 min at 4 °C to remove debris. Approximately 90% of the clear supernatant fraction was transferred to a separate tube. Samples (500 µL) were then spiked with a 100× stock solution 100 µM, 0.5 mM, and 10 mM of compound in DMSO, respectively for 1, 5 and 100 µM final concentrations, transferred to the top of the filter chambers, and allowed to equilibrate for 15 min prior to centrifugation. The filtrate tubes were centrifuged at 14,000g for 15 min at 4 °C. Next, 50 µL of the filtrate was precipitated with 300 µL of acetonitrile containing 250 ng/mL carbutamide as the internal standard and the samples were analyzed by LC/MS/MS as described previously.

[00135] Pharmacokinetics and Exposure Analysis

[00136] PK model fitting of the concentration vs. time profile data for Comparator A obtained from single doses of 10, 50, and 250 mg/kg was completed using Phoenix WinNonLin 8.1 (Certara L. P., Princeton, NJ). A 2-compartment model with an

extravascular first-order absorption rate input provided the best fit of the subcutaneous PK obtained across the dose range. Parameter estimates were used to interpolate unbound exposures above concentrations (MICs) summarized in Table 4 considering a protein binding of 22% value determined for Comparator A.

Table 4. Percent Time Above MIC Estimates of Comparator A in Plasma Following Subcutaneous Administration q3h to CD-1 Mice

Dose mg/kg	Concentration (MIC), µg/mL				
	0.25	0.5	1	2	4
6.25	38.3	30.7	23.3	15.7	9.0
12.5	48.3	38.3	30.0	23.3	16.7
25	61.7	48.3	39.0	30.0	23.3
50	78.3	61.7	48.3	39.3	30.0
200	100.0	100.0	78.3	61.7	48.3
250	100.0	100.0	85.0	66.7	52.3

[00137] In consideration of Comparator A and Example 6 MICs of 0.25 and 4 µg/mL, Time>MIC estimates of 45% and 14.5% were estimated at the 10 mg/kg q3h dose level and 78% and 30% at the 50 mg/kg q3h dose level, respectively. Based on the observation that greater than 50% Time>MIC is required for bactericidal activity for this compound class and the identical degree of bacterial burden reduction was observed across both dose arms for Comparator A and Example 6, the data suggests complete conversion of Example 6 to Comparator A once absorbed systemically from the subcutaneous compartment.

[00138] Conversion of Example 6 in Mouse and Human Plasma

[00139] The conversion of Example 6 to Comparator A was evaluated *ex-vivo* in mouse and human plasma at 37°C prepared from K₂EDTA tubes and compared to incubations run at the same concentration in phosphate buffered saline (PBS). Aliquots (25 µL) were taken at 0, 0.25, 0.5, 1, 2, 4, 6, and 24 hours following compound addition and assayed by LC-MS/MS as previously described. The concentration of Example 6 was 31.5 µM in the incubation. Samples were assayed for Example 6 and Comparator A concentrations to determine mass balance (Example 6+ Comparator A relative to initial Example 6 concentration) and determined the first-order degradation/conversion of Example 6 to Comparator A. The results are summarized in Table 5.

[00140] Rapid and quantitative conversion of Example 6 to Comparator A was observed in mouse and human plasma. The conversion of Example 6 to Comparator A in mouse plasma

was consistent with the observed efficacy in the neutropenic lung infection model following subcutaneous administration of Example 6.

Table 5. Conversion of EXAMPLE 6 to COMPARATOR A in Mouse and Human Plasma at 37°C at a Concentration of 31.5 μ M over 24 hours

Matrix	Half-life (hours)	Example 6+ Comparator A (μ M)	Percent converted. (%)
Phosphate Buffered Saline	10	ND	ND
Mouse Plasma	0.4	31.5	100
Human Plasma	2	31.5	100

ND = not determined

[00141] Stability of Comparator A and Example 6 at 10 and 100 mg/mL in Water For Injection (WFI) at Room Temperature and 2-4°C.

