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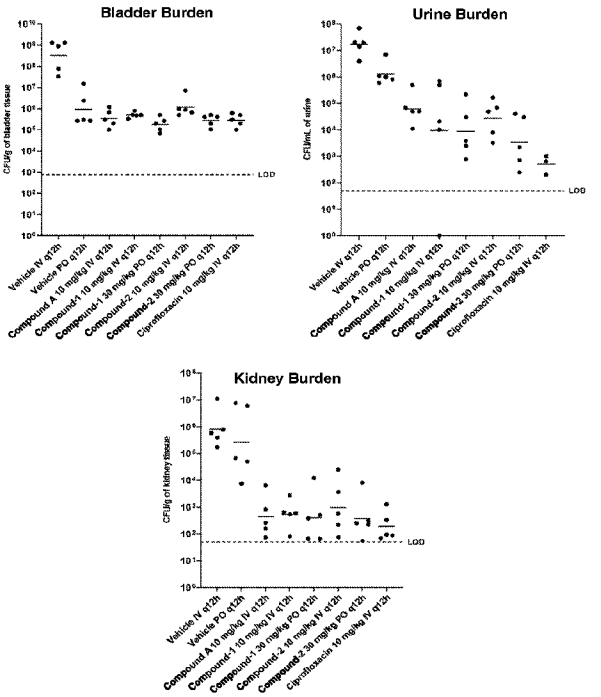
(54) **Titre : INHIBITEURS DE LPXC ET LEURS UTILISATIONS**
(54) **Title: LPXC INHIBITORS AND USES THEREOF**

Figure 1



(57) **Abrégé/Abstract:**
Provided herein are LpxC inhibitor compounds, as well as pharmaceutical compositions comprising said compounds, and methods of use thereof in the treatment of disease that would benefit from treatment with an LpxC inhibitor, including gram-negative bacterial infections such as urinary tract infections and the like.

Date Submitted: 2024/03/27

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Abstract:

Provided herein are LpxC inhibitor compounds, as well as pharmaceutical compositions comprising said compounds, and methods of use thereof in the treatment of disease that would benefit from treatment with an LpxC inhibitor, including gram-negative bacterial infections such as urinary tract infections and the like.

LPXC INHIBITORS AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Patent Application No. 63/249,166, filed on September 28, 2021, which is incoporated herein by reference in its entirety.

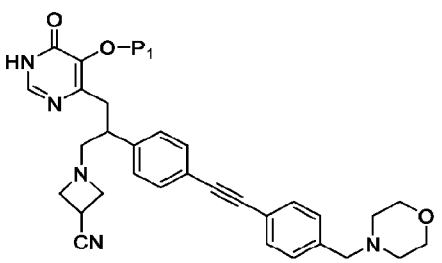
BACKGROUND

[0002] A need exists in the medicinal arts for the effective treatment of illness caused by bacterial infection.

BRIEF SUMMARY OF THE INVENTION

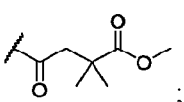
[0003] Provided herein are LpxC inhibitor compounds, as well as pharmaceutical compositions comprising said compound, and methods of use thereof in the treatment of disease that would benefit from treatment with an LpxC inhibitor, including gram-negative bacterial infections such as urinary tract infections and the like.

[0004] In one aspect, provided herein is a compound having the structure of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-P(=O)(OR^1)_2$, $-(CR^3R^4)-O-P(=O)(OR^1)_2$, $-S(=O)_2OR^1$, $-(CR^3R^4)-O-S(=O)_2OR^1$, $-S(=O)_2R^2$, $-(CR^3R^4)-O-S(=O)_2R^2$, $-C(=O)R^2$, $-(CR^3R^4)-O-C(=O)R^2$, $-C(=O)OR^2$, $-(CR^3R^4)-O-C(=O)OR^2$, $-C(=O)-O-(CR^3R^4)-O-C(=O)R^2$, $-C(=O)NR^5R^6$, or  ;

each R^1 is independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

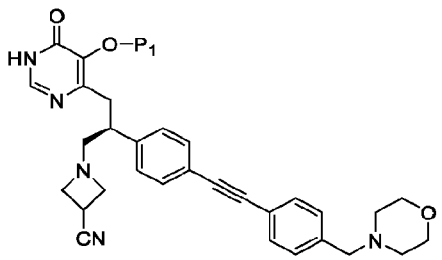
R^2 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

R^5 and R^6 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4- to 6-membered heterocycloalkyl which is unsubstituted or is substituted with 1, 2, or 3 substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, C_3-C_6 cycloalkyl, and 4- to 6-membered heterocycloalkyl.

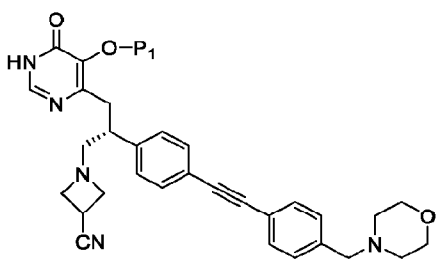
[0005] In some embodiments, the compound has the structure of Formula (Ia):



Formula (Ia),

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof.

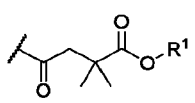
[0006] In some embodiments, the compound has the structure of Formula (Ib):



Formula (Ib),

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof.

[0007] In some embodiments,

P_1 is $-P(=O)(OR^1)_2$, $-CH_2-O-P(=O)(OR^1)_2$, $-S(=O)_2OR^1$, $-S(=O)_2R^2$, $-C(=O)OR^2$, $-(CHR^4)-O-C(=O)OR^2$, $-C(=O)-O-(CHR^4)-O-C(=O)R^2$, $-C(=O)R^2$, $-CH_2-O-C(=O)R^2$, $-C(=O)NR^5R^6$, or  ;

each R^1 is independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl;

R^2 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl;

R^4 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl; and

R^5 and R^6 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl;

or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4- to 6-membered heterocycloalkyl which is unsubstituted or is substituted with 1 or 2 substituents selected from the group consisting of C_1-C_4 alkyl and 4- to 6-membered heterocycloalkyl.

[0008] In some embodiments,

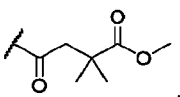
each R^1 is independently hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$;

R^2 is $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, or $C(CH_3)_3$;

R^4 is hydrogen, $-CH_3$, or phenyl; and

R^5 and R^6 are each independently hydrogen, $-CH_3$, or $-CH_2CH_3$;

or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4- to 6-membered heterocycloalkyl which is unsubstituted or is substituted with 1 or 2 substituents selected from the group consisting of C_1-C_4 alkyl and 4- to 6-membered heterocycloalkyl.

[0009] In some embodiments, P_1 is $-P(=O)(OH)_2$, $-CH_2-O-P(=O)(OH)_2$, $-S(=O)_2OH$, $-S(=O)_2CH_3$, $-C(=O)OCH_2CH_3$, $-(CH(CH_3))-O-C(=O)OCH(CH_3)_2$, $-(CH(CH_3))-O-C(=O)OCH_2CH_3$, $-C(=O)-O-(CH(phenyl))-O-C(=O)C(CH_3)_3$, $-C(=O)C(CH_3)_3$, $-CH_2-O-C(=O)C(CH_3)_3$, $-C(=O)N(CH_3)_2$, or  .

[0010] In another aspect, disclosed herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical compositions are formulated for administration to a mammal by intravenous administration or oral administration. In some embodiments, the pharmaceutical compositions are in the form of a tablet, a pill, a capsule, a liquid, a suspension, a dispersion, or a solution.

[0011] In another aspect, disclosed herein is a method of treating a gram-negative bacterial infection in a patient in need thereof comprising administering to the patient a compound disclosed herein, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof. In some embodiments, the gram-negative bacterial infection is selected from pneumonia, sepsis, cystic fibrosis, intra-abdominal infection, skin infection and urinary tract infection. In some embodiments, the gram-negative bacterial infection is selected from chronic urinary tract infection, complicated urinary tract infection, cystitis, pyelonephritis, urethritis, recurrent urinary tract infections, bladder infections, urethral infections and kidney infections. In some embodiments, the gram-negative bacterial infection is chronic urinary tract infections. In some embodiments, the gram-negative bacterial infection is complicated urinary tract infections. In some embodiments, the compound has no effect on gram-positive bacteria.

[0012] In some embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, is administered to the patient by I.V. injection or infusion. In other embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, is administered to the patient orally.

[0013] In some embodiments, the administration is to treat an existing infection. In other embodiments, the administration is provided as prophylaxis.

[0014] Articles of manufacture, which include packaging material, the LpxC inhibitory compounds described herein, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, within the packaging material, and a label that indicates that the compound or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, or composition thereof, is used for modulating the activity of LpxC, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from modulation of LpxC activity, are provided.

[0015] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

INCORPORATION BY REFERENCE

[0016] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference for the specific purposes identified herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **Figure 1** shows the average terminal burden of *E. coli* UTI 89 in urine, bladder, and kidney at the conclusion of a 96 h urinary tract infection study.

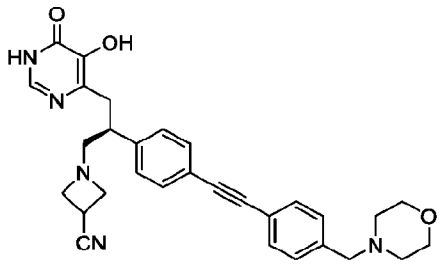
[0018] **Figure 2** shows the average terminal burden of *K. pneumoniae* BAA-1705 in urine, bladder, and kidney at the conclusion of a 96 h urinary tract infection study.

DETAILED DESCRIPTION OF THE INVENTION

[0019] Provided herein are LpxC inhibitor compounds, as well as pharmaceutical compositions comprising said compound, and methods of use thereof in the treatment of disease that would benefit from treatment with an LpxC inhibitor, including gram-negative bacterial infections such as urinary tract infections and the like. In some embodiments, the compounds provided herein are prodrugs of Compound A.

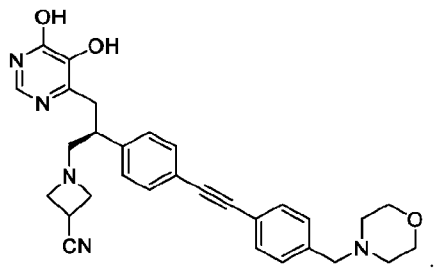
Compound A

[0020] Compound A refers to (S)-1-(3-(5-hydroxy-6-oxo-1,6-dihydropyrimidin-4-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)azetidine-3-carbonitrile which has the chemical structure shown below.



(Compound A).

[0021] Compound A is also known as (*S*)-1-(3-(5,6-dihydroxypyrimidin-4-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)azetidine-3-carbonitrile, which is a tautomer of the above structure and has the chemical structure shown below.



[0022] Compound A is a potent inhibitor of UDP-{3-O-[(R)-3-hydroxymyristoyl]}-N-acetylglucosamine deacetylase (LpxC). LpxC is an essential enzyme involved in the first committed step in lipid A biosynthesis for gram-negative bacteria. Lipid A is an essential component of the outer membrane of gram-negative bacteria. LpxC is highly conserved across strains of gram-negative bacteria, making LpxC an attractive target to treat gram-negative infections.

[0023] Compound A is an LpxC inhibitor that is useful in the methods of treatment described herein. In gram-negative bacterial cell lines, Compound A is a potent inhibitor, exhibiting MIC values of < 1 μg/mL against *E. coli* and *K. pneumoniae* cell lines. Additionally, Compound A does not inhibit gram-positive bacterial cell lines, such as *S. aureus*.

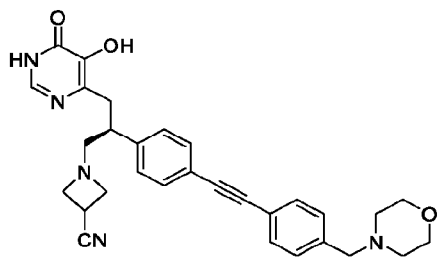
[0024] The preparation and use of Compound A has been previously described (see, WO 2020/061375, US 2021/0221796, WO 2021/195260, and US 2021/0309651 each of which is incorporated by reference in its entirety).

Prodrugs

[0025] The term "prodrug" is meant to indicate a compound that is, in some embodiments, converted under physiological conditions or by solvolysis to a biologically active compound. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug is typically inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, e.g., Bundgard, H., Design of Prodrugs (1985), pp. 7 9, 21 24 (Elsevier,

Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Prodrugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987. The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound in vivo when such prodrug is administered to a mammalian subject. Prodrugs of an active compound, as described herein, are prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, benzoate, phosphate, sulfonate, carbonate, and carbamate derivatives of alcohol or amine functional groups in the active compounds and the like.

[0026] In some aspects, disclosed herein is a prodrug of Compound A:



(Compound A)

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein: the prodrug group is attached to a hydroxy or amino group of Compound A; and wherein the prodrug moiety comprises a phosphate, sulfonate, sulfate, ester, carbonate, or carbamate group.

[0027] In some embodiments, the prodrug is attached to a hydroxy group of Compound A. In some embodiments, the prodrug is attached to an amino group of Compound A.

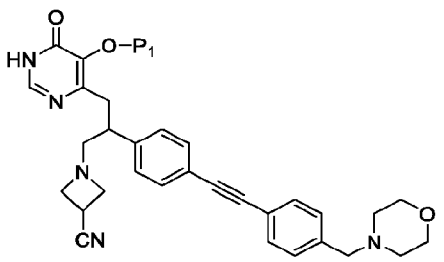
[0028] In some embodiments the prodrug moiety comprises a phosphate group. In some embodiments the prodrug moiety comprises a sulfonate group. In some embodiments the prodrug moiety comprises a sulfate group. In some embodiments the prodrug moiety comprises an ester group. In some embodiments the prodrug moiety comprises a carbonate group. In some embodiments the prodrug moiety comprises a carbamate group.

[0029] While Compound A is highly active in *in vitro* cell based assays, in some instances its low physiological solubility leads to challenges using it *in vivo*. In some embodiments, the solubility of Compound A is increased by using a prodrug of Compound A. In some embodiments, a prodrug of Compound A provided herein, for example, a phosphate prodrug, has a 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, or more than 10-fold

increase in solubility relative to Compound A under physiological conditions. In some embodiments, the solubility of Compound A under physiological conditions, for example at pH 7.4, is < 1 mg/mL. In some embodiments, the solubility of a prodrug of Compound A provided herein, for example, a phosphate prodrug, is > 10 mg/mL under the same physiological conditions.

