SOLID FORMS OF AN ORALLY-DELIVERED BETA-LACTAMASE INHIBITOR AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 62/828,349 filed April 2, 2019, which is hereby incorporated by reference in its entirety.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under Grant number R43AI109879 awarded by the National Institutes of Health (NIH), Grant number R44AI109879 awarded by the National Institutes of Health (NIH), Grant number R01AI111539 awarded by the National Institutes of Health (NIH), and Contract number HHSN272201600029C awarded by the National Institutes of Health (NIH). The government has certain rights in the invention.

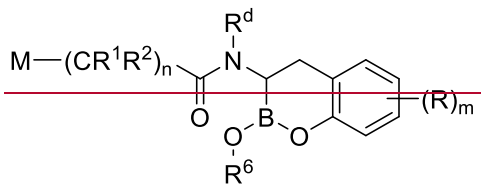
BACKGROUND OF THE INVENTION

[0003] Antibiotics are the most effective drugs for treating bacteria-infectious diseases. They are largely used in the clinic because of their good antibacterial effect with limited side effects. Among them, the beta-lactam class of antibiotics (for example, penicillins, cephalosporins, monobactams and carbapenems) are preferred because their effect is bactericidal, and their target is absent in eukaryotic cells with consequent low toxicity.

[0004] To counter the efficacy of the various beta-lactams, bacteria have evolved to produce variants of beta-lactam deactivating enzymes called beta-lactamases, and in the ability to share this tool both vertically and horizontally inter- and intra-species. These beta-lactamases are categorized as “serine” or “metallo” based, respectively, based on the presence of a key serine or zinc in the enzyme active site. The rapid induction, selection and spread of this mechanism of bacterial resistance can severely limit the whole class of beta-lactam treatment options in the hospital and in the community. There is a need for effective and safe therapeutic agents that can treat such resistant infections.

SUMMARY

~~**[0004a]** In an aspect of the present disclosure, there is provided a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:~~



~~Formula (I);~~

~~wherein:~~

M is hydrogen, halogen, $-CD_3$, $-CF_3$, $-CN$, $-OR^4$, $-C(=O)R^4$, $-C(=O)NR^4R^5$, $-SR^4$, $-S(=O)R^4$, $-S(=O)_2R^4$, $-S(=O)_2NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)NR^4R^5$, $-NR^4S(=O)_2R^5$, or alkynyl;

each R^1 and R^2 is independently hydrogen, deuterium, halogen, $-OR^4$, $-SR^4$, $-NR^4R^5$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, or optionally substituted C_1-C_6 aminoalkyl;

or R^1 and R^2 are taken together with the carbon to which they are attached to form an optionally substituted cycloalkyl;

or when n is at least 2, two R^1 on adjacent carbons are taken together to form a double bond;

or when n is at least 2, two R^1 and two R^2 on adjacent carbons are taken together to form a triple bond;

n is 0, 1, 2, 3, 4, 5, or 6;

each R is independently $-COOR^3$, R^a, R^b, or R^e;

m is 0, 1, 2, 3, or 4;

R^3 is R^{31}, $-(R^{30})_qOR^{31}$, $-(R^{30})_qO(R^{30})_qOR^{31}$, $-R^{30}OC(O)R^{31}$, $-R^{30}OC(O)OR^{31}$, $-R^{30}OC(O)NHR^{31}$, or $-R^{30}OC(O)N(R^{31})_2$;

each q is independently 2, 3, 4, 5, or 6;

each R^{30} is independently $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, or optionally substituted 1,1-cyclopropylene;

each R^{31} is independently optionally substituted C_1-C_{12} alkyl, optionally substituted C_1-C_{12} haloalkyl, optionally substituted C_1-C_{12} hydroxyalkyl, optionally substituted C_1-C_{12} aminoalkyl, optionally substituted C_1-C_{12} alkoxyalkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted (C_1-C_6 alkyl)cycloalkyl, optionally substituted (C_1-C_6 alkyl)heterocycloalkyl, optionally substituted (C_1-C_6 alkyl)aryl, or optionally substituted (C_1-C_6 alkyl)heteroaryl; or

two R^{31} are taken together with the nitrogen to which they are attached to form a heterocycloalkyl;

R^a, R^b, and R^e are independently hydrogen, deuterium, halogen, $-OR^4$, $-NR^4R^5$, $-SR^4$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

