LPXC INHIBITORS AND USES THEREOF

CROSS-REFERENCE

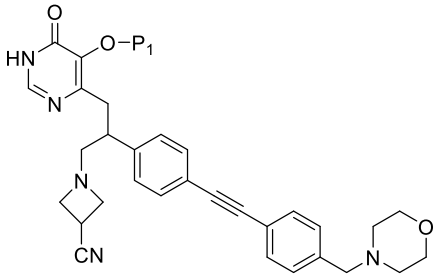
[0001] This application claims benefit of U.S. Provisional Patent Application No. 63/249,166, filed on September 28, 2021, which is incoporated herein by reference in its entirety.

BACKGROUND

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

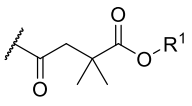
BRIEF SUMMARY

[0002a] In an aspect of the present disclosure, there is provided a compound having the structure of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt or 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;

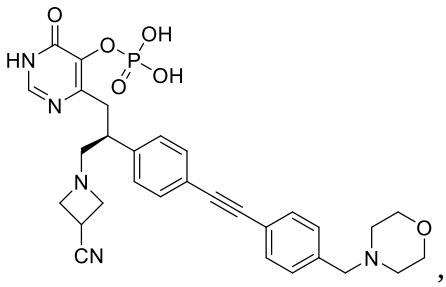
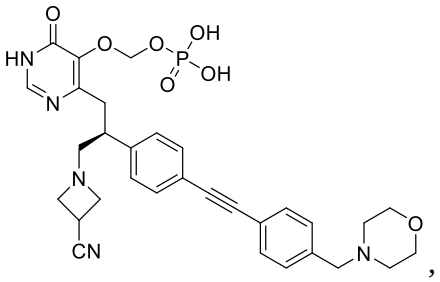
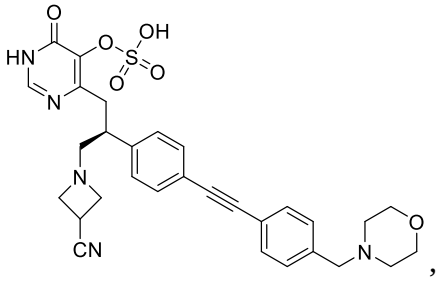
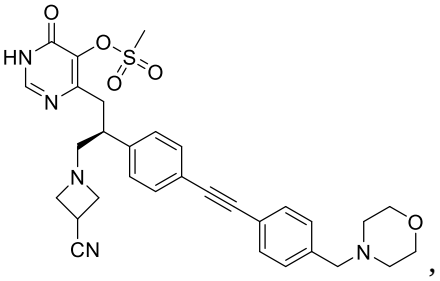
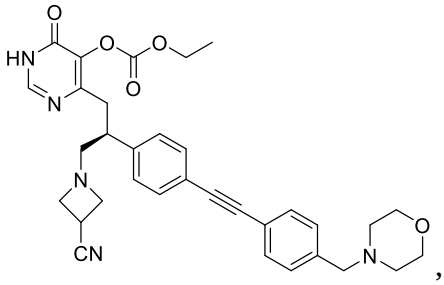
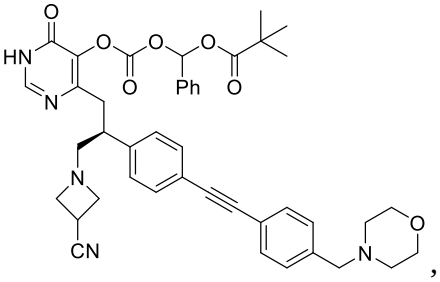
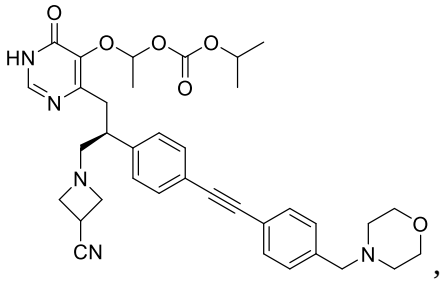
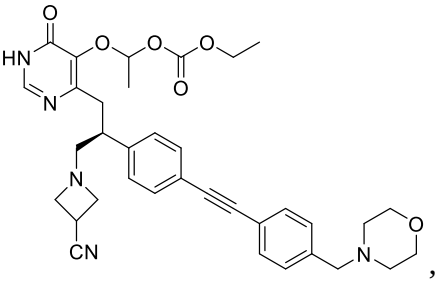
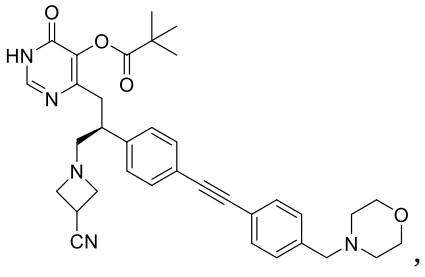
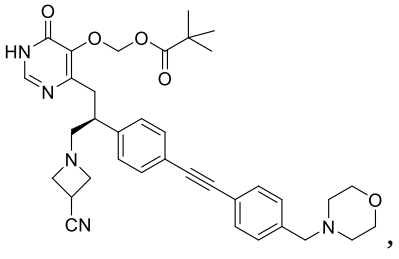
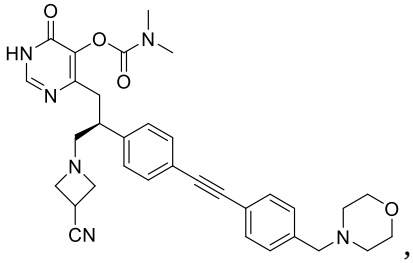
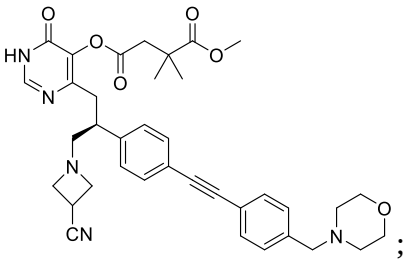
R^2 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl;