Compounds

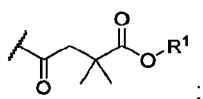
[0030] In another aspect, provided herein is a compound having the structure of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-P(=O)(OR^1)_2$, $-(CR^3R^4)-O-P(=O)(OR^1)_2$, $-S(=O)_2OR^1$, $-(CR^3R^4)-O-S(=O)_2OR^1$, $-S(=O)_2R^2$, $-(CR^3R^4)-O-S(=O)_2R^2$, $-C(=O)R^2$, $-(CR^3R^4)-O-C(=O)R^2$, $-C(=O)OR^2$, $-(CR^3R^4)-O-C(=O)OR^2$, $-C(=O)-O-(CR^3R^4)-O-C(=O)R^2$, $-C(=O)NR^5R^6$, or



;

each R^1 is independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

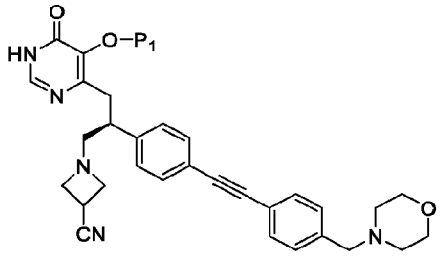
R^2 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

R^5 and R^6 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4- to 6-membered heterocycloalkyl which is unsubstituted or is substituted with 1, 2, or 3 substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, C_3-C_6 cycloalkyl, and 4- to 6-membered heterocycloalkyl.

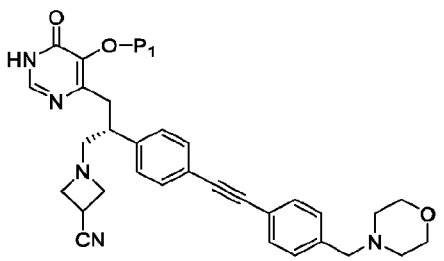
[0031] In some embodiments, the compound has the structure of Formula (Ia):



Formula (Ia),

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof.

[0032] In some embodiments, the compound has the structure of Formula (Ib):



Formula (Ib),

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof.

[0033] For any and all of the embodiments, substituents are selected from among a subset of the listed alternatives. For example, in some embodiments, R^3 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl. In some embodiments, R^3 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl. In some emboidments, R^3 is hydrogen, $-CH_3$, or phenyl. In some embodiments, R^3 is hydrogen or C_1-C_4 alkyl. In some embodiments, R^3 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, or $-C(CH_3)_3$. In some emboidments, R^3 is hydrogen or $-CH_3$. In some embodiments, R^3 is hydrogen.

[0034] In some embodiments, R^4 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl. In some embodiments, R^4 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl. In some emboidments, R^4 is hydrogen, $-CH_3$, or phenyl. In some embodiments, R^4 is hydrogen or C_1-C_4 alkyl. In some embodiments, R^4 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, or $-C(CH_3)_3$. In some emboidments, R^4 is hydrogen or $-CH_3$. In some embodiments, R^4 is hydrogen.

[0035] In some embodiments, R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl. In some embodiments, R^3 and R^4 are each independently hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl. In some emboidments, R^3

and R^4 are each independently hydrogen, $-CH_3$, or phenyl. In some embodiments, R^3 and R^4 are each independently hydrogen or C_1-C_4 alkyl. In some embodiments, R^3 and R^4 are each independently hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, or $-C(CH_3)_3$. In some emboidments, R^3 and R^4 are each independently hydrogen or $-CH_3$. In some embodiments, R^3 and R^4 are each hydrogen.

[0036] In some embodiments, each R^1 is independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl. In some embodiments, each R^1 is independently hydrogen or C_1-C_4 alkyl. In some embodiments, each R^1 is independently hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, or $-C(CH_3)_3$. In some embodiments, each R^1 is independently hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, each R^1 is hydrogen.

[0037] In some embodiments, R^2 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl. In some embodiments, R^2 is C_1-C_4 alkyl. In some embodiments, R^2 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, or $-C(CH_3)_3$. In some embodiments, R^2 is $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, or $-C(CH_3)_3$.

[0038] In some embodiments, P_1 is $-P(=O)(OR^1)_2$ or $-(CR^3R^4)$-O-$P(=O)(OR^1)_2$. In some embodiments, P_1 is $-P(=O)(OR^1)_2$ or $-(CR^3R^4)$-O-$P(=O)(OR^1)_2$; each R^1 is independently hydrogen or C_1-C_4 alkyl; and R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl. In some embodiments, P_1 is $-P(=O)(OR^1)_2$ or $-CH_2$-O-$P(=O)(OR^1)_2$; and each R^1 is independently hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, P_1 is $-P(=O)(OH)_2$ or $-CH_2$-O-$P(=O)(OH)_2$.

[0039] In some embodiments, P_1 is $-P(=O)(OR^1)_2$. In some embodiments, P_1 is $-P(=O)(OR^1)_2$; and each R^1 is independently hydrogen or C_1-C_4 alkyl. In some embodiments, P_1 is $-P(=O)(OR^1)_2$; and each R^1 is independently hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, P_1 is $-P(=O)(OH)_2$.

[0040] In some embodiments, P_1 is $-(CR^3R^4)$-O-$P(=O)(OR^1)_2$. In some embodiments, P_1 is $-(CR^3R^4)$-O-$P(=O)(OR^1)_2$; each R^1 is independently hydrogen or C_1-C_4 alkyl; and R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl. In some embodiments, P_1 is $-CH_2$-O-$P(=O)(OR^1)_2$; and each R^1 is independently hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, P_1 is $-CH_2$-O-$P(=O)(OH)_2$.

[0041] In some embodiments, P_1 is $-S(=O)_2OR^1$ or $-(CR^3R^4)$-O-$S(=O)_2OR^1$. In some embodiments, P_1 is $-S(=O)_2OR^1$ or $-(CR^3R^4)$-O-$S(=O)_2OR^1$; R^1 is hydrogen or C_1-C_4 alkyl; and R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl. In some embodiments, P_1 is $-S(=O)_2OR^1$. In some embodiments, P_1 is $-(CR^3R^4)$-O-$S(=O)_2OR^1$. In some

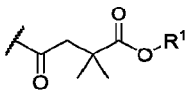
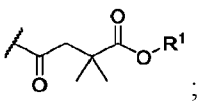
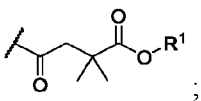
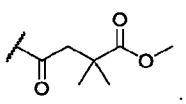
embodiments, P_1 is $-S(=O)_2OR^1$; and R^1 is hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, P_1 is $-S(=O)_2OH$.

[0042] In some embodiments, P_1 is $-S(=O)_2R^2$ or $-(CR^3R^4)-O-S(=O)_2R^2$. In some embodiments, P_1 is $-S(=O)_2R^2$ or $-(CR^3R^4)-O-S(=O)_2R^2$; R^2 is C_1-C_4 alkyl; and R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl. In some embodiments, P_1 is $-S(=O)_2R^2$ or $-(CR^3R^4)-O-S(=O)_2R^2$; R^2 is C_1-C_4 alkyl; and R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl. In some embodiments, P_1 is $-S(=O)_2R^2$. In some embodiments, P_1 is $-(CR^3R^4)-O-S(=O)_2R^2$. In some embodiments, P_1 is $-S(=O)_2R^2$; and R^2 is $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, P_1 is $-S(=O)_2CH_3$.

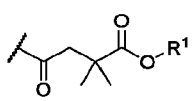
[0043] In some embodiments, P_1 is $-C(=O)OR^2$, $-(CR^3R^4)-O-C(=O)OR^2$, or $-C(=O)-O-(CR^3R^4)-O-C(=O)R^2$. In some embodiments, P_1 is $-C(=O)OR^2$, $-(CR^3R^4)-O-C(=O)OR^2$, or $-C(=O)-O-(CR^3R^4)-O-C(=O)R^2$; R^2 is C_1-C_4 alkyl; and R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl. In some embodiments, P_1 is $-C(=O)OR^2$, $-(CHR^4)-O-C(=O)OR^2$, or $-C(=O)-O-(CHR^4)-O-C(=O)R^2$; R^2 is $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$; and R^4 is hydrogen, $-CH_3$, or phenyl. In some embodiments, P_1 is $-C(=O)OR^2$. In some embodiments, P_1 is $-(CR^3R^4)-O-C(=O)OR^2$. In some embodiments, P_1 is $-C(=O)-O-(CR^3R^4)-O-C(=O)R^2$.

[0044] In some embodiments, P_1 is $-C(=O)R^2$ or $-(CR^3R^4)-O-C(=O)R^2$. In some embodiments, P_1 is $-C(=O)R^2$ or $-(CR^3R^4)-O-C(=O)R^2$; R^2 is C_1-C_4 alkyl; and R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl. In some embodiments, P_1 is $-C(=O)R^2$ or $-CH_2-O-C(=O)R^2$; R^2 is $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, or $C(CH_3)_3$. In some embodiments, P_1 is $-C(=O)R^2$. In some embodiments, P_1 is $-(CR^3R^4)-O-C(=O)R^2$.

[0045] In some embodiments, P_1 is $-C(=O)NR^5R^6$. In some embodiments, R^5 and R^6 are each independently hydrogen, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl. In some embodiments, R^5 and R^6 are each independently hydrogen or C_1-C_4 alkyl. In some embodiments, R^5 and R^6 are each independently hydrogen, $-CH_3$, or $-CH_2CH_3$. In some embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4- to 6-membered heterocycloalkyl which is unsubstituted or is substituted with 1 or 2 substituents selected from the group consisting of C_1-C_4 alkyl and 4- to 6-membered heterocycloalkyl.

[0046] In some embodiments, P_1 is  . In some embodiments, P_1 is  ; and R^1 is hydrogen or C_1-C_4 alkyl. In some embodiments, P_1 is  ; and R^1 is hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, P_1 is  .

[0047] In some embodiments,

P_1 is $-P(=O)(OR^1)_2$, $-CH_2-O-P(=O)(OR^1)_2$, $-S(=O)_2OR^1$, $-S(=O)_2R^2$, $-C(=O)OR^2$, $-(CHR^4)-O-C(=O)OR^2$, $-C(=O)-O-(CHR^4)-O-C(=O)R^2$, $-C(=O)R^2$, $-CH_2-O-C(=O)R^2$, $-C(=O)NR^5R^6$, or  ;

each R^1 is independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl;

R^2 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl;

R^4 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl; and

R^5 and R^6 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl;

or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4- to 6-membered heterocycloalkyl which is unsubstituted or is substituted with 1 or 2 substituents selected from the group consisting of C_1-C_4 alkyl and 4- to 6-membered heterocycloalkyl.

[0048] In some embodiments,

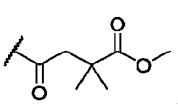
each R^1 is independently hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$;

R^2 is $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, or $C(CH_3)_3$;

R^4 is hydrogen, $-CH_3$, or phenyl; and

R^5 and R^6 are each independently hydrogen, $-CH_3$, or $-CH_2CH_3$;

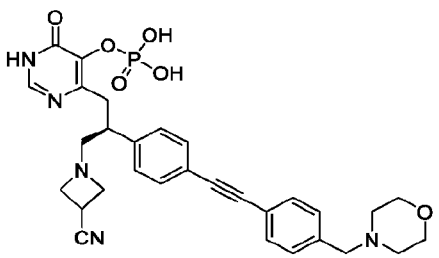
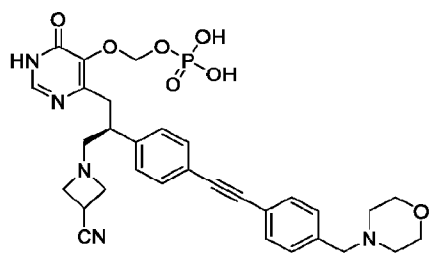
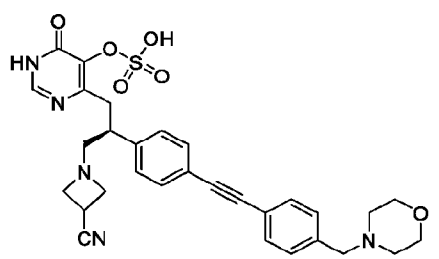
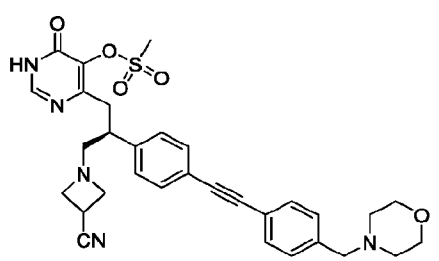
or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4- to 6-membered heterocycloalkyl which is unsubstituted or is substituted with 1 or 2 substituents selected from the group consisting of C_1-C_4 alkyl and 4- to 6-membered heterocycloalkyl.

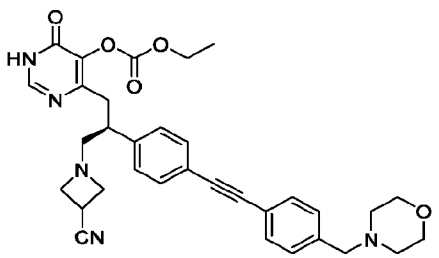
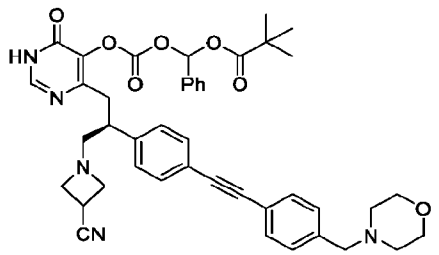
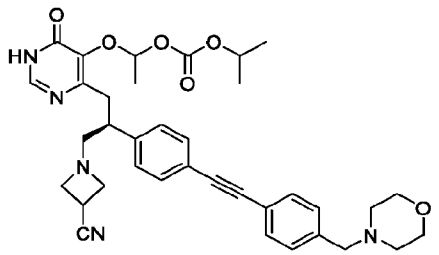
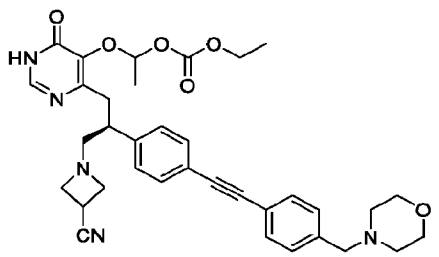
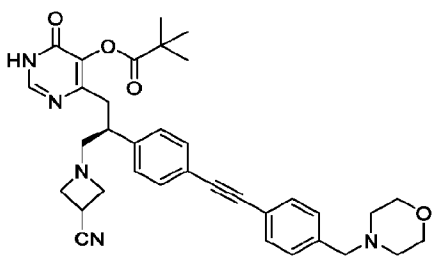
[0049] In some embodiments, P_1 is $-P(=O)(OH)_2$, $-CH_2-O-P(=O)(OH)_2$, $-S(=O)_2OH$, $-S(=O)_2CH_3$, $-C(=O)OCH_2CH_3$, $-(CH(CH_3))-O-C(=O)OCH(CH_3)_2$, $-(CH(CH_3))-O-C(=O)OCH_2CH_3$, $-C(=O)-O-(CH(phenyl))-O-C(=O)C(CH_3)_3$, $-C(=O)C(CH_3)_3$, $-CH_2-O-C(=O)C(CH_3)_3$, $-C(=O)N(CH_3)_2$, or  .