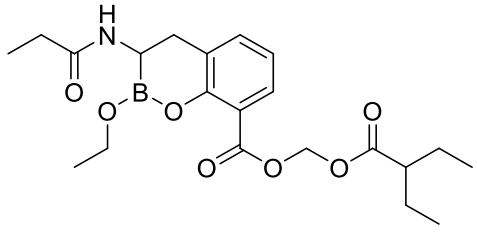
R^d is hydrogen or optionally substituted C_1-C_6 alkyl;

R^4 and R^5 are independently hydrogen, $-OH$, $-CN$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

or R^4 and R^5 taken together with the nitrogen to which they are attached to form an optionally substituted heterocycloalkyl; and

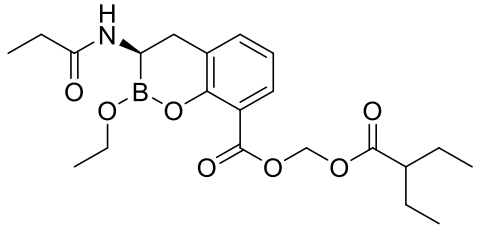
~~R^6 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 deuteroalkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted (C_1-C_6 alkyl)cycloalkyl, optionally substituted (C_1-C_6 alkyl)heterocycloalkyl, optionally substituted (C_1-C_6 alkyl)aryl, or optionally substituted (C_1-C_6 alkyl)heteroaryl.~~

[0004a] In an aspect of the present disclosure, there is provided a compound that is:



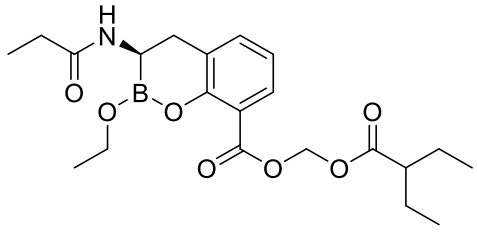
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[0004b] In another aspect of the present disclosure, there is provided a compound that is:



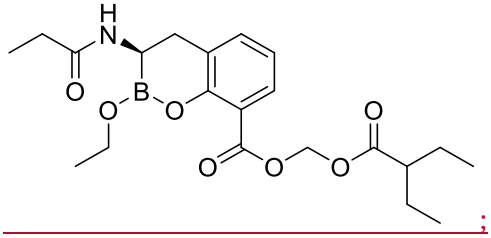
or a pharmaceutically acceptable salt or solvate thereof.

[0004c] In a further aspect of the present disclosure, there is provided a compound that is:



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[~~0004b~~0004d] In another aspect of the present disclosure, there is provided a crystalline form of the compound disclosed herein,



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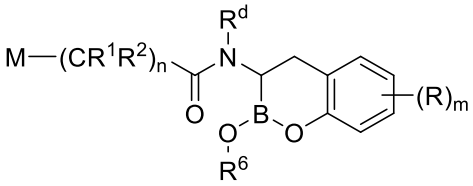
wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern comprising characteristic peaks at 6.1 °±0.1° 2θ, 9.9 °±0.1° 2θ, and 16.0 °±0.1° 2θ.

[0004c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

[0004d] In another aspect of the present disclosure, there is provided a compound disclosed herein, for use in treating a bacterial infection in a subject, wherein the compound is to be administered in combination with a therapeutically effective amount of a beta-lactam antibiotic.

[0004e] In a further aspect of the present disclosure, there is provided a use of compound disclosed herein, in the manufacture of a medicament for treating a bacterial infection in a subject, wherein the compound is to be administered in combination with a therapeutically effective amount of a beta-lactam antibiotic.

[0005] Disclosed herein is a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



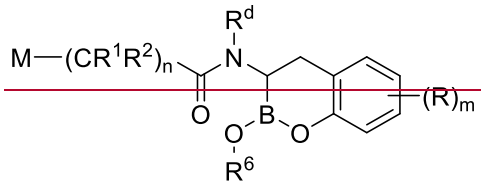
Formula (I)

wherein:

CLAIMS

WHAT IS CLAIMED:

1. A compound of Formula (I) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I);

wherein:

M is hydrogen, halogen, CD_3, CF_3, CN, OR^4, $C(=O)R^4$, $C(=O)NR^4R^5$, SR^4, $S(=O)R^4$, $S(=O)_2R^4$, $S(=O)_2NR^4R^5$, NR^4R^5, $NR^4C(=O)R^5$, $NR^4C(=O)NR^4R^5$, $NR^4S(=O)_2R^5$, or alkynyl;

each R^1 and R^2 is independently hydrogen, deuterium, halogen, OR^4, SR^4, NR^4R^5, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, or optionally substituted C_1-C_6 aminoalkyl;

or R^1 and R^2 are taken together with the carbon to which they are attached to form an optionally substituted cycloalkyl;

or when n is at least 2, two R^1 on adjacent carbons are taken together to form a double bond;

or when n is at least 2, two R^1 and two R^2 on adjacent carbons are taken together to form a triple bond;

n is 0, 1, 2, 3, 4, 5, or 6;

each R is independently $COOR^3$, R^a, R^b, or R^c;

m is 0, 1, 2, 3, or 4;

R^3 is R^{31}, $(R^{30})_qOR^{31}$, $(R^{30})_qO(R^{30})_qOR^{31}$, $R^{30}OC(O)R^{31}$, $R^{30}OC(O)OR^{31}$, $R^{30}OC(O)NHR^{31}$, or $R^{30}OC(O)N(R^{31})_2$;

each q is independently 2, 3, 4, 5, or 6;

each R^{30} is independently CH_2, $CH(CH_3)$, $C(CH_3)_2$, or optionally substituted 1,1-cyclopropylene;

each R^{31} is independently optionally substituted C_1-C_{12} alkyl, optionally substituted C_1-C_{12} haloalkyl, optionally substituted C_1-C_{12} hydroxyalkyl, optionally substituted C_1-C_{12} aminoalkyl, optionally substituted C_1-C_{12} alkoxyalkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted (C_1-C_6 alkyl)cycloalkyl, optionally substituted (C_1-C_6 alkyl)heterocycloalkyl, optionally substituted (C_1-C_6 alkyl)aryl, or optionally substituted (C_1-C_6 alkyl)heteroaryl; or

two R^{31} are taken together with the nitrogen to which they are attached to form a heterocycloalkyl;

R^a, R^b, and R^c are independently hydrogen, deuterium, halogen, $-OR^4$, $-NR^4R^5$, $-SR^4$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

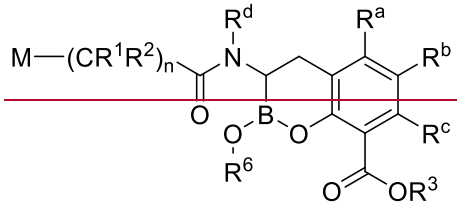
R^d is hydrogen or optionally substituted C_1-C_6 alkyl;

R^4 and R^5 are independently hydrogen, $-OH$, $-CN$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

or R^4 and R^5 taken together with the nitrogen to which they are attached to form an optionally substituted heterocycloalkyl; and

R^6 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 haloalkyl, optionally substituted C_1-C_6 hydroxyalkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 deuteroalkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted (C_1-C_6 alkyl)cycloalkyl, optionally substituted (C_1-C_6 alkyl)heterocycloalkyl, optionally substituted (C_1-C_6 alkyl)aryl, or optionally substituted (C_1-C_6 alkyl)heteroaryl.

2. The compound of claim 1, wherein the compound is of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (Ia).

3. The compound of claim 1 or 2, wherein R^a, R^b, and R^c are independently hydrogen, halogen, $-OR^4$, $-NR^4R^5$, $-SR^4$, or optionally substituted C_1-C_6 alkyl.

4. The compound of any one of claims 1-3, wherein R^a, R^b, and R^c are independently hydrogen, halogen, $-OH$, or $-OCH_3$.

5. The compound of any one of claims 1-4, wherein R^a, R^b, and R^c are hydrogen.

6. The compound of any one of claims 1-5, wherein R^d is hydrogen or C_1-C_4 alkyl.

7. The compound of any one of claims 1-6, wherein R^d is hydrogen.

8. The compound of any one of claims 1-7, wherein n is 0, 1, 2, or 3.

9. The compound of any one of claims 1-8, wherein n is 2.

10. The compound of any one of claims 1-8, wherein n is 1.

11. The compound of any one of claims 1-10, wherein each R^1 and R^2 are independently hydrogen, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 haloalkyl.

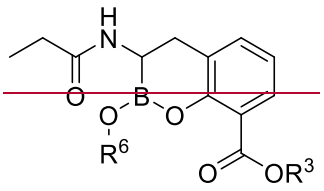
12. The compound of any one of claims 1-11, wherein each R^1 and R^2 are independently hydrogen or halogen.