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;

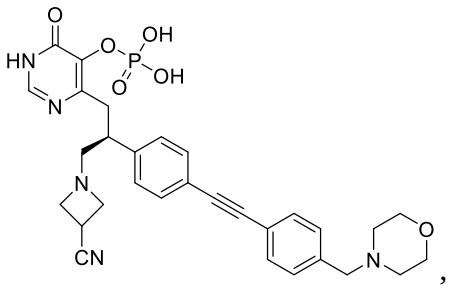
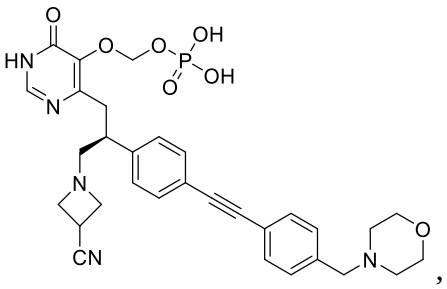
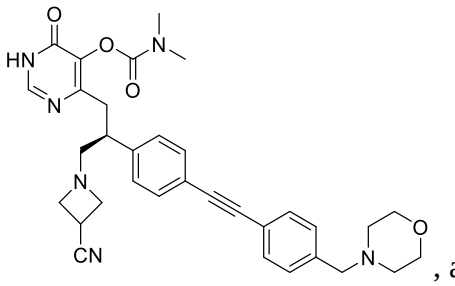
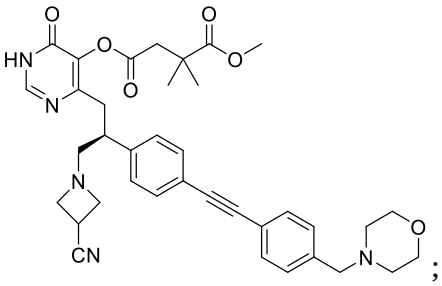
or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4- to 6-membered heterocycloalkyl which is unsubstituted or is substituted with 1 or 2 substituents selected from the group consisting of C_1-C_4 alkyl and 4- to 6-membered heterocycloalkyl.

[0002b] In another aspect of the present disclosure, there is provided a compound selected from:


,

,

,

,

,

,

,

,

,

,

, and

;

or a pharmaceutically acceptable salt or solvate thereof.

[0002c] In a further aspect of the present disclosure, there is provided a compound selected from:


,

,

, and

;

or a pharmaceutically acceptable salt or solvate thereof.

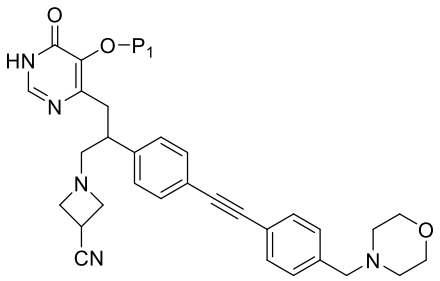
[0002d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0002e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a gram-negative bacterial infection.