[00142] The solution stability of Comparator A and Example 6 was assessed in parallel at ambient (room) temperature over the course of 21 hours at concentrations of 10 and 100 mg/mL in Water For Injection (WFI). Serial samples (25 μ L) were obtained at approximately 0, 0.5, 1, 2, 4, 6, 8, and 20 hours following solubilization and assayed by LC-MS/MS as described previously. First order degradation rate constants of Comparator A and Example 6 were determined from regression of the concentration vs. time data. Results are summarized in Table 6 for stability of Comparator A and Example 6 at ambient (room) temperature and 2-4°C.

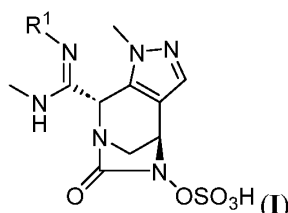
Table 6. Stability of Comparator A and Example 6 in Water For Injection (WFI) at Room Temperature and 2-4°C.

Compound	Concentration, mg/mL	Half-life (hours)	
		Room Temperature	2-4°C
Comparator A	10	>144	>144
	100	17	>144
Example 6	10	>144	>144
	100	129	>144

[00143] The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

Listing of Claims:

1. A compound of the Formula I:

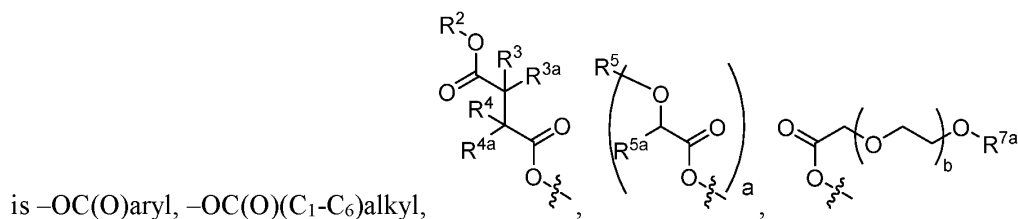


or a pharmaceutically acceptable salt thereof, wherein

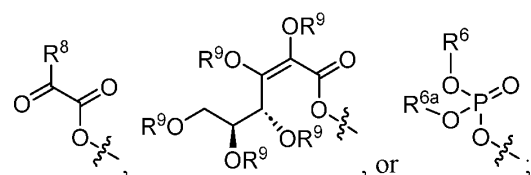
$R^1 - OC(O)R^A$, and

R^A is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, and optionally substituted (C_1-C_{20}) alkyl, wherein said optionally substituted (C_1-C_{20}) alkyl may be interrupted with one or more heteroatoms selected from O, N, and S, and wherein two adjacent hydrogen atoms on the same carbon atom of one or more carbons on said (C_1-C_{20}) alkyl may be taken together to form $=O$.

2. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1



is $-OC(O)$ aryl, $-OC(O)(C_1-C_6)$ alkyl,



R^2 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, and optionally substituted (C_1-C_6) alkyl, wherein said optionally substituted (C_1-C_6) alkyl may be interrupted with one or more heteroatoms selected from O, N, and S;

R³, R^{3a}, R⁴, and R^{4a} are each independently selected from hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, OH, -OC(O)(C₁-C₆)alkyl, O(C₁-C₆)alkylO(C₁-C₆)alkyl, -O(C₁-C₆)alkylC(O)(C₁-C₆)alkyl, and -O(C₁-C₆)alkylC(O)(C₁-C₆)alkyl;

R⁵ is selected from hydrogen, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, optionally substituted (C₁-C₆)alkyl, -C(O)(C₁-C₂₀)alkyl, -C(O)aryl, -C(O)heterocyclyl, -C(O)heteroaryl, wherein each of said (C₁-C₂₀)alkyl, aryl, heterocyclyl, and heteroaryl on the -C(O) group are optionally substituted and wherein said (C₁-C₂₀)alkyl on the -C(O) group may be interrupted with one or more heteroatoms selected from O, N, and S, and wherein two adjacent hydrogen atoms on the same carbon atom of one or more carbons on said (C₁-C₂₀)alkyl may be taken together to form =O;