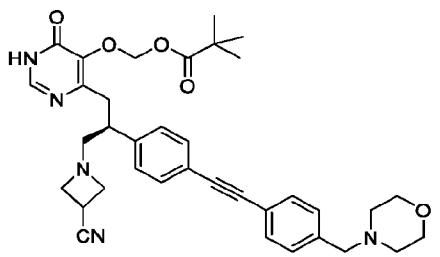
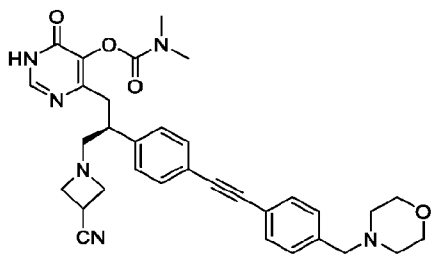
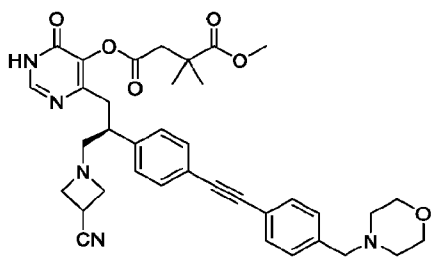
[0050] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0051] Exemplary compounds of Formula (I) include the compounds described in Table 1:

Table 1:

Compound No.	Structure	Name
1		(S)-4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl dihydrogen phosphate
2		(S)-((4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)methyl dihydrogen phosphate
3		(S)-4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl hydrogen sulfate
4		(S)-4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl methanesulfonate

Compound No.	Structure	Name
5		(S)-4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl ethyl carbonate
6		((((4-((S)-3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)carbonyl)oxy)(phenyl)methyl pivalate
7		1-((4-((S)-3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)ethyl isopropyl carbonate
8		1-((4-((S)-3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)ethyl ethyl carbonate
9		(S)-4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl pivalate

Compound No.	Structure	Name
10		(S)-((4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)methyl pivalate
11		(S)-4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl dimethylcarbamate
12		(S)-4-(4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl) 1-methyl 2,2-dimethylsuccinate

[0052] In some embodiments, the compound is a pharmaceutically acceptable salt of a compound in Table 1. In some embodiments, the compound is a pharmaceutically acceptable solvate of a compound of Table 1.

Definitions

[0053] Unless otherwise stated, the following terms used in this application have the definitions given below. The use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0054] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to fifteen carbon atoms (*e.g.*, C_1-C_{15} alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkyl). In

other embodiments, an alkyl comprises one carbon atom (*e.g.*, C_1 alkyl). In other embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond.

[0055] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like.

[0056] "Cycloalkyl" refers to a stable monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, containing no unsaturation, having from three to fifteen carbon atoms. In certain embodiments, a cycloalkyl comprises three to ten carbon atoms. In other embodiments, a cycloalkyl comprises three to six carbon atoms. Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The cycloalkyl is attached to the rest of the molecule by a single bond.

[0057] "Heterocycloalkyl" refers to a stable 3- to 18-membered ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur, containing no unsaturation. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which optionally includes fused, bridged, or spirocyclic ring systems. The heteroatoms in the heterocycloalkyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. In certain embodiments the heterocycloalkyl comprises three to ten atoms in the ring. In other embodiments, the heterocycloalkyl comprises from four to six atoms in the ring. Examples of monocyclic heterocycloalkyl radicals include, but are not limited to, aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, tetrahydropyran, morpholine, thiomorpholine, dioxane, dithiane, azepane, oxepane, and homomorpholine. The heterocycloalkyl is attached to the rest of the molecule through any atom of the ring(s), for example a carbon atom (C-linked heterocycloalkyl) or a nitrogen atom (N-linked heterocycloalkyl).

[0058] "Heteroaryl" refers to a radical derived from a 3- to 18-membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, the heteroaryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with

the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. In certain embodiments, the heteroaryl is a monocyclic heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. In other embodiments, the heteroaryl is a 6-membered heteroaryl. Examples of monocyclic heteroaryls include, but are not limited to, pyrrole, furan, thiophene, imidazole, pyrazole, oxathiole, isoxathiole, oxazole, isoxazole, thiazole, isothiazole, triazole, oxadiazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, and triazine. The heteroaryl is attached to the rest of the molecule through any atom of the ring.

[0059] The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[0060] The term "modulate" as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[0061] The term "modulator" as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist, antagonist, degrader, or combinations thereof. In some embodiments, a modulator is an antagonist.

[0062] The terms "administer," "administering", "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein. In some embodiments, the compounds and compositions described herein are administered orally. In some embodiments, the compounds and compositions described herein are administered intravenously.

[0063] The terms "co-administration" or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[0064] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered, which will relieve to

some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is optionally determined using techniques, such as a dose escalation study.

[0065] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[0066] The term "pharmaceutical combination" as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. the LpxC inhibitory compound disclosed herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. the LpxC inhibitory compound disclosed herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[0067] The terms "article of manufacture" and "kit" are used as synonyms.

[0068] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[0069] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms,

inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Further Forms of Compounds

[0070] "Pharmaceutically acceptable," as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material is administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0071] The term "pharmaceutically acceptable salt" refers to a form of a therapeutically active agent that consists of a cationic form of the therapeutically active agent in combination with a suitable anion, or in alternative embodiments, an anionic form of the therapeutically active agent in combination with a suitable cation. Handbook of Pharmaceutical Salts: Properties, Selection and Use. International Union of Pure and Applied Chemistry, Wiley-VCH 2002. S.M. Berge, L.D. Bighley, D.C. Monkhouse, J. Pharm. Sci. 1977, 66, 1-19. P. H. Stahl and C. G. Wermuth, editors, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Weinheim/Zürich:Wiley-VCH/VHCA, 2002. Pharmaceutical salts typically are more soluble and more rapidly soluble in stomach and intestinal juices than non-ionic species and so are useful in solid dosage forms. Furthermore, because their solubility often is a function of pH, selective dissolution in one or another part of the digestive tract is possible and this capability can be manipulated as one aspect of delayed and sustained release behaviours. Also, because the salt-forming molecule can be in equilibrium with a neutral form, passage through biological membranes can be adjusted.

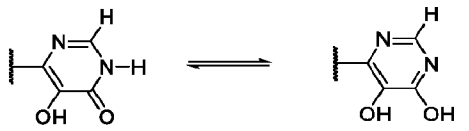
[0072] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound disclosed herein with an acid. In some embodiments, the compound disclosed herein (i.e. free base form) is basic and is reacted with an organic acid or an inorganic acid. Inorganic acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and metaphosphoric acid. Organic acids include, but are not limited to, 1-hydroxy-2-naphthoic acid; 2,2-dichloroacetic acid; 2-hydroxyethanesulfonic acid; 2-oxoglutaric acid; 4-acetamidobenzoic acid; 4-aminosalicylic acid; acetic acid; adipic acid; ascorbic acid (L); aspartic acid (L); benzenesulfonic acid; benzoic acid; camphoric acid (+); camphor-10-sulfonic acid (+); capric acid (decanoic acid); caproic acid (hexanoic acid); caprylic acid (octanoic acid); carbonic acid; cinnamic acid; citric acid; cyclamic acid; dodecylsulfuric acid; ethane-1,2-disulfonic acid; ethanesulfonic acid; formic acid; fumaric acid; galactaric acid;

gentisic acid; glucoheptonic acid (D); gluconic acid (D); glucuronic acid (D); glutamic acid; glutaric acid; glycerophosphoric acid; glycolic acid; hippuric acid; isobutyric acid; lactic acid (DL); lactobionic acid; lauric acid; maleic acid; malic acid (- L); malonic acid; mandelic acid (DL); methanesulfonic acid; naphthalene-1,5-disulfonic acid; naphthalene-2-sulfonic acid; nicotinic acid; oleic acid; oxalic acid; palmitic acid; pamoic acid; phosphoric acid; proprionic acid; pyroglutamic acid (- L); salicylic acid; sebacic acid; stearic acid; succinic acid; sulfuric acid; tartaric acid (+ L); thiocyanic acid; toluenesulfonic acid (*p*); and undecylenic acid.

[0073] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound disclosed herein with a base. In some embodiments, the compound disclosed herein is acidic and is reacted with a base. In such situations, an acidic proton of the compound disclosed herein is replaced by a metal ion, e.g., lithium, sodium, potassium, magnesium, calcium, or an aluminum ion. In some cases, compounds described herein coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, meglumine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, compounds described herein form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydroxide, lithium hydroxide, and the like. In some embodiments, the compounds provided herein are prepared as a sodium salt, calcium salt, potassium salt, magnesium salt, meglumine salt, N-methylglucamine salt or ammonium salt.

[0074] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein optionally exist in unsolvated as well as solvated forms.

[0075] A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. In some instances, the heterocyclic LpxC inhibitory compounds disclosed herein exist in tautomeric forms. The structures of said compounds are illustrated in the one tautomeric form for clarity. The alternative tautomeric forms are expressly included in this disclosure, such as, for example, the structures illustrated below.



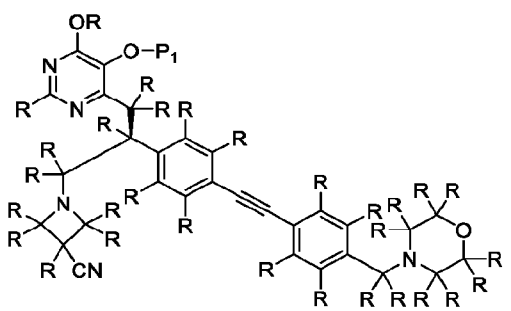
[0076] In some embodiments, sites on the organic radicals (e.g. alkyl groups, aromatic rings) of compounds disclosed herein are susceptible to various metabolic reactions. Incorporation of appropriate substituents on the organic radicals will reduce, minimize or eliminate this metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, deuterium, an alkyl group, a haloalkyl group, or a deuteroalkyl group.

[0077] In another embodiment, the compounds described herein are labeled isotopically (e.g. with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[0078] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine chlorine, iodine, phosphorus, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{32}P and ^{33}P. In one aspect, isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. In one aspect, substitution with isotopes such as deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or altered metabolic pathways to reduce undesirable metabolites or reduced dosage requirements.

[0079] In some embodiments, one or more hydrogen atoms on the compound disclosed herein are replaced with deuterium. In some embodiments, substitution with deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements.

[0080] In one aspect, described is a compound with the following structure:



wherein,

each R is independently selected from hydrogen or deuterium, and

P_1 is as described herein, where each hydrogen atom can be optionally replaced with a deuterium atom,

or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof.

[0081] In some embodiments, the compounds disclosed herein possess one or more stereocenters and each stereocenter exists independently in either the *R* or *S* configuration. For example, in some embodiments, the compound disclosed herein exists in the *R* configuration when one stereocenter is present. In other embodiments, the compound disclosed herein exists in the *S* configuration when one stereocenter is present. In some embodiments, the compound disclosed herein exists in the *RR* configuration when two stereocenters are present. In some embodiments, the compound disclosed herein exists in the *RS* configuration when two stereocenters are present. In some embodiments, the compound disclosed herein exists in the *SS* configuration when two stereocenters are present. In some embodiments, the compound disclosed herein exists in the *SR* configuration when two stereocenters are present.

[0082] The compounds presented herein include all diastereomeric, individual enantiomers, atropisomers, and epimeric forms as well as the appropriate mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen *(E)*, and zusammen *(Z)* isomers as well as the appropriate mixtures thereof.

[0083] Individual stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns or the separation of diastereomers by either non-chiral or chiral chromatographic columns or crystallization and recrystallization in a proper solvent or a mixture of solvents. In certain embodiments, compounds disclosed herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure individual enantiomers. In some embodiments, resolution of individual enantiomers of compounds disclosed herein is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers of compounds disclosed herein are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of stereoisomers of compounds disclosed herein is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques,

Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981. In some embodiments, stereoisomers are obtained by stereoselective synthesis.

[0084] Separation of individual enantiomers from a racemic mixture is possible by the use of chiral supercritical fluid chromatography (SFC) or chiral high performance liquid chromatography (HPLC). In some embodiments, enantiomers described herein are separated from each other by the use of chiral SFC or chiral HPLC. In some embodiments, compounds disclosed herein that include one or more chiral centers (e.g. compounds disclosed herein that include the moiety trans-octahydro-1H-pyrido[3,4-b]morpholin-6-yl) are separated into individual enantiomers using chiral SFC or chiral HPLC. A wide variety of conditions and suitable columns are available.

[0085] Daicel polysaccharide chiral stationary phases (CSPs) are among the columns used for chiral SFC separations. In some embodiments, Daicel analytical immobilised and coated CHIRALPAK and CHIRALCEL HPLC columns can be used for SFC analysis.

[0086] In some embodiments, screening for the suitability of using a SFC column is performed on the four main immobilised phases (CHIRALPAK IA, IB, IC and ID) and the four main coated columns (CHIRALPAK AD and AS and CHIRALCEL OD and OJ), with varying concentrations of organic modifier. A variety of column phases are available, including but not limited to OD and OJ, OX and OZ chlorinated phases, and a range of complementary cellulose based CHIRALCEL phases including OA, OB, OC, OF, OG and OK.

