LPXC INHIBITORS AND USES THEREOF

CROSS-REFERENCE

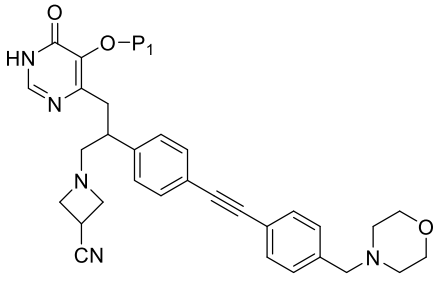
[0001] This application claims benefit of U.S. Provisional Patent Application No. 63/249,166, filed on September 28, 2021, which is incoporated herein by reference in its entirety.

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 $-P(=O)(OR^1)_2$, $-CH_2-O-P(=O)(OR^1)_2$;

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

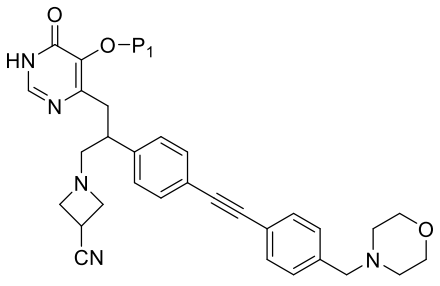
[0002b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0002c] 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.

[0002d] 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.

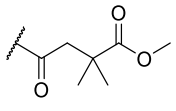
[0004] In one example, provided herein is a compound having the structure of Formula (I):



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;

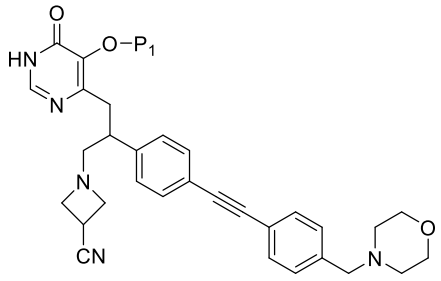
R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

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;

CLAIMS

WHAT IS CLAIMED IS:

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



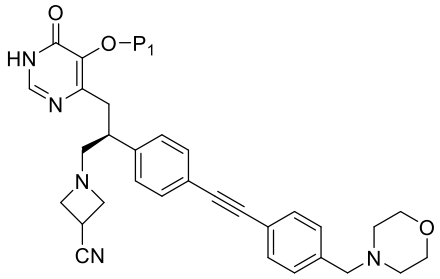
Formula (I),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

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

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

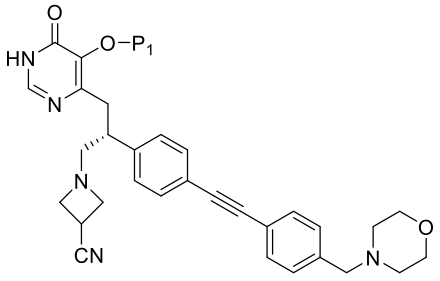
2. The compound of claim 1, having the structure of Formula (Ia):



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, $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$.

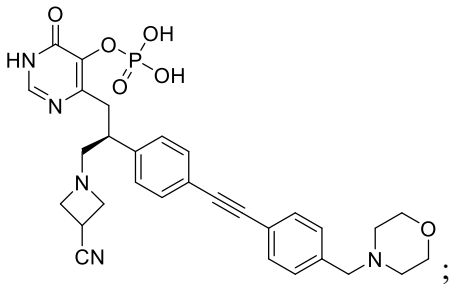
5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein:

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

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

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

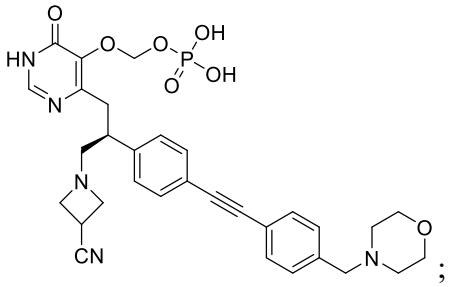
7. The compound of claim 1, wherein the compound is:



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or a pharmaceutically acceptable salt or solvate thereof.

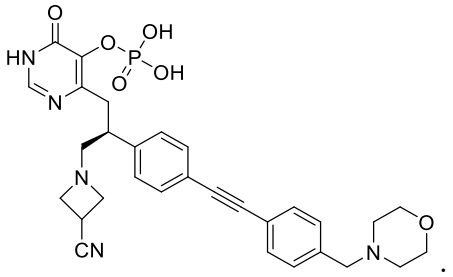
8. The compound of claim 1, wherein the compound is:



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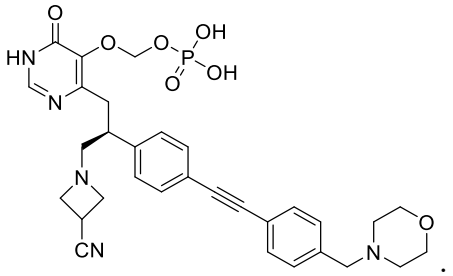
or a pharmaceutically acceptable salt or solvate thereof.

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



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



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11. A pharmaceutical composition comprising the compound of any one of claims 1-10, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

12. Use of a compound of any one of claims 1-10, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a gram-negative bacterial infection.

13. The use of claim 12, wherein the gram-negative bacterial infection is selected from pneumonia, sepsis, cystic fibrosis, intra-abdominal infection, skin infection and urinary tract infection.
14. The use of claim 12, wherein the gram-negative bacterial infection is selected from chronic urinary tract infection, complicated urinary tract infection, cystitis, pyelonephritis, urethritis, recurrent urinary tract infection, bladder infection, urethral infection and kidney infection.
15. The use of any one of claims 12-14, wherein the gram-negative bacterial infection is chronic urinary tract infection.
16. The use of any one of claims 12-14, wherein the gram-negative bacterial infection is complicated urinary tract infection.
17. A compound of any one of claims 1-10, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.