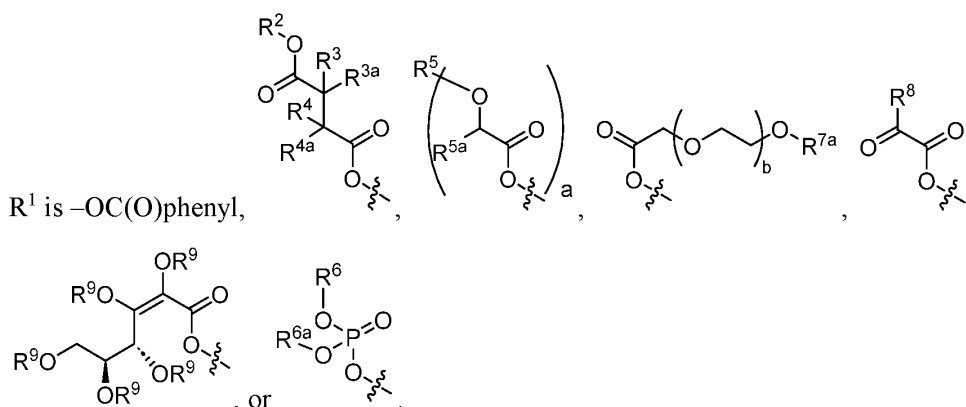
R^{5a}, R⁷, R^{7a}, and R⁸ are each independently (C₁-C₆)alkyl;

R⁶ and R^{6a} are each independently hydrogen, aryl, or (C₁-C₆)alkyl;

each R⁹ is independently hydrogen or (C₁-C₆)alkyl; and

a and b are both integers ranging from 1 to 20.

3. The compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein



4. The compound of Claim 2 or 3, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen or (C₁-C₄)alkyl.

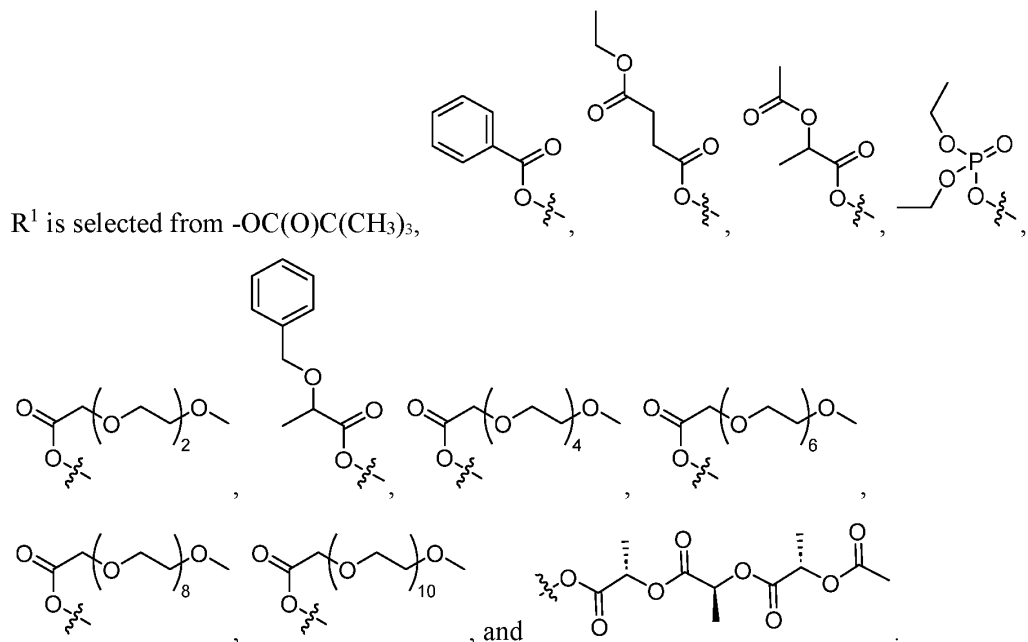
5. The compound of any one of Claims 2 to 4, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen or CH₃.