[0087] Non-limiting examples of chiral selectors contemplated for use in the separation of enantiomers include amylose tris (3, 5-dimethylphenylcarbamate), cellulose tris (3, 5-dimethylphenylcarbamate), cellulose tris (3, 5-dichlorophenylcarbamate), amylose tris (3-chlorophenylcarbamate), amylose tris (3, 5-dichlorophenylcarbamate), amylose tris (3-chloro, 4-methylphenylcarbamate), amylose tris ((S)-alpha-methylbenzylcarbamate), amylose tris (5-chloro-2-methylphenylcarbamate), cellulose tris (4-methylbenzoate), cellulose tris (4-chloro-3-methylphenylcarbamate), and cellulose tris (3-chloro-4-methylphenylcarbamate).

[0088] Non-limiting examples of chiral columns contemplated for use in the separation of enantiomers include CHIRALPAK IA SFC, CHIRALPAK AD-H SFC, CHIRALPAK IB SFC, CHIRALCEL OD-H SFC, CHIRALPAK IC SFC, CHIRALPAK ID SFC, CHIRALPAK IE SFC, CHIRALPAK IF SFC, CHIRALPAK AZ-H SFC, CHIRALPAK AS-H SFC, CHIRALPAK AY-H SFC, CHIRALCEL OJ-H SFC, CHIRALCEL OX-H SFC, and CHIRALCEL OZ-H SFC.

[0089] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

[0090] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphydryl groups. Metabolites of the compounds disclosed herein are optionally identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds.

Pharmaceutical Compositions

[0091] In certain embodiments, the LpxC inhibitory compound as described herein is administered as a pure chemical. In other embodiments, the LpxC inhibitory compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[0092] Provided herein is a pharmaceutical composition comprising at least one LpxC inhibitory compound as described herein, or a stereoisomer, pharmaceutically acceptable salt, or solvate thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.,* the subject or patient) of the composition.

[0093] One embodiment provides a pharmaceutical composition comprising the LpxC inhibitory compound as described herein, or a pharmaceutically acceptable salt, or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0094] In some embodiments, the pharmaceutical composition is in a dosage form for dosing or administration by injection. In some embodiments, the pharmaceutical composition is in a dosage form for intravenous (I.V.) injection or infusion, or intramuscular, subcutaneous, or intradermal injection. In some embodiments, the pharmaceutical composition is in a dosage

form for I.V. injection or infusion. In some embodiments, the pharmaceutical composition is a solution.

[0095] In some embodiments, the pharmaceutical composition is in a dosage form for oral dosing or administration. In some embodiments, the dosage form is a liquid. In some embodiments, the dosage form is a suspension, solution, syrup, or elixir. In some embodiments, the dosage form is a suspension. In some embodiments, the dosage form is a nanosuspension. In some embodiments, the dosage form is a solution. In other embodiments, the dosage form is a tablet or a capsule.

[0096] In some embodiments, the at least one pharmaceutically acceptable excipient is a co-solvent, oil, surfactant, complexing agent, a solubilizing polymer, a P-gp modulator, a buffering agent, or a combination thereof.

[0097] In certain embodiments, the heterocyclic LpxC inhibitory compound disclosed herein is substantially pure, in that it contains less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as unreacted intermediates or synthesis by-products that are created, for example, in one or more of the steps of a synthesis method.

[0098] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome), or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

LpxC, Lipid A and Gram-Negative Bacteria

[0099] Metalloproteins influence a vast diversity of biological systems, biological processes, and diseases. For example, UDP-{3-O-[(R)-3-hydroxymyristoyl]}-N-acetylglucosamine deacetylase (LpxC) is an essential enzyme involved in the first committed step in lipid A biosynthesis for gram-negative bacteria. Lipid A is an essential component of the outer membrane of gram-negative bacteria. LpxC is a zinc(II)-dependent metalloenzyme, with two histidines and an aspartic acid residue bound to the zinc(II) ion. Structures of LpxC show the zinc(II) ion is bound to two water molecules, both of which have been implicated in the mechanism of the enzyme. LpxC is highly conserved across strains of gram-negative bacteria, making LpxC an attractive target to treat gram-negative infections.

[00100] In recent years, there has been an increase in resistant and multi-drug resistant strains of bacteria. Thus, there is a need for new antibiotics, especially with new mechanisms of action. There remains a need for metalloprotein modulators of LpxC useful in the field of therapeutics, diagnostics, and research.

[00101] One embodiment provides a method of inhibiting UDP-{3-O-[(R)-3-hydroxymyristoyl]}-N-acetylglucosamine deacetylase enzyme comprising contacting the enzyme with the LpxC inhibitory compounds disclosed herein.

Methods of Treatment

[00102] Disclosed herein are methods of treating disease wherein the inhibition of bacterial growth is indicated. Such disease includes gram-negative bacterial infection. In some embodiments, the method of treating a gram-negative bacterial infection in a patient in need thereof comprises administering to the patient a pharmaceutical composition comprising an LpxC inhibitory compound disclosed herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the gram-negative bacterial infection is selected from pneumonia, sepsis, cystic fibrosis, intra-abdominal infection, skin infections and urinary tract infection. In some embodiments, the gram-negative bacterial infection is a urinary tract infection (UTI), a hospital acquired/ventilator-associated pneumonia (HAP/VAP), or an intra-abdominal infection (IAI). In some embodiments, the gram-negative bacterial infection is selected from chronic urinary tract infections, complicated urinary tract infections, cystitis, pyelonephritis, urethritis, recurrent urinary tract infections, bladder infections, urethral infections, and kidney infections. In some embodiments, the compounds described herein are used for the treatment of chronic urinary tract infections. In some embodiments, the compounds described herein are used for the treatment of complicated urinary tract infections. In other embodiments, the compounds described herein are used for the treatment of complicated intra-abdominal infection. In some embodiments, the compounds described herein are used for the treatment of chronic intra-abdominal infection. In other embodiments, the compounds described herein are used for the treatment of hospital acquired pneumonia (HAP) or ventilator associated pneumonia (VAP). In some embodiments the administration is to treat an existing infection. In some embodiments the administration is provided as prophylaxis.

[00103] In some embodiments, the LpxC inhibitory compounds described herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, are used for treating conditions caused by the bacterial production of endotoxin and, in particular, by gram-negative bacteria and bacteria that use LpxC in the biosynthesis of lipopolysaccharide (LPS) or endotoxin. In some embodiments, the method of treating a condition caused by

endotoxin or LPS in a patient in need thereof comprises administering to the patient a pharmaceutical composition comprising an LpxC inhibitory compound disclosed herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, and a pharmaceutically acceptable excipient. In another embodiment, the heterocyclic LpxC inhibitory compounds and formulations as described herein are useful in the treatment of conditions that are caused or exacerbated by the bacterial production of lipid A and LPS or endotoxin, such as sepsis, septic shock, systemic inflammation, localized inflammation, chronic obstructive pulmonary disease (COPD) and acute exacerbations of chronic bronchitis (AECB). In some embodiments, the method of treating a condition caused by endotoxin or LPS in a patient in need thereof comprises administering to the patient a pharmaceutical composition comprising the LpxC inhibitory compounds disclosed herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, and a pharmaceutically acceptable excipient, wherein the condition caused by endotoxin or LPS is selected from sepsis, septic shock, systemic inflammation, localized inflammation, chronic obstructive pulmonary disease (COPD) and acute exacerbations of chronic bronchitis (AECB).

[00104] In other embodiments, the LpxC inhibitory compounds described herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, can be used for the treatment of a serious or chronic respiratory tract infection or complicated urinary tract infections including serious lung and nosocomial infections such as those caused by *Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Kluyvera ascorbata, Kluyvera cryocrescense, Shigella sonnei, Proteus mirabilis, Serratia marcescens, Stenotrophomonas maltophilia, Pseudomonas aeruginosa, Burkholderia cepacia, Acinetobacter baumannii, Alcaligenes xylosoxidans, Flavobacterium meningosepticum, Providencia sluarlii* and *Citrobacter freundii, Haemophilus influenzae, Kluyvera species, Legionella species, Moraxella catarrhalis, Enterobacter species, Acinetobacter species, Klebsiella species, Burkholderia species* and *Proteus species,* and infections caused by other bacterial species such as *Neisseria species, Shigella species, Salmonella species, Helicobacler pylori, Vibrionaceae* and *Bordetella* species as well as the infections caused by a *Brucella* species, *Francisella tularensis* and/or *Yersinia pestis.*

[00105] In one embodiment provided herein is a method of treating a gram-negative bacterial infection in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising an LpxC inhibitory compound disclosed herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, and at least one pharmaceutically acceptable excipient.

[00106] One embodiment provides a method wherein the gram-negative bacterial infection is selected from pneumonia, sepsis, cystic fibrosis, intra-abdominal infection, skin infection and urinary tract infection.

[00107] One embodiment provides a method wherein the gram-negative bacterial infection is selected from chronic urinary tract infection, complicated urinary tract infection, cystitis, pyelonephritis, urethritis, recurrent urinary tract infections, bladder infections, urethral infections and kidney infections.

[00108] One embodiment provides a method wherein the gram-negative bacterial infection is chronic urinary tract infections. One embodiment provides a method wherein the gram-negative bacterial infection is complicated urinary tract infections. One embodiment provides a method wherein the administration is to treat an existing infection. One embodiment provides a method wherein the administration is provided as prophylaxis.

[00109] In some embodiments, the LpxC inhibitory compounds described herein, or isotopic variants, tautomers, prodrugs, pharmaceutically acceptable salts, solvates, or hydrates thereof, are not active against gram-positive bacteria. In some embodiments, the LpxC inhibitory compounds described herein, or isotopic variants, tautomers, prodrugs, pharmaceutically acceptable salts, solvates, or hydrates thereof, are not active against *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Bacillus thuringiensis*, *Lactobacillus rhamnosus*, *Staphylococcus epidermidis*, *Bifidobacterium breve*, *Clostridium difficile*, *Clostridium sordellii*, *Peptostreptococcus anaerobius*, *Streptococcus pneumoniae*, *Corynebacterium jeikeium*, *Propionibacterium acnes*, *Listeria monocytogenes*, and/or *Nocardia cyriacigeorgica* complex. Most gut bacteria are Gram-positive, including *C. difficile*. Therefore, in some embodiments, the lack of activity against gram-positive bacteria is a benefit. In some embodiments, use of the LpxC inhibitory compounds described herein, or isotopic variants, tautomers, prodrugs, pharmaceutically acceptable salts, solvates, or hydrates thereof, to treat a gram-negative bacterial infection, as described herein, has no effect on the gut microflora and thus reduces the risk of secondary infections from, for example, *C. difficile*.

Combination Therapy

[00110] In some instances, Gram-negative bacteria are more resistant to a larger number of antibacterials and chemotherapeutic agents than are gram-positive bacteria due in part to their outer membrane, which acts as an efficient permeability barrier.

[00111] A survey of recently reported antibacterials of natural origin showed that over 90% lacked activity against *Escherichia coli*, although they were active against gram-positive bacteria. Young and Silver (J. Bacteriol. 173(12):3609-14 (1991)) demonstrated that an envA1 strain, having an altered outer membrane, is sensitive to a variety of large and hydrophobic

antibacterials to which wild type *E. coli* is resistant. Additionally, Vaara, et al., (Antimicrobial Agents and Chemotherapy 37(11):2255-2260 (1993)) review a variety of outer membrane-defective mutants of *E coli* and *S. typhimurium* that show greater susceptibility than the corresponding wild type strain to a variety of antibacterial agents.

[00112] In some embodiments, the present invention provides synergistic combinations of antibacterial agents with the LpxC inhibitory compounds or pharmaceutical compositions disclosed herein. In some embodiments, the LpxC inhibitory compounds disclosed herein have both intrinsic antibacterial properties as well the ability to improve permeability of the outer membrane of gram-negative bacteria to other antibacterial agents. In some embodiments, the antibacterial agent is selected from the group consisting of vancomycin, linezolid, azithromycin, imipenem, teicoplanin, daptomycin, clindamycin, rifampin, cefotaxime, gentamicin, novobiocin, and telavancin.

[00113] The use of such synergistic combinations of drugs could have many advantages over conventional single compound therapy, including lowered side-effects of the antibacterial agent due to lower doses used or to shorter time of treatment, more rapid cure of infection shortening hospital stays, increasing spectrum of pathogens controlled, and decreasing incidence of development of resistance to antibiotics.

Methods of Dosing and Treatment Regimens

[00114] In one embodiment, the LpxC inhibitory compounds disclosed herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, are used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from modulation of LpxC activity. Methods for treating any of the diseases or conditions described herein in a mammal in need of such treatment, involves administration of pharmaceutical compositions that include the LpxC inhibitory compounds disclosed herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, in therapeutically effective amounts to said mammal.

[00115] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00116] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00117] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg-2000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00118] In one embodiment, the daily dosages appropriate for the LpxC inhibitory compounds disclosed herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, described herein are from about 0.01 to about 50 mg/kg per body weight. In some embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00119] In any of the aforementioned aspects are further embodiments in which the effective amount of the LpxC inhibitory compounds disclosed herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal.

[00120] In some embodiments, the LpxC inhibitory compound disclosed herein, or an isotopic variant, tautomer, prodrug, pharmaceutically acceptable salt, solvate, or hydrate thereof, is administered is dose selected from about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, and about 400 mg. In some embodiments, the dose is administered once a day. In some embodiments, the dose is administered twice a day.

Articles of Manufacture and Kits

[00121] Disclosed herein, in certain embodiments, are kits and articles of manufacture for use with one or more methods described herein. In some embodiments, additional components of the kit comprises a carrier, package, or container that is compartmentalized to receive one or more

containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, plates, syringes, and test tubes. In one embodiment, the containers are formed from a variety of materials such as glass or plastic.

[00122] The articles of manufacture provided herein contain packaging materials. Examples of pharmaceutical packaging materials include, but are not limited to, bottles, tubes, bags, containers, and any packaging material suitable for a selected formulation and intended mode of use.

[00123] For example, the container(s) include one or more of the compounds described herein. Such kits optionally include an identifying description or label or instructions relating to its use in the methods described herein.