[0002f] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

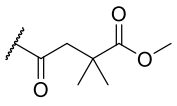
[0003] Provided herein are LpxC inhibitor compounds, as well as pharmaceutical compositions comprising said compound, and methods of use thereof in the treatment of disease that would benefit from treatment with an LpxC inhibitor, including gram-negative bacterial infections such as urinary tract infections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

[0004] In one example, 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;

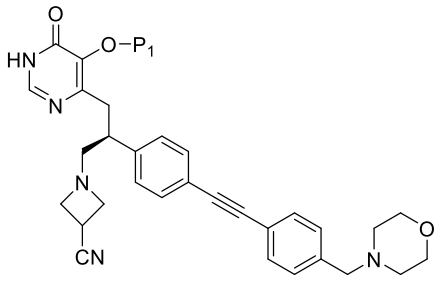
R^2 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

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.

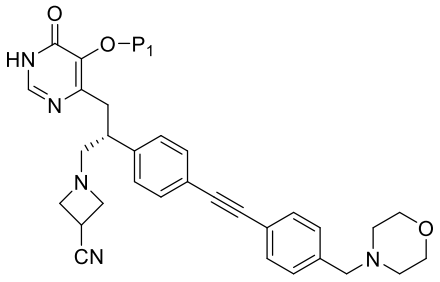
[0005] In some examples, the compound has the structure of Formula (Ia):



Formula (Ia),

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

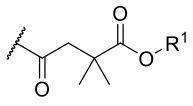
[0006] In some examples, the compound has the structure of Formula (Ib):



Formula (Ib),

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

[0007] In some examples,

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 examples,

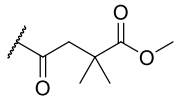
each R^1 is independently hydrogen, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$;

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 examples, 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 example, 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 examples, the pharmaceutical compositions are formulated for administration to a mammal by intravenous administration or oral administration. In some examples, 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 example, 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 examples, the gram-negative bacterial infection is selected from pneumonia, sepsis, cystic fibrosis, intra-abdominal infection, skin infection and urinary tract infection. In some examples, 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 examples, the gram-negative bacterial infection is chronic urinary tract infections. In some examples, the gram-negative bacterial infection is complicated urinary tract infections. In some examples, the compound has no effect on gram-positive bacteria.

[0012] In some examples, 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 examples, the compound disclosed herein, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof, is administered to the patient orally.

[0013] In some examples, the administration is to treat an existing infection. In other examples, 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 examples, 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.

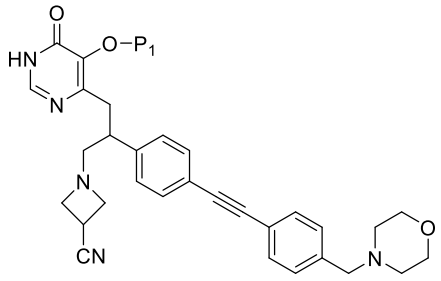
Compound A

[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.

CLAIMS

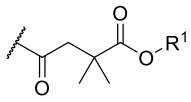
WHAT IS CLAIMED IS:

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



Formula (I),

or a pharmaceutically acceptable salt or 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;

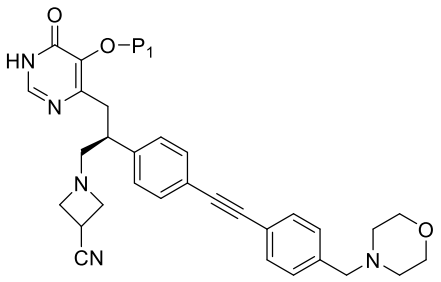
R^2 is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or phenyl;

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.

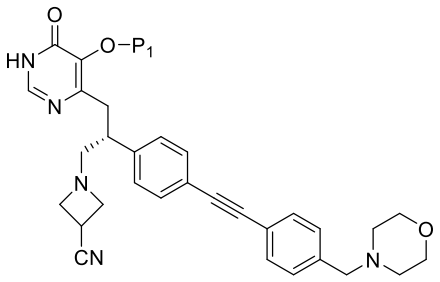
2. The compound of claim 1, having the structure of Formula (Ia):



Formula (Ia),

or a pharmaceutically acceptable salt or solvate thereof.

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


Formula (Ib),

or a pharmaceutically acceptable salt or solvate thereof.

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

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

   R^2 is C_1-C_4 alkyl;

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

   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.

5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or 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.

6. The compound of claim 5, or a pharmaceutically acceptable salt or 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 $-CH(CH_3)_2$.