13. The compound of any one of claims 1-12, wherein each R^1 and R^2 are hydrogen.

14. The compound of any one of claims 1-13, wherein M is hydrogen, -CN, $-C(=O)R^4$, or alkynyl.

15. The compound of any one of claims 1-14, wherein M is hydrogen.

16. The compound of any one of claims 1-15, wherein the compound is of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (Ib).

17. The compound of any one of claims 1-16, wherein R^3 is R^{31}.

18. The compound of any one of claims 1-16, wherein R^3 is $-R^{30}OC(O)R^{31}$ or $-R^{30}OC(O)OR^{31}$.

19. The compound of any one of claims 1-16, wherein R^3 is $-R^{30}OC(O)R^{31}$.

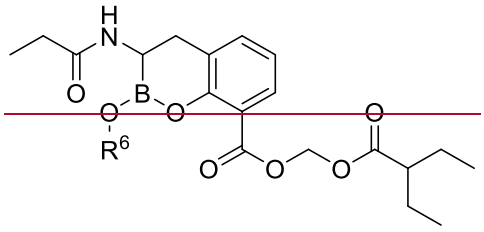
20. The compound of any one of claims 1-19, wherein R^{30} is independently $-CH_2-$ or $-CH(CH_3)-$.

21. The compound of any one of claims 1-20, wherein R^{30} is independently $-CH_2-$.

22. The compound of any one of claims 1-21, wherein each R^{31} is independently optionally substituted C_1-C_{12} alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted aryl.

23. The compound of any one of claims 1-21, wherein each R^{31} is independently optionally substituted C_1-C_{12} alkyl.

24. The compound of any one of claims 1-23, wherein the compound is of Formula (Ic), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:

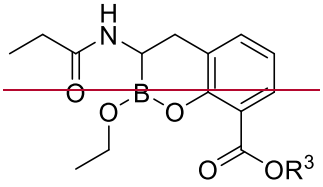


~~Formula (Ic).~~

~~25. The compound of any one of claims 1-24, wherein R^6 is C_1-C_6 alkyl.~~

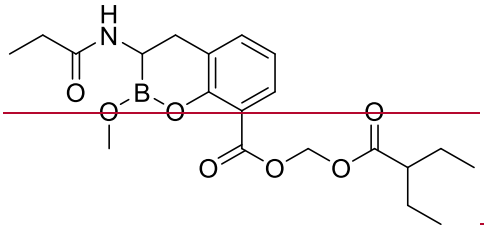
~~26. The compound of any one of claims 1-25, wherein R^6 is methyl, ethyl, propyl, or butyl.~~

~~27. The compound of any one of claims 1-16, wherein the compound is of Formula (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:~~



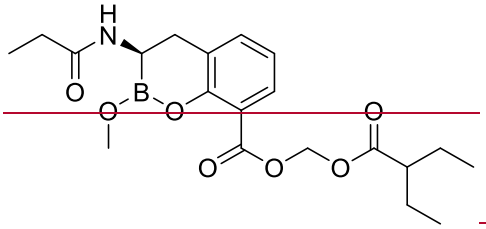
~~Formula (Id).~~

~~28. The compound of claim 1, wherein the compound is:~~



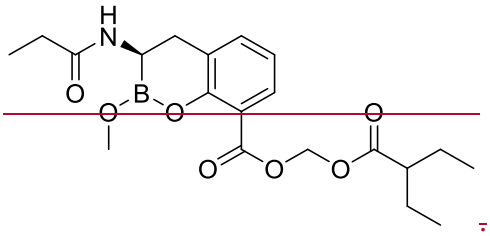
~~or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.~~

~~29. The compound of claim 1, wherein the compound is:~~

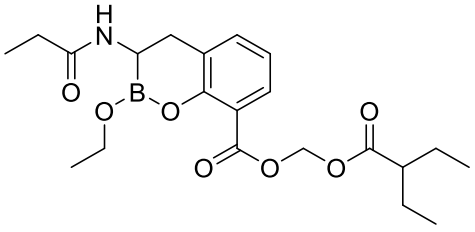


~~or a pharmaceutically acceptable salt or solvate thereof.~~

~~30. The compound of claim 1, wherein the compound is:~~

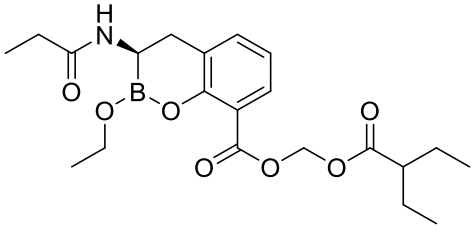