[00124] A kit typically includes labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[00125] In one embodiment, a label is on or associated with the container. In one embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In one embodiment, a label is used to indicate that the contents are to be used for a specific therapeutic application. The label also indicates directions for use of the contents, such as in the methods described herein.

[00126] Other embodiments and uses will be apparent to one skilled in the art in light of the present disclosures. The following examples are provided merely as illustrative of various embodiments and shall not be construed to limit the invention in any way.

EXAMPLES

I. Chemical Synthesis

[00127] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Anhydrous solvents and oven-dried glassware were used for synthetic transformations sensitive to moisture and/or oxygen. Yields were not optimized. Reaction times are approximate and were not optimized. Column chromatography and thin layer chromatography (TLC) were performed on silica gel unless otherwise noted. Spectra are given in ppm (δ) and coupling constants, J are reported in Hertz. For proton spectra the solvent peak was used as the reference peak.

[00128] The following abbreviations and terms have the indicated meanings throughout:

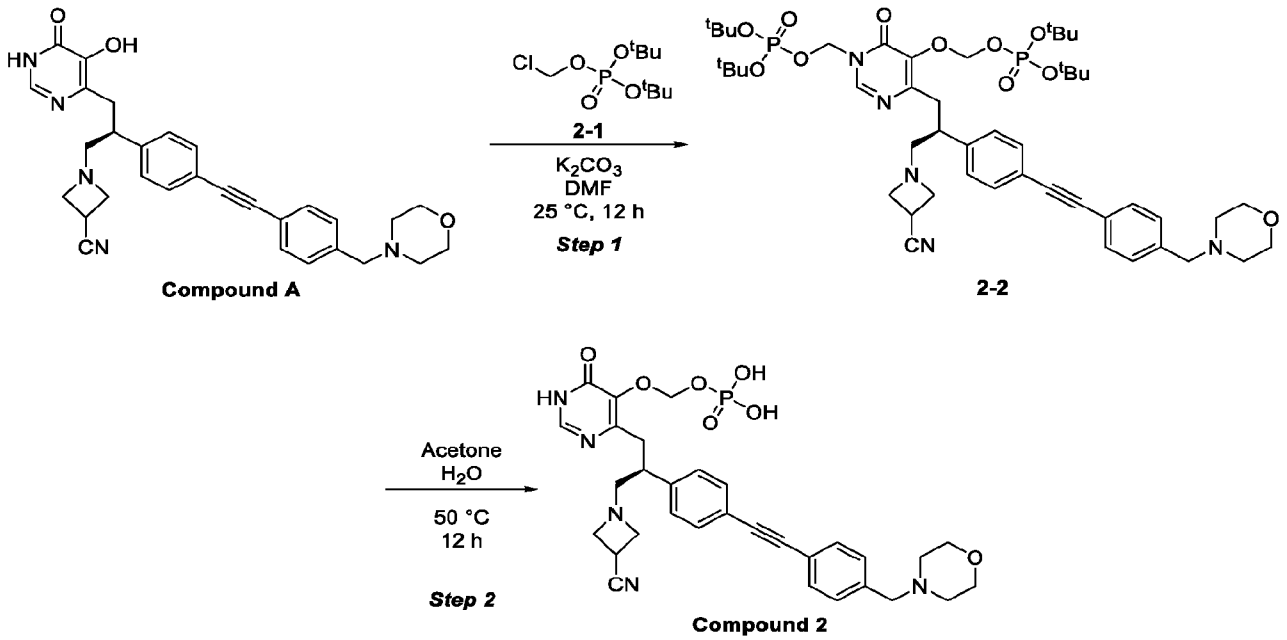
ACN	=	acetonitrile
DCM	=	dichloromethane
DMF	=	N,N-Dimethylformamide
EtOAc	=	ethyl acetate
g	=	gram
h or hr	=	hour
HPLC	=	high pressure liquid chromatography
LCMS	=	liquid chromatography-mass spectrometry
m/z	=	mass-to-charge ratio
mg	=	milligram
min	=	minute
mL	=	milliliter
mmol	=	millimole
PBS	=	phosphate-buffered saline
RP-HPLC	=	reverse phase-high pressure liquid chromatography
rt or RT	=	room temperature
TFA	=	trifluoroacetic acid

[00129] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1: Preparation of (*S*)-1-(3-(5,6-dihydroxypyrimidin-4-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)azetidine-3-carbonitrile (Compound A)

[00130] The preparation and use of Compound A has been previously described (see, WO 2020/061375, US 2021/0221796, WO 2021/195260, and US 2021/0309651 each of which is incorporated by reference in its entirety).

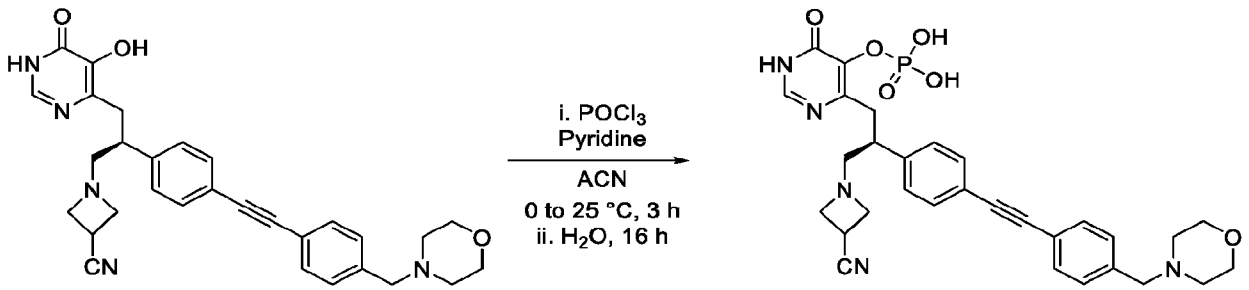
Example 2: Preparation of (S)-((4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)methyl dihydrogen phosphate (Compound 2)



[00131] Step 1: To a stirred suspension of **Compound A** (0.2 g, 0.392 mmol) in DMF (10 mL), were added potassium carbonate (0.054 g, 0.392 mmol) and di-tert-butyl(chloromethyl)phosphate (**2-1**, 0.508 g, 1.962 mmol) at 25 °C. After stirring for 12 h, LCMS showed complete consumption of starting material and the formation of mono and dialkylated products. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude product was triturated with diethyl ether. The solid precipitated was filtered through Buchner funnel. The filtrate was further purified by column chromatography (SiO_2 100-200 mesh; EtOAc and DCM) to afford **2-2** (200 mg, 45%) as gum. LCMS: Calculated for $C_{48}H_{69}N_5O_{11}P_2$: 954.05 (Exact mass: 953.45); Observed: 953.9 $[M+1]^+$.

[00132] Step 2: A solution of **2-2** (0.1 g, 0.105 mmol) in acetone (5 mL) and water (5 mL) was heated at 50 °C for 12 h. The progress of the reaction was monitored by LCMS. The volatiles were evaporated under reduced pressure and the crude product was purified by reversed phase prep HPLC (0.1% TFA in water buffer and acetonitrile) to afford **Compound 2** (12.26 mg, 19%) as an off-white solid. LCMS: Calculated for $C_{31}H_{34}N_5O_7P$: 619.61; Observed: 620.0 $[M+1]^+$.

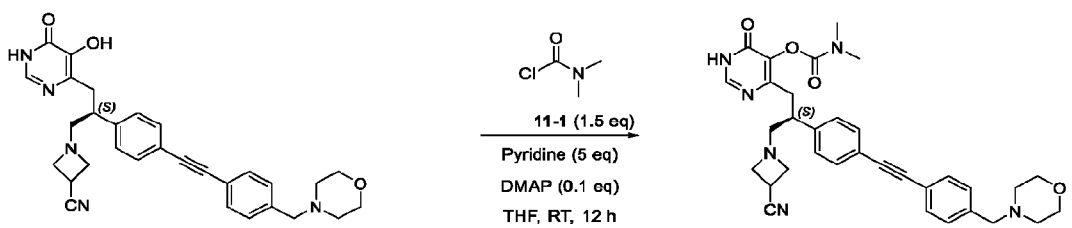
Example 3: Preparation of (S)-4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl dihydrogen phosphate (Compound 1)



Compound A Compound 1

[00133] To a solution of **Compound A** (0.2 g, 0.392 mmol) in pyridine (8 mL), was added phosphoryl trichloride (0.093 mL, 0.995 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. To this reaction mixture was added acetonitrile (9.6 mL) and stirred at 25 °C for 2 h. The reaction was quenched with water (10 mL) and stirred for 16 h at 25 °C. The reaction mixture was concentrated. The resulting crude product was purified by reversed phase preparative HPLC (10 mM ammonium bicarbonate buffer and acetonitrile) to afford **Compound 1** (45 mg, 19%) as pale pink solid. LC-MS: Calculated for $C_{30}H_{32}N_5O_6P$: 589.59, Observed: 590.7 $[M+1]^+$.

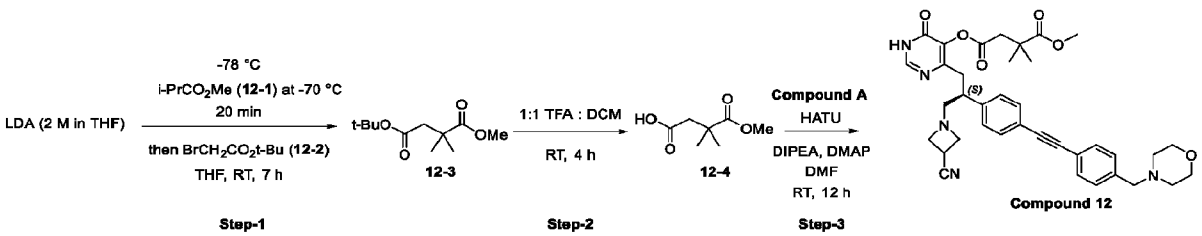
Example 4: Preparation of (S)-4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl dimethylcarbamate (Compound 11)



Compound A Compound 11

[00134] To a stirred suspension of **Compound A** (0.25 g, 0.491 mmol) in THF (25 ml), pyridine (0.198 ml, 2.453 mmol), dimethylcarbamoyl chloride, **1-1** (0079 g, 0.736 mmol) and 4-dimethylaminopyridine (5.99 mg, 0.049 mmol) were added and stirred at 25 °C for 12 h. The reaction mixture was filtered off to remove unreacted starting material, the filtrate was concentrated under reduced pressure and the crude product was purified by reverse phase prep HPLC in 0.1% TFA/ acetonitrile to afford **Compound 11** as an off-white solid. Yield: 30 mg, (10% yield). LC-MS: Calculated for $C_{33}H_{36}N_6O_4$: 580.68, Observed: 581.0 $[M+H]^+$; 603 $(M+Na)^+$; 291 $(M+2)^{2+}/2$.

Example 5: Preparation of (S)-4-(4-(3-(3-cyanoazetidin-1-yl)-2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)propyl)-6-oxo-1,6-dihydropyrimidin-5-yl) 1-methyl 2,2-dimethylsuccinate (Compound 12)



Step 1: A solution of lithium diisopropylamide (2 M in THF, 4.90 mL, 9.79 mmol) was diluted with Tetrahydrofuran (15 mL), and the mixture was cooled to -78 °C. methyl isobutyrate (**12-1**, 1 g, 9.79 mmol) was added dropwise and the mixture was stirred at -70 °C to -65 °C for 20 minutes. *tert*-butyl 2-bromoacetate (**12-2**, 5.6 mL, 11.74 mmol) was added dropwise. The reaction mixture was allowed to warm to RT and stirred for 7 h. TLC showed consumption of starting material. The reaction mixture was quenched with saturated NH_4Cl (aq). The aqueous layer was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford 4-(*tert*-butyl) 1-methyl 2,2-dimethylsuccinate (**12-3**, 1 g, 4.62 mmol, 47 % yield) as brown oil. The crude mass as such taken to the next step.

Step 2: A solution of 50% TFA (10.00 mL) in DCM (10 mL) was added to 4-(*tert*-butyl) 1-methyl 2,2-dimethylsuccinate (**12-3**, 1 g, 4.62 mmol) and stirred at RT for 4 h. TLC showed consumption of starting material. The reaction mixture was concentrated under reduced pressure to remove TFA and DCM. The reaction mixture was basified with 10% sodium bicarbonate solution (30 mL), washed with DCM. The aqueous layer was acidified with 0.1 N HCl and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain 4-methoxy-3,3-dimethyl-4-oxobutanoic acid (**12-4**, 0.7 g, 3.69 mmol, 80 % yield) as brown oil. The crude mass as such taken to the next step. LC-MS: Calculated for $C_7H_{12}O_4$: 160.17; Observed : 161 $[M+H]^+$ and 143 $[M-H_2O]^+$.

Step 3: To a stirred solution of 4-methoxy-3,3-dimethyl-4-oxobutanoic acid (**12-4**, 0.100 g, 0.196 mmol), HATU (0.298 g, 0.785 mmol), N-ethyl-N-isopropylpropan-2-amine (0.101 g, 0.785 mmol) in DMF (2 mL), 4-(dimethylamino)pyridine (0.024 g, 0.196 mmol) were added and stirred. **Compound A** (0.1 g, 0.196 mmol) in DMF (2 mL) was added and stirred at RT for 12 h. The reaction mixture was washed with water and extracted with ethyl acetate (2x20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by preparatory HPLC to obtain **Compound 12** (45

mg, 0.067 mmol, 34 % yield) as white solid. LC-MS: Calculated for $C_{37}H_{41}N_5O_6$: 651.76; Observed : 652.2 $[M+H]^+$; 510 [M-acyl group]$^+$; 326.7 $[M+2]^{2+}/2$.

Example 6: Thermal Solubility

[00135] Solubility of the compounds was assessed in 100mM potassium phosphate buffer at pH 7.4 after 24 hours at room temperature.

[00136] Accurately weighed K_2HPO_4 (2.79 g) and KH_2PO_4 (0.54 g) were dissolved in 90 mL of Milli-Q water and mixed well. Volume was made upto 200 mL with Milli- Q water and mixed well. The prepared phosphate buffer was stored at 2-8°C and used within a month.

[00137] Approximately 30 mg of test compound was added to approximately 1 mL of the potassium phosphate buffer, pH 7.4. If the visual inspection indicated precipitation, no further compound is added. If the visual inspection indicated a clear solution, further increments of compound were added until the solution was no longer clear.