6. The compound of any one of Claims 2 to 5, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen or (C₁-C₄)alkyl.
7. The compound of any one of Claims 2 to 6, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen or CH₃.
8. The compound of any one of Claims 2 to 7, or a pharmaceutically acceptable salt thereof, wherein R^4 is (C₁-C₄)alkyl.
9. The compound of any one of Claims 2 to 8, or a pharmaceutically acceptable salt thereof, wherein R^4 is CH₃.
10. The compound of any one of Claims 2 to 9, or a pharmaceutically acceptable salt thereof, wherein R^{4a} is (C₁-C₄)alkyl.
11. The compound of any one of Claims 2 to 10, or a pharmaceutically acceptable salt thereof, wherein R^{4a} is CH₃.
12. The compound of any one of Claims 2 to 11, or a pharmaceutically acceptable salt thereof, wherein R^5 is (C₁-C₄)alkyl, (C₁-C₄)alkyl(phenyl), or -C(O)(C₁-C₁₀)alkyl, wherein said (C₁-C₁₀)alkyl is interrupted with one or more O atoms, and wherein two adjacent hydrogen atoms on the same carbon atom of one or more carbons on said (C₁-C₁₀)alkyl are taken together to form =O.
13. The compound of any one of Claims 2 to 12, or a pharmaceutically acceptable salt thereof, wherein R^5 is CH₃, CH₂(phenyl), or -C(O)(CH)CH₃OC(O)CHCH₃OC(O)CH₃.
14. The compound of any one of Claims 2 to 13, or a pharmaceutically acceptable salt thereof, wherein R^{5a} is (C₁-C₄)alkyl.
15. The compound of any one of Claims 2 to 14, or a pharmaceutically acceptable salt thereof, wherein R^{5a} is CH₃.

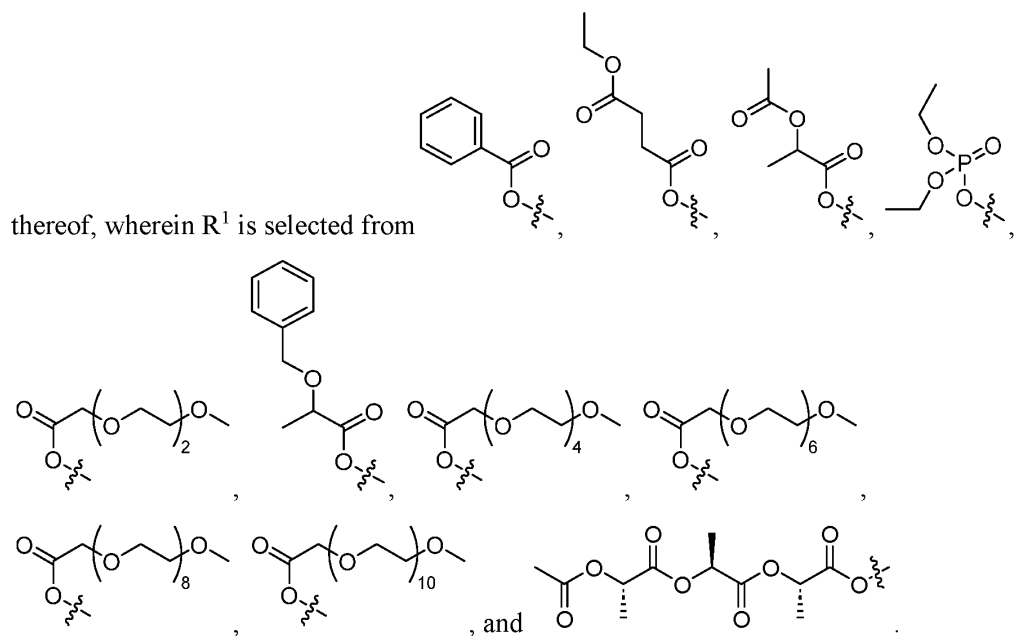
16. The compound of any one of Claims 2 to 15, or a pharmaceutically acceptable salt thereof, wherein R^6 is (C₁-C₄)alkyl.
17. The compound of any one of Claims 2 to 16, or a pharmaceutically acceptable salt thereof, wherein R^6 is CH₂CH₃.
18. The compound of any one of Claims 2 to 17, or a pharmaceutically acceptable salt thereof, wherein R^{6a} is (C₁-C₄)alkyl.
19. The compound of any one of Claims 2 to 18, or a pharmaceutically acceptable salt thereof, wherein R^{6a} is CH₂CH₃.
20. The compound of any one of Claims 2 to 19, or a pharmaceutically acceptable salt thereof, wherein R^7 is (C₁-C₄)alkyl.
21. The compound of any one of Claims 2 to 20, or a pharmaceutically acceptable salt thereof, wherein R^7 is CH₃.
22. The compound of any one of Claims 2 to 21, or a pharmaceutically acceptable salt thereof, wherein R^{7a} is (C₁-C₄)alkyl.
23. The compound of any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein R^{7a} is CH₃.
24. The compound of any one of Claims 1 to 23, or a pharmaceutically acceptable salt thereof, wherein a is 1.
25. The compound of any one of Claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein b is an integer from 2 to 10.
26. The compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein b is 2, 4, 6, 8, or 10.