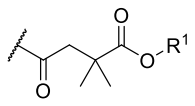
7. The compound of claim 5, or a pharmaceutically acceptable salt or solvate thereof, wherein:

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

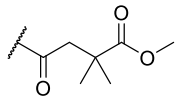
8. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein:

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

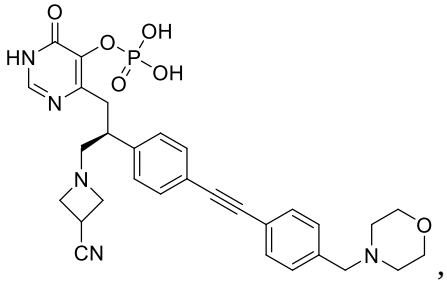
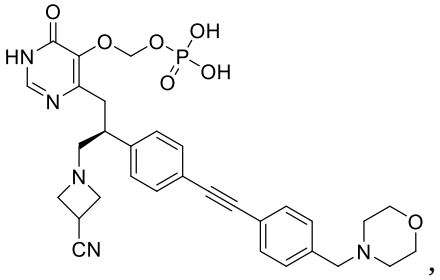
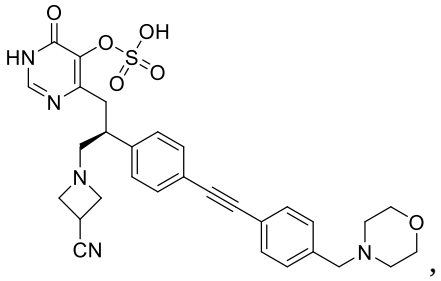
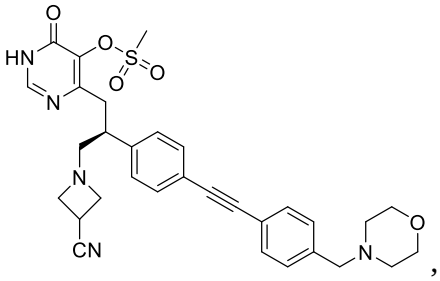
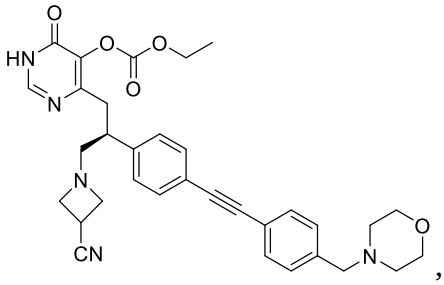
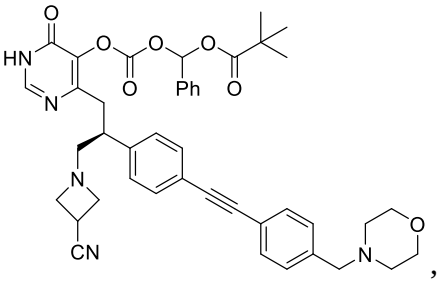
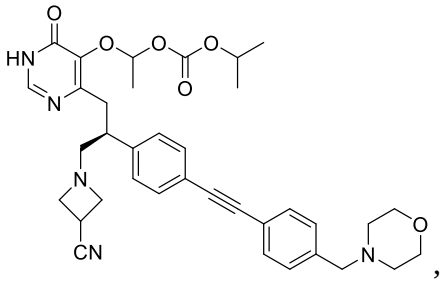
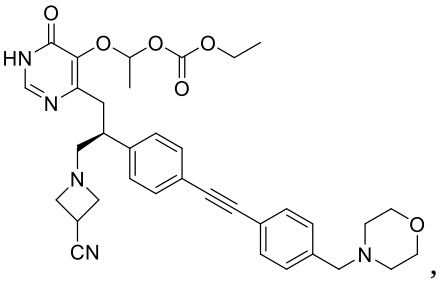
9. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein:

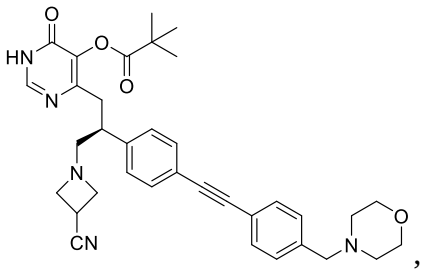
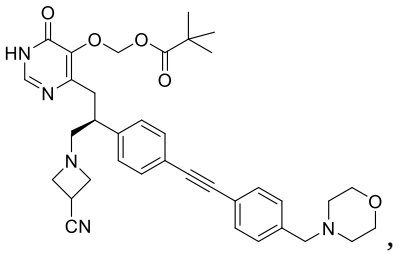
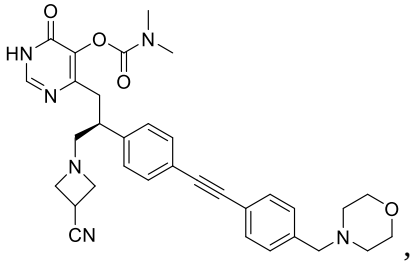
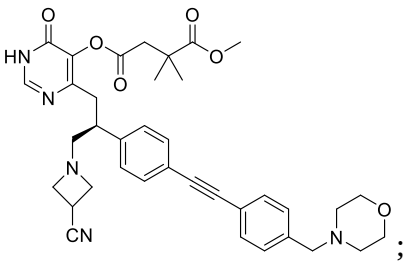
   P_1 is .

10. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or 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 .

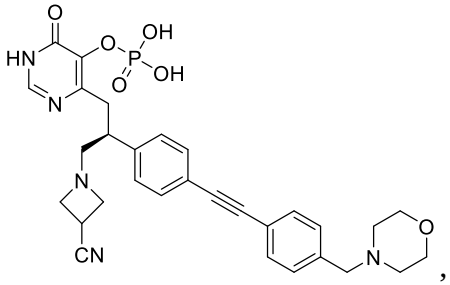
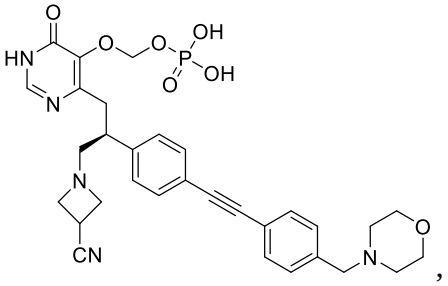
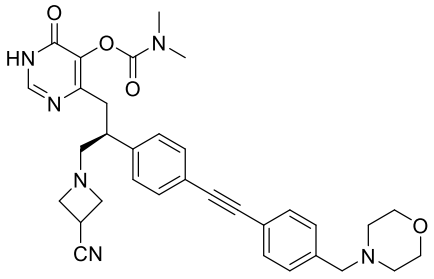
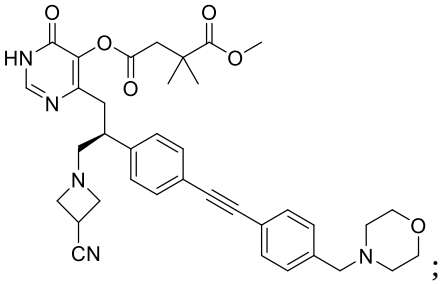
11. A compound selected from:

,
,
,
,
,
,
,
,


,

,

, and

;

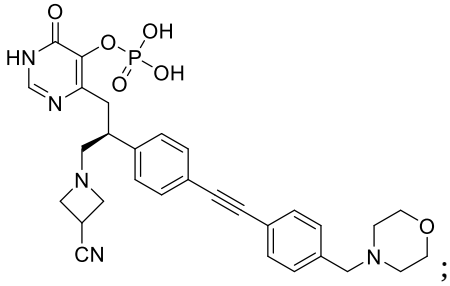
or a pharmaceutically acceptable salt or solvate thereof.

12. A compound selected from:


,

,

, and

;

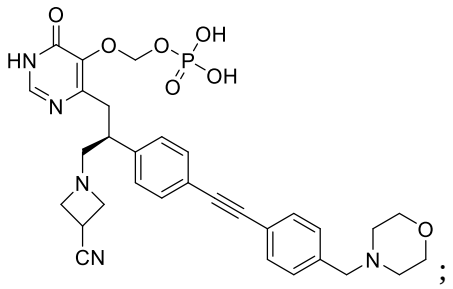
or a pharmaceutically acceptable salt or solvate thereof.

13. The compound of claim 1, wherein the compound is:


;

or a pharmaceutically acceptable salt or solvate thereof.

14. The compound of claim 1, wherein the compound is:



;

or a pharmaceutically acceptable salt or solvate thereof.

15. A pharmaceutical composition comprising the compound of any one of claims 1-14, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.
16. Use of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a gram-negative bacterial infection.
17. The use of claim 16, wherein the gram-negative bacterial infection is selected from pneumonia, sepsis, cystic fibrosis, intra-abdominal infection, skin infection and urinary tract infection.
18. The use of claim 16, 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.
19. The use of any one of claims 16-18, wherein the gram-negative bacterial infection is chronic urinary tract infection.
20. The use of any one of claims 16-18, wherein the gram-negative bacterial infection is complicated urinary tract infection.
21. A compound of any one of claims 1-14, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.