[00138] Test compounds and assay controls (caffeine) were further incubated for 24 h at 25°C temperature on a thermomixer at a shaking speed of 1200 rpm. After incubation, the samples (200 µL) were transferred to a filtration plate to which a plate was attached at bottom for collecting the filtrate. The plate was centrifuged at 4000 rpm for 2 min and the filtrate was collected in the attached bottom plate. The filtrates were diluted using filtered buffer based on the initial amount of compound added. All samples were analysed by HPLC-UV method against 8 point calibration curve with concentrations ranging from 2.5 µg/mL to 1000 µg/mL.

HPLC-UV Method

IIPLC	Shimadzu	
Column	Waters X Bridge, C18, 3.5µ, 50*4.6mm	
MP-A	0.1% Formic acid in Milli Q water	
MP-B	Acetonitrile - 100%	
Flow Rate	1.2 mL/min	
Run time	5.5 min	
Injection Volume	4 µL	
Gradient Condition		
TIME (min)	**A (%)**	**B (%)**
0.01	95	5
2.50	35	65
3.00	5	95
4.00	5	95
4.50	95	5
5.50	95	5

[00139] Compound 1 has a thermal solubility of ≥ 3 mg/mL.

[00140] Compound 2 has a thermal solubility of ≥ 3 mg/mL.

[00141] Compound A has a thermal solubility of < 0.05 mg/mL.

[00142] Compound A, hydrochloride salt has a thermal solubility of < 0.05 mg/mL.

Example 7: Kinetic Solubility

[00143] Solubility of the compounds was assessed in 10 mM phosphate-buffered saline (PBS) at pH 7 at final concentrations of 20, 40, and 50 mg/mL of test compound.

[00144] Experiments with **Compound 1** yielded clear solutions at concentrations of 20, 40, and 50 mg/mL after vortex mixing. All solutions remained soluble after storage at 4 °C for 20 hours.

[00145] Experiments with **Compound 2** yielded milky suspensions at concentrations of 20, 40, and 50 mg/mL after vortex mixing. After sonication in a 40 °C water bath for 30 min, there was no change in appearance. Clear solutions were observed after treatment with 1M HCL (final pH of 4) and 10 seconds of vortexing. Addition of 1M NaOH (final pH of 7) and 10 seconds of vortexing produced clear solutions.

Example 8: Pharmacokinetics (PK)

[00146] Stock solutions of test compounds were prepared at 2.5 or 5.0 mg/mL in 10 mM PBS. Male Sprague–Dawley (SD) rats (n = 3 per group) or beagle dogs (n = 3 per group) were administered test compound by either IV or oral administration. For IV-administered compounds, a three hour infusion was used. For PO-administered compounds, a single bolus dose was used.

[00147] After initiation of IV dosing (or after PO bolus dosing), whole blood samples were collected at 1, 3, 3.5, 4, 6, 8, and 24 hour timepoints. All samples were collected into Plasma K2-EDTA collection tubes and processed to separate plasma from red blood cells.

[00148] Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to analyze all plasma samples, with both the test compound and the active agent **Compound A** being quantified. The lower limit of quantitation (LLOQ) for both rats and dogs was 1 ng/mL.

[00149] Administration of **Compound 1** yields a dose-dependent plasma exposures of **Compound A** after IV or PO administration, demonstrating its utility as a prodrug of **Compound A**. While concentrations of prodrug **Compound 1** show rapid decrease after administration (<100 ng/mL after 4h for all routes and doses tested in rat, and after 6 h in dog), the released **Compound A** shows systemic exposure after both oral and IV administration (Tables 2-3).

Table 2. Plasma Concentration and Pharamcokinetics of Compound A After Administration of Compound 1 in Male Sprague–Dawley (SD) Rats (n = 3 per group)

Dose (mg/kg) of Compound 1	37.5	75	75
Route of Administration	IV	IV	PO
C_{max} (ng/mL)	9038	28492	7627
T_{max} (h)	3	3	0.67
$T_{1/2}$ (h)	2.90	2.67	3.83
T_{last} (h)	8-24	24	24
$AUC_{0\text{-}last}$ (h*ng/mL)	31889	92792	22732

Table 3. Plasma Concentration and Pharamcokinetics of Compound A After Administration of Compound 1 in Beagle Dogs (n = 3 per group)

Dose (mg/kg) of Compound 1	12.5	25	25
Route of Administration	IV	IV	PO
C_{max} (ng/mL)	1176	2507	3350
T_{max} (h)	3	3	0.67
$T_{1/2}$ (h)	4.18	3.83	5.72
T_{last} (h)	24	24	8-24
$AUC_{0\text{-}last}$ (h*ng/mL)	4500	8451	6184

II. Biological Evaluation

Example 9: Treatment of Urinary Tract Infection

[00150] Compound A and its prodrugs as disclosed herein were tested in an *in vivo* mouse model for Urinary Tract Infection. Briefly, mice were infected with *E. coli* UTI 89 to cause a UTI infection and were treated with compounds disclosed herein.

Procedure:

[00151] Five days prior to infection, C3H/HeNR female mice were preconditioned with drinking water containing 5% glucose. Mice were rendered unconscious using parenteral anaesthesia (ketamine/medetomidine) then 0.05 mL of a bacterial suspension of *E. coli* UTI 89 (1.2×10^9 CFU/mL (6.2×10^7 CFU/mouse) was administered transurethrally into the bladder to cause an ascending UTI infection.

[00152] IV or PO treatment was started 24 h post infection with 3, 10, 15 mg/kg/dose IV Compound A; 3, 10, 15, 30 mg/kg/dose IV Compound 1; 3, and 10 mg/kg/dose IV Compound 2; and 30 mg/kg/dose oral of either Compound 1 or 2 administered every 12 hours for 3 days (six doses total). Ciprofloxacin was given as a control at 10 mg/kg/dose IV every 12 hours. Compound A was formulated in 10% DMSO, 5% Cremophor, 85% SFI; the remaining compounds used a sterile phosphate-buffered saline (PBS) formulation. Each group was comprised of five mice each.

[00153] Urine, bladder, and kidney were harvested at 24 h (pre-treatment group only) and 96 h post infection and quantitatively cultured.

Results:

[00154] Table 4 and Figure 1 summarize the results, showing the average terminal burden of *E. coli* UTI 89 in urine, bladder, and kidney at the conclusion of the study (96 hours).

Table 4. Terminal Burden of *E. coli* UTI 89 in Urine, Bladder, and Kidney

Treatment Group	Urine Terminal Burden (CFU/mL)	Bladder Terminal Burden (CFU/mL)	Kidney Terminal Burden (CFU/mL)
Vehicle IV	1.73×10^7	3.32×10^8	8.18×10^5
Vehicle PO	1.30×10^6	9.59×10^5	2.63×10^5
Compound A 3 mg/kg/dose IV	3.03×10^5	2.57×10^5	3.72×10^3
Compound A 10 mg/kg/dose IV	6.26×10^4	3.48×10^5	4.44×10^2
Compound A 15 mg/kg/dose IV	3.78×10^3	2.62×10^5	1.21×10^2
Compound 1 3 mg/kg/dose IV	2.93×10^5	2.64×10^6	4.74×10^4
Compound 1 10 mg/kg/dose IV	9.40×10^3	5.05×10^5	5.24×10^2
Compound 1 15 mg/kg/dose IV	3.59×10^3	9.57×10^4	1.28×10^2
Compound 1 30 mg/kg/dose PO	8.73×10^3	1.81×10^5	4.04×10^2
Compound 2 3 mg/kg/dose IV	4.69×10^4	5.15×10^5	2.52×10^3
Compound 2 10 mg/kg/dose IV	2.73×10^4	1.17×10^6	9.67×10^2
Compound 2 30 mg/kg/dose PO	3.41×10^3	2.82×10^5	3.81×10^2
Ciprofloxacin 10 mg/kg/dose IV	5.07×10^2	2.85×10^5	1.88×10^2

[00155] Treatment with Compound A, Compound 1, and Compound 2 resulted in statistically significant reductions in bacterial burden in urine relative to vehicle-treated controls. There was

no significant difference in efficacy between equivalent doses of Compound A, Compound 1, and Compound 2 administered by IV adminstration.

[00156] Treatment with Compound A, Compound 1, and Compound 2 by IV administration resulted in reductions in bacterial burden in bladder relative to the vehicle-treated controls.

[00157] Treatment with Compound A, Compound 1, and Compound 2 by IV administration resulted in statistically significant reductions in bacterial burden in kidney relative to the vehicle-treated control. PO administration of Compound 1 and Compound 2 was also efficacious. There was no significant difference in efficacy between equivalent doses of Compound A, Compound 1, and Compound 2 administered by IV adminstration.

[00158] The experiment was repeated using *K. pneumoniae* BAA-1705 (MDR; MIC_{90} strain). Table 5 and Figure 2 summarize the results, showing the average terminal burden of *K. pneumoniae* BAA-1705 in urine, bladder, and kidney at the conclusion of the study (96 hours).

Table 5. Terminal Burden of *K. pneumoniae* BAA-1705 in Urine, Bladder, and Kidney

Treatment Group	Urine Terminal Burden (CFU/mL)	Bladder Terminal Burden (CFU/mL)	Kidney Terminal Burden (CFU/mL)
Vehicle IV	5.09×10^3	4.58×10^0	3.92×10^4
Vehicle PO	6.23×10^3	2.76×10^1	3.63×10^4
Compound A 10 mg/kg/dose IV	2.72×10^0	9.29×10^1	3.47×10^2
Compound A 30 mg/kg/dose IV	7.41×10^3	BLoD	7.48×10^1
Compound A 60 mg/kg/dose IV	BLoD	BLoD	3.17×10^0
Compound A 90 mg/kg/dose PO	7.06×10^0	BLoD	3.01×10^1
Compound 1 11.5 mg/kg/dose IV	2.15×10^1	BLoD	1.72×10^1
Compound 1 35 mg/kg/dose IV	BLoD	BLoD	BLoD
Compound 1 69.5 mg/kg/dose IV	BLoD	4.58×10^0	BLoD
Compound 1 104.5 mg/kg/dose PO	2.51×10^0	BLoD	BLoD
Ciprofloxacin 10 mg/kg/dose IV	1.78×10^2	2.27×10^1	1.88×10^3

Treatment Group	Urine Terminal Burden (CFU/mL)	Bladder Terminal Burden (CFU/mL)	Kidney Terminal Burden (CFU/mL)
Ciprofloxacin 10 mg/kg/dose PO	9.71×10^2	4.05×10^2	2.59×10^4

BLoD = below limit of detection

[00159] Treatment with Compound A, Compound 1, and Compound 2 resulted in statistically significant reductions in bacterial burden in urine relative to vehicle-treated controls and the ciprofloxacin control (except for the 30 mg/kg IV Compound A experiment).

[00160] Treatment with Compound A, Compound 1, and Compound 2 resulted in statistically significant reductions in bacterial burden in kidney relative to vehicle-treated controls and the ciprofloxacin control. Furthermore, treatment with Compound 1 resulted in bacterial loads below the limit of detection for all routes of administration.

III. Pharmaceutical Compositions

Example A-1: Parenteral Pharmaceutical Composition

[00161] To prepare a parenteral pharmaceutical composition suitable for administration by injection (subcutaneous, intravenous), 1-100 mg of a compound Formula (I), or a pharmaceutically acceptable salt, or a pharmaceutally acceptable solvate thereof, is dissolved in sterile water and then mixed with 10 mL of 0.9% sterile saline. A suitable buffer is optionally added as well as optional acid or base to adjust the pH. The mixture is incorporated into a dosage unit form suitable for administration by injection

Example A-2: Oral Solution

[00162] To prepare a pharmaceutical composition for oral delivery, a sufficient amount of a compound of Formula (I), or a pharmaceutically acceptable salt, or a pharmaceutally acceptable solvate thereof, is added to water (with optional solubilizer(s),optional buffer(s) and taste masking excipients) to provide a 20 mg/mL solution.

Example A-3: Oral Tablet

[00163] A tablet is prepared by mixing 20-50% by weight of a compound of Formula (I), or a pharmaceutically acceptable salt, or a pharmaceutally acceptable solvate thereof, 20-50% by weight of microcrystalline cellulose, 1-10% by weight of low-substituted hydroxypropyl cellulose, and 1-10% by weight of magnesium stearate or other appropriate excipients. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 100 -500 mg.

Example A-4: Oral Capsule

[00164] To prepare a pharmaceutical composition for oral delivery, 10-500 mg of a compound of Formula (I), or a pharmaceutically acceptable salt, or a pharmaceutally acceptable solvate thereof, is mixed with starch or other suitable powder blend. The mixture is incorporated into an oral dosage unit such as a hard gelatin capsule, which is suitable for oral administration.

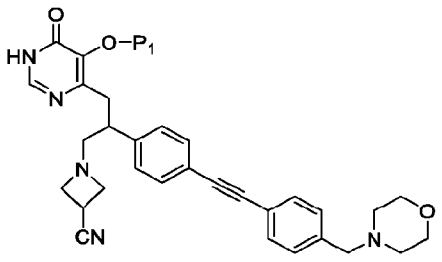
[00165] In another embodiment, 10-500 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is placed into Size 4 capsule, or size 1 capsule (hypromellose or hard gelatin) and the capsule is closed.

[00166] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

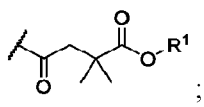
1. A compound having the structure of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-P(=O)(OR^1)_2$, $-(CR^3R^4)-O-P(=O)(OR^1)_2$, $-S(=O)_2OR^1$, $-(CR^3R^4)-O-S(=O)_2OR^1$, $-S(=O)_2R^2$, $-(CR^3R^4)-O-S(=O)_2R^2$, $-C(=O)R^2$, $-(CR^3R^4)-O-C(=O)R^2$, $-C(=O)OR^2$, $-(CR^3R^4)-O-C(=O)OR^2$, $-C(=O)-O-(CR^3R^4)-O-C(=O)R^2$, $-C(=O)NR^5R^6$, or



;

each R^1 is independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

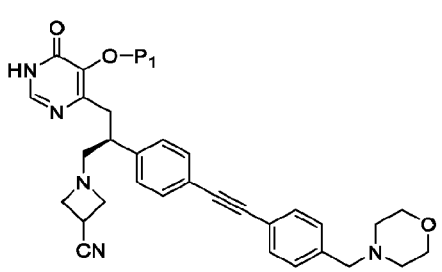
R^2 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

R^5 and R^6 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4- to 6-membered heterocycloalkyl which is unsubstituted or is substituted with 1, 2, or 3 substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, C_3-C_6 cycloalkyl, and 4- to 6-membered heterocycloalkyl.