27. The compound of any one of Claims 1 to 26, or a pharmaceutically acceptable salt thereof, wherein b is 2.

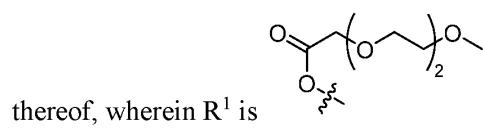
28. The compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein



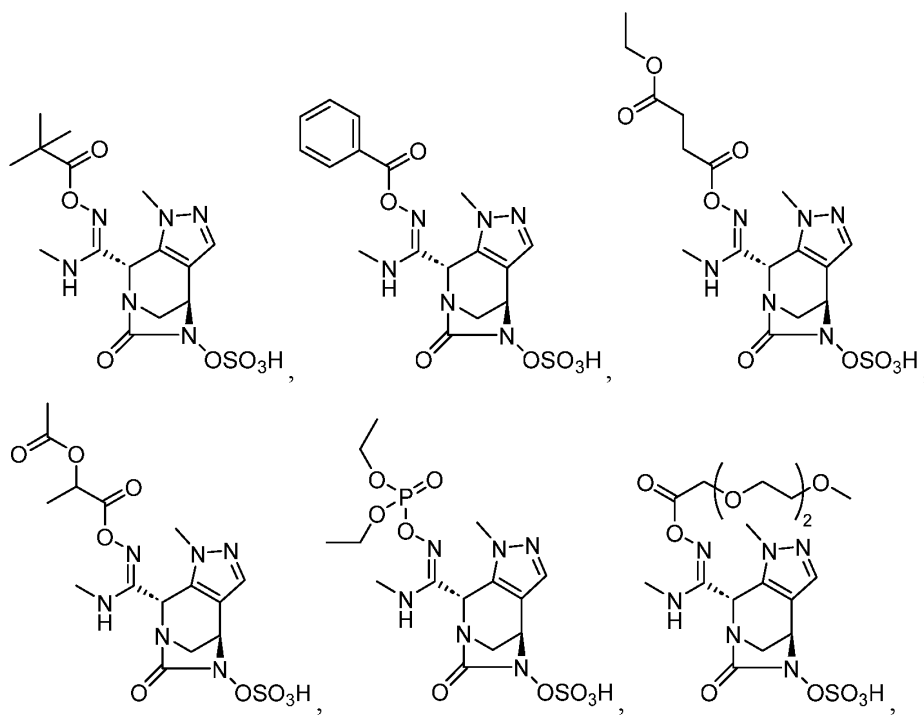
29. The compound of any one of Claims 1 to 28, or a pharmaceutically acceptable salt