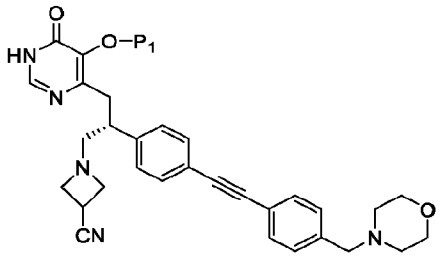
2. The compound of claim 1, having the structure of Formula (Ia):



Formula (Ia),

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof.

3. The compound of claim 1, having the structure of Formula (Ib):



Formula (Ib),

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

R^3 and R^4 are each hydrogen.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

each R^1 is independently hydrogen or C_1-C_4 alkyl.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

each R^1 is independently hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

each R^1 is hydrogen.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

R^2 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

R^2 is C_1-C_4 alkyl.

11. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-P(=O)(OR^1)_2$ or $-(CR^3R^4)$-O-$P(=O)(OR^1)_2$;

each R^1 is independently hydrogen or C_1-C_4 alkyl; and

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl.

12. The compound of claim 11, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-P(=O)(OR^1)_2$ or $-CH_2-O-P(=O)(OR^1)_2$; and

each R^1 is independently hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$.

13. The compound of claim 11 or claim 12, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-P(=O)(OH)_2$ or $-CH_2-O-P(=O)(OH)_2$.

14. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-S(=O)_2OR^1$ or $-(CR^3R^4)-O-S(=O)_2OR^1$;

R^1 is hydrogen or C_1-C_4 alkyl; and

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl.

15. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-S(=O)_2R^2$ or $-(CR^3R^4)-O-S(=O)_2R^2$;

R^2 is C_1-C_4 alkyl; and

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl.

16. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-C(=O)OR^2$, $-(CR^3R^4)-O-C(=O)OR^2$, or $-C(=O)-O-(CR^3R^4)-O-C(=O)R^2$;

R^2 is C_1-C_4 alkyl; and

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl.

17. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-C(=O)R^2$ or $-(CR^3R^4)-O-C(=O)R^2$;

R^2 is C_1-C_4 alkyl; and

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl.

18. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-C(=O)NR^5R^6$.

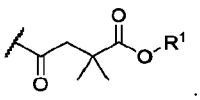
19. The compound of claim 18, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

R^5 and R^6 are each independently hydrogen or C_1-C_4 alkyl.

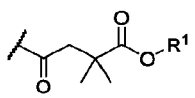
20. The compound of claim 18, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4- to 6-membered heterocycloalkyl which is unsubstituted or is substituted with 1 or 2 substituents selected from the group consisting of C_1-C_4 alkyl and 4- to 6-membered heterocycloalkyl.

21. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is  .

22. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-P(=O)(OR^1)_2$, $-CH_2-O-P(=O)(OR^1)_2$, $-S(=O)_2OR^1$, $-S(=O)_2R^2$, $-C(=O)OR^2$, $-(CHR^4)-O-C(=O)OR^2$, $-C(=O)-O-(CHR^4)-O-C(=O)R^2$, $-C(=O)R^2$, $-CH_2-O-C(=O)R^2$, $-C(=O)NR^5R^6$, or  ;

each R^1 is independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl;

R^2 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl;

R^4 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl; and

R^5 and R^6 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl;

or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4- to 6-membered heterocycloalkyl which is unsubstituted or is substituted with 1 or 2 substituents selected from the group consisting of C_1-C_4 alkyl and 4- to 6-membered heterocycloalkyl.

23. The compound of claim 21, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

each R^1 is independently hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$;

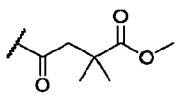
R^2 is $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, or $C(CH_3)_3$;

R^4 is hydrogen, $-CH_3$, or phenyl; and

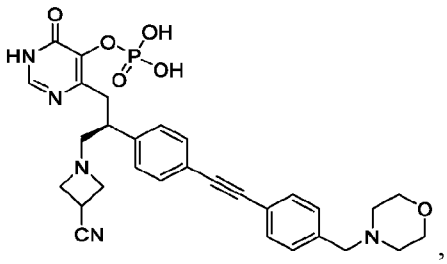
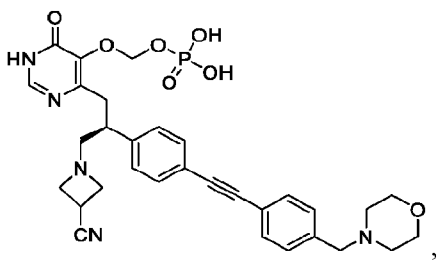
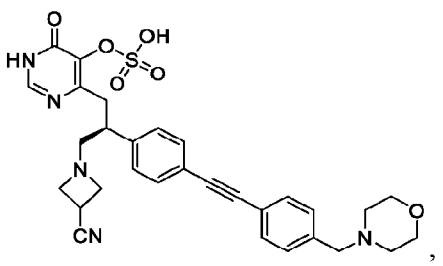
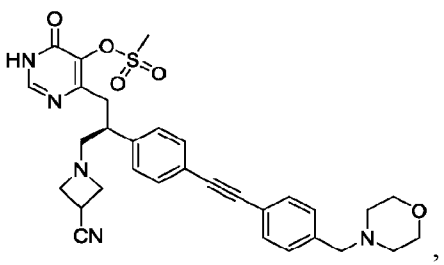
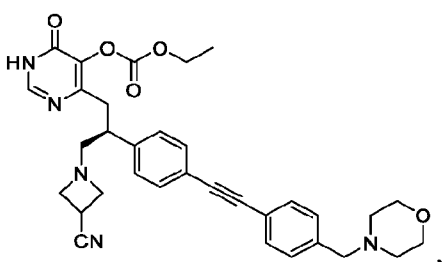
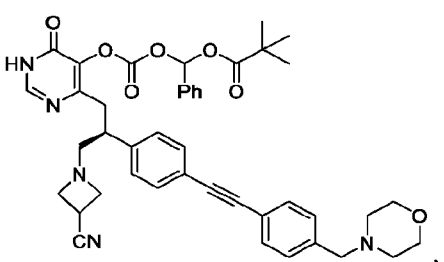
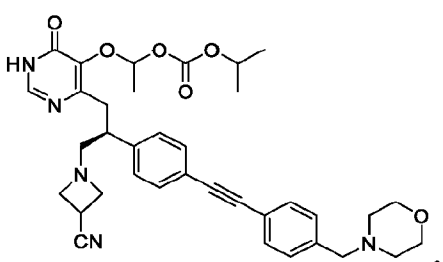
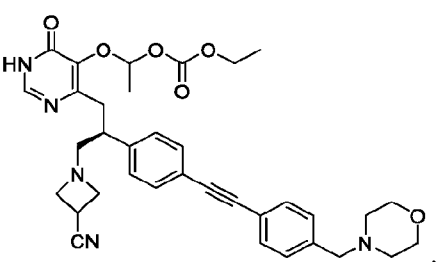
R^5 and R^6 are each independently hydrogen, $-CH_3$, or $-CH_2CH_3$;

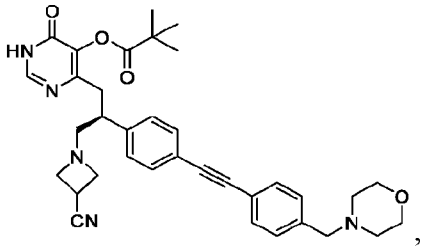
or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4- to 6-membered heterocycloalkyl which is unsubstituted or is substituted with 1 or 2 substituents selected from the group consisting of C_1-C_4 alkyl and 4- to 6-membered heterocycloalkyl.

24. The compound of claim 21, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

P_1 is $-P(=O)(OH)_2$, $-CH_2-O-P(=O)(OH)_2$, $-S(=O)_2OH$, $-S(=O)_2CH_3$, $-C(=O)OCH_2CH_3$, $-(CH(CH_3))-O-C(=O)OCH(CH_3)_2$, $-(CH(CH_3))-O-C(=O)OCH_2CH_3$, $-C(=O)-O-(CH(phenyl))-O-C(=O)C(CH_3)_3$, $-C(=O)C(CH_3)_3$, $-CH_2-O-C(=O)C(CH_3)_3$, $-C(=O)N(CH_3)_2$, or  .

25. A compound selected from:

 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,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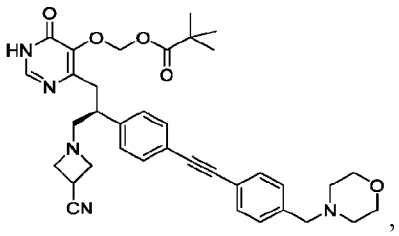
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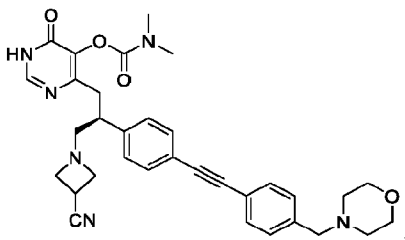
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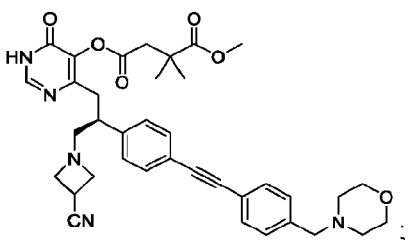
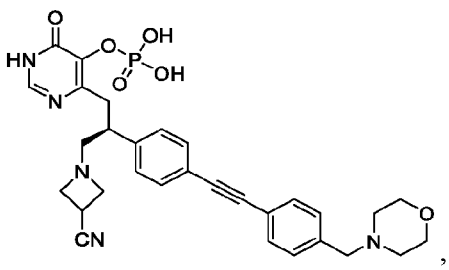

;

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof.

26. A compound selected from: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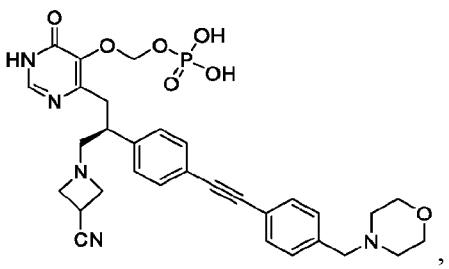
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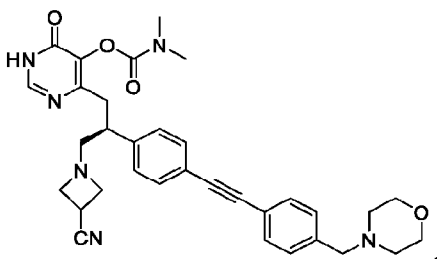
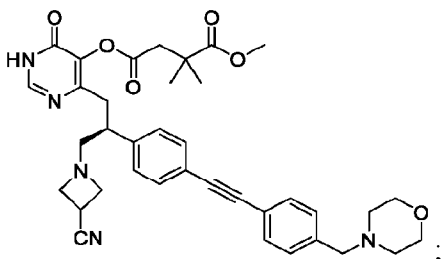
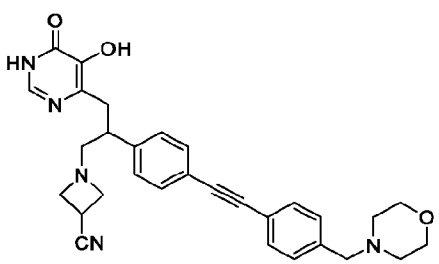

, and

;

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof.

27. A compound that is a prodrug of Compound A:

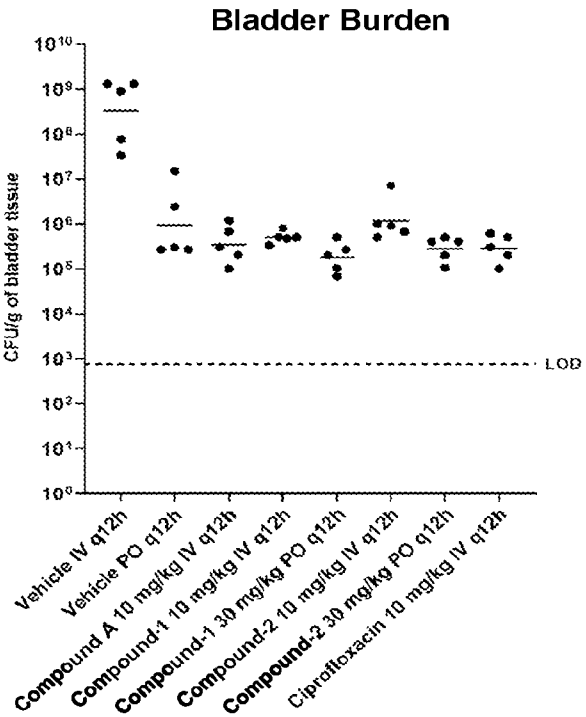

(Compound A)

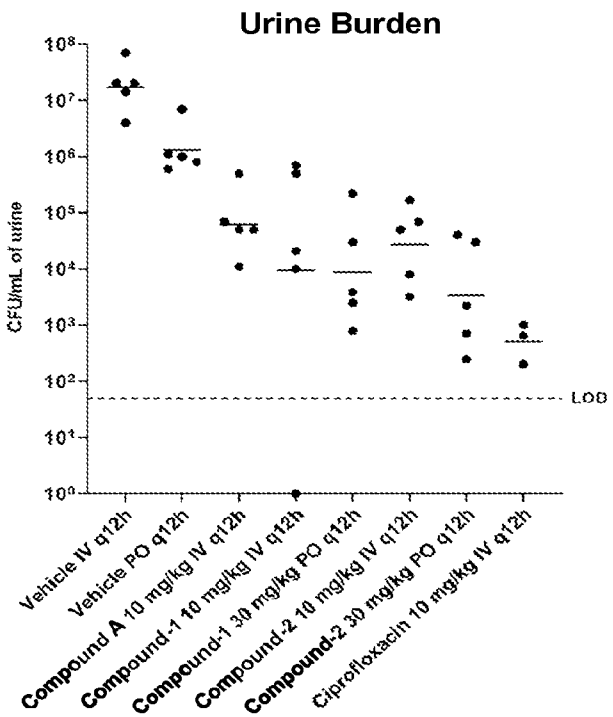
or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, wherein:

the prodrug group is attached to a hydroxy or amino group of Compound A; and wherein the prodrug moiety comprises a phosphate, sulfonate, sulfate, ester, carbonate, or carbamate.