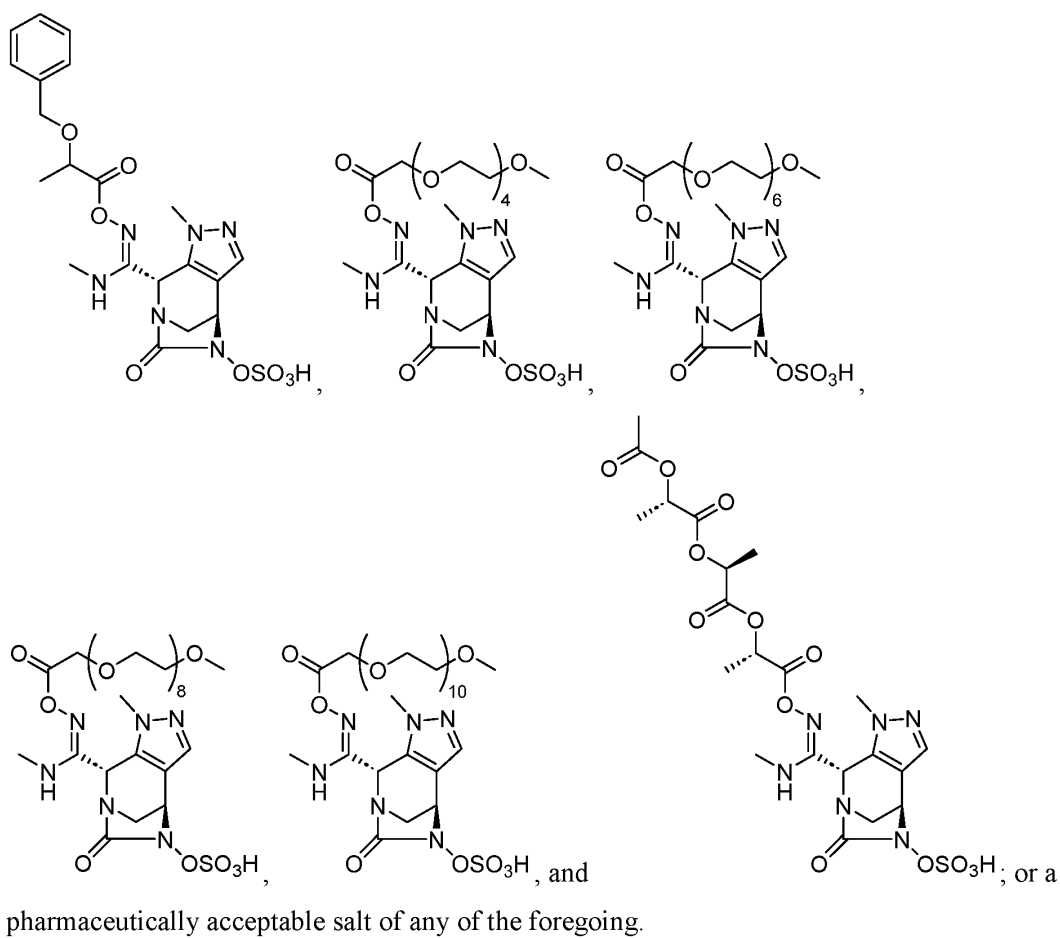


30. The compound of any one of Claims 1 to 29, or a pharmaceutically acceptable salt

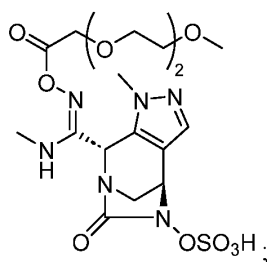


31. The compound of Claim 1, wherein the compound is selected from





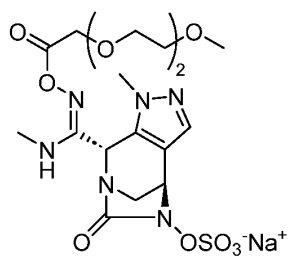
32. The compound of Claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

33. The pharmaceutically acceptable salt of any one of Claims 1 to 32, wherein the pharmaceutically acceptable salt is a sodium salt.

34. The compound of Claim 1, wherein the compound is a pharmaceutically acceptable salt having the structural formula:



35. A pharmaceutical composition comprising a compound of any one of Claims 1 to 34, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.
36. A method of treating a bacterial infection in a subject in need thereof comprising administering to the subject an effective amount of a compound of any one of Claims 1 to 34, or a pharmaceutically acceptable salt thereof, or the composition of Claim 35.
37. The method of Claim 36, wherein the bacterial infection is caused by a Gram-negative bacteria.
38. The method of Claim 36 or 37, wherein the bacterial infection is caused by *P. aeruginosa*.
39. The method of Claim 36 or 37, wherein the bacterial infection is caused by *Enterobacteriaceae*.
40. The method of Claim 36 or 37, wherein the bacterial infection is caused by *E. coli*, *K. pneumoniae*, or *Acinetobacter* spp.
41. The method of Claim 40, wherein the bacterial infection is caused by a pathogen selected from *Burkholderia* spp., *B. anthracis*, *Y. pestis*, and *F. tularensis*.
42. A method of inhibiting bacterial Penicillin Binding Protein 3 (PBP3) and optionally inhibiting bacterial PBP1a/b in a subject in need thereof comprising administering to the subject an effective amount of a compound of any one of Claims 1 to 34, or a pharmaceutically acceptable salt thereof, or the composition of Claim 35.