28. The compound of claim 27, wherein the prodrug moiety comprises a phosphate.
29. The compound of claim 27, having the structure of the compound of any one of claims 1-26, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof.
30. A pharmaceutical composition comprising the compound of any one of claims 1-29, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, and at least one pharmaceutically acceptable excipient.
31. The pharmaceutical composition of claim 30, wherein the pharmaceutical composition is formulated for administration to a mammal by intravenous administration or oral administration.
32. The pharmaceutical composition of claim 30, wherein the pharmaceutical composition is in the form of a tablet, a pill, a capsule, a liquid, a suspension, a dispersion, or a solution.
33. A method of treating a gram-negative bacterial infection in a patient in need thereof comprising administering to the patient the compound of any one of claims 1-29.
34. The method of claim 33, wherein the gram-negative bacterial infection is selected from pneumonia, sepsis, cystic fibrosis, intra-abdominal infection, skin infection and urinary tract infection.
35. The method of claim 33, wherein the gram-negative bacterial infection is selected from chronic urinary tract infection, complicated urinary tract infection, cystitis, pyelonephritis, urethritis, recurrent urinary tract infections, bladder infections, urethral infections and kidney infections.
36. The method of any one of claims 33-35, wherein the gram-negative bacterial infection is chronic urinary tract infection.
37. The method of any one of claims 33-35, wherein the gram-negative bacterial infection is complicated urinary tract infection.
38. The method of any one of claims 33-37, wherein the composition is administered to the patient by I.V. injection.
39. The method of any one of claims 33-37, wherein the composition is administered to the patient by I.V. infusion.
40. The method of any one of claims 33-37, wherein the composition is administered to the patient orally.
41. The method of any one of claims 33-40, wherein the administration is to treat an existing infection.
42. The method of any one of claims 33-40, wherein the administration is provided as prophylaxis.

Figure 1





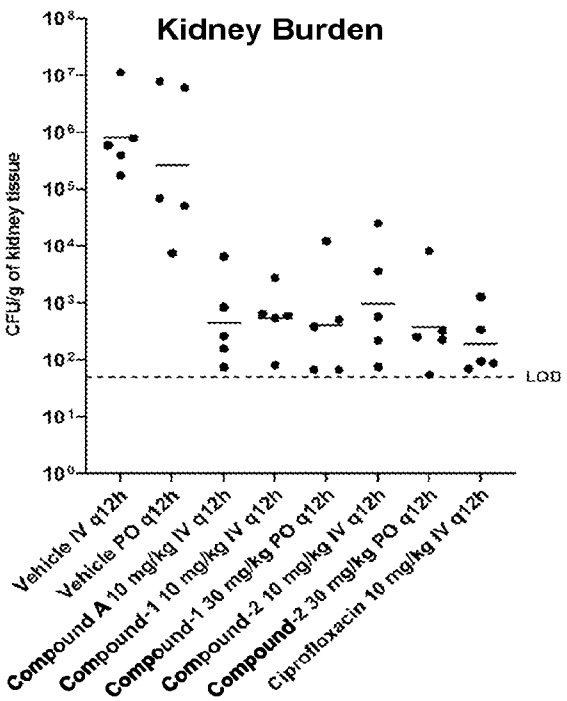


Figure 2

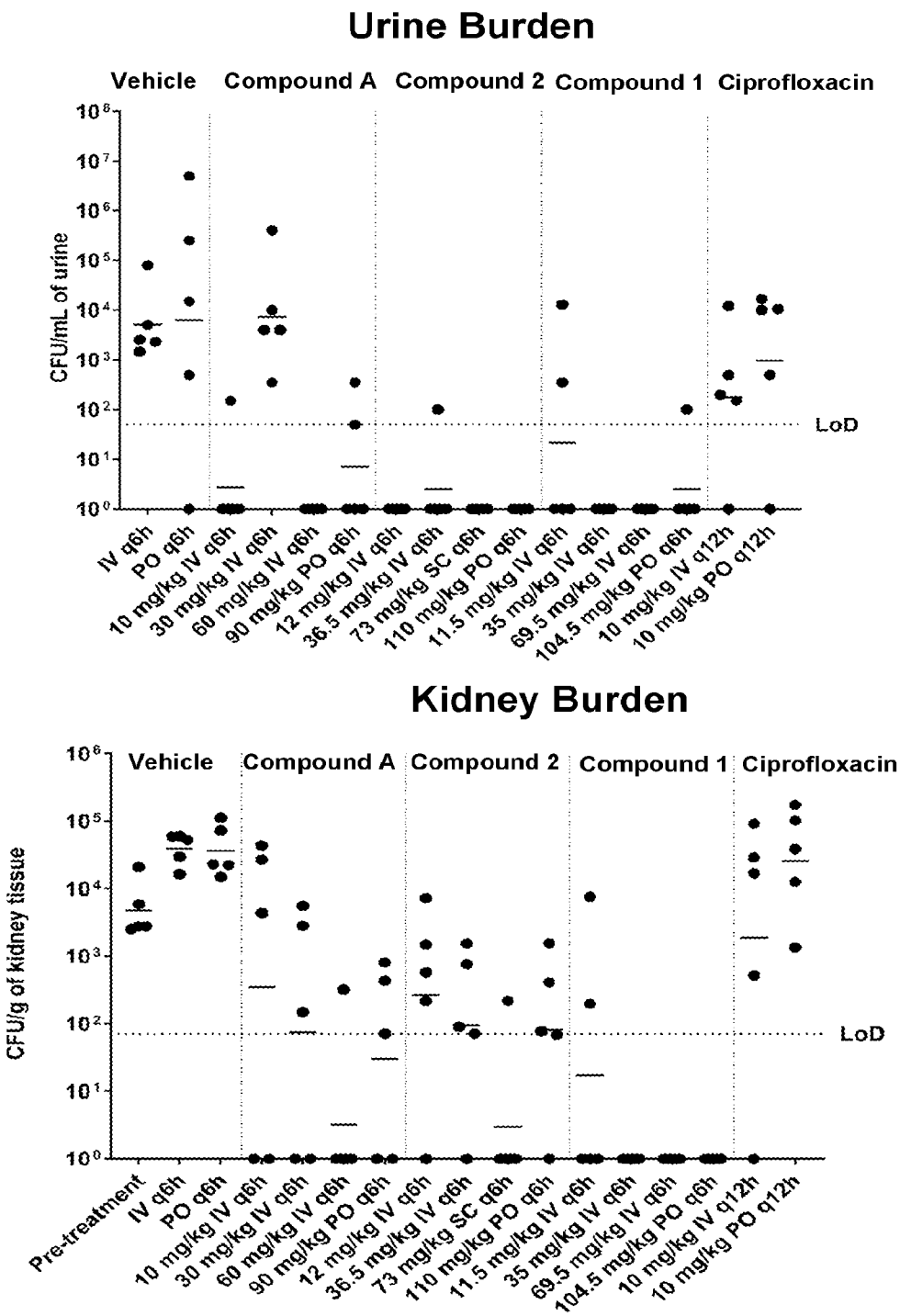
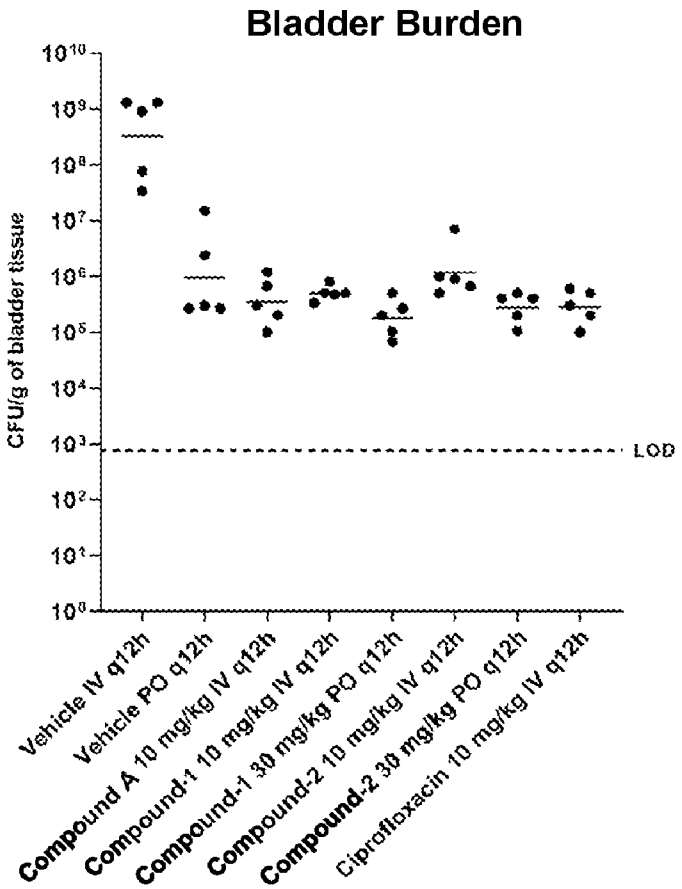
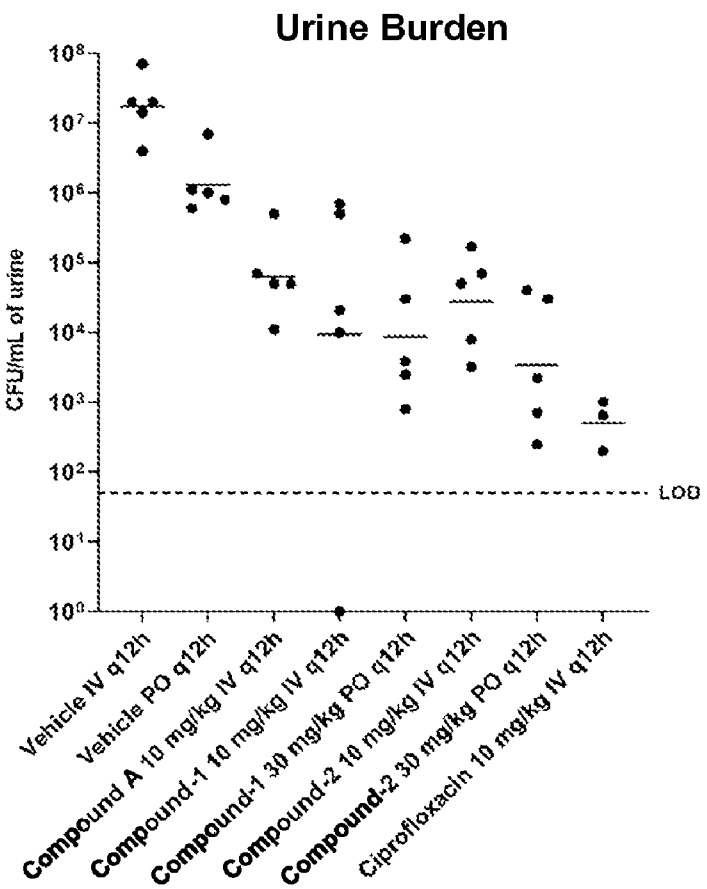
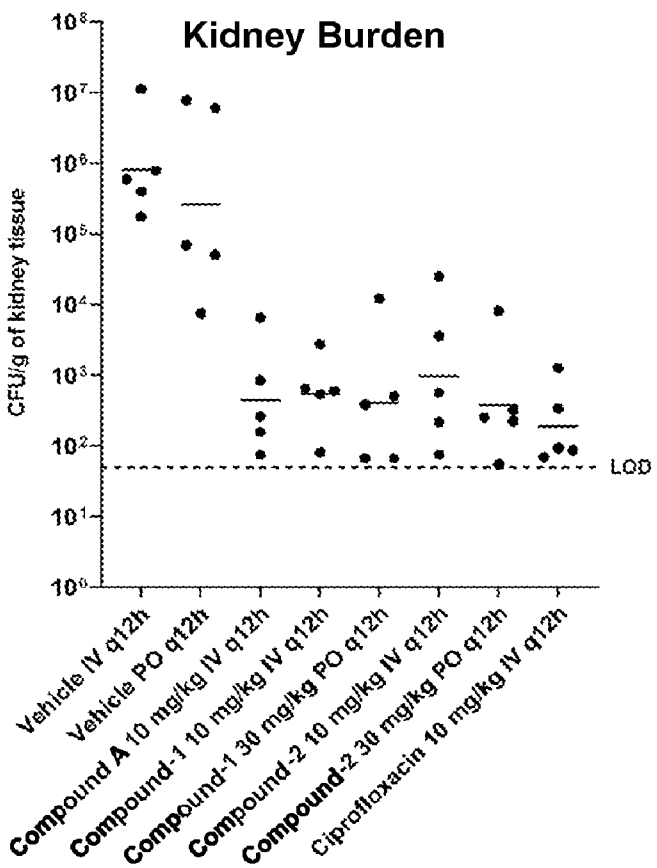


Figure 1


Bladder Burden
CFU/g of bladder tissue
LOD
Vehicle IV q12h
Vehicle PO q12h
Compound A 10 mg/kg IV q12h
Compound-1 10 mg/kg IV q12h
Compound-1 30 mg/kg PO q12h
Compound-2 10 mg/kg IV q12h
Compound-2 30 mg/kg PO q12h
Ciprofloxacin 10 mg/kg IV q12h


Urine Burden
CFU/mL of urine
LOD
Vehicle IV q12h
Vehicle PO q12h
Compound A 10 mg/kg IV q12h
Compound-1 10 mg/kg IV q12h
Compound-1 30 mg/kg PO q12h
Compound-2 10 mg/kg IV q12h
Compound-2 30 mg/kg PO q12h
Ciprofloxacin 10 mg/kg IV q12h


Kidney Burden
CFU/g of kidney tissue
LOD
Vehicle IV q12h
Vehicle PO q12h
Compound A 10 mg/kg IV q12h
Compound-1 10 mg/kg IV q12h
Compound-1 30 mg/kg PO q12h
Compound-2 10 mg/kg IV q12h
Compound-2 30 mg/kg PO q12h
Ciprofloxacin 10 mg/kg IV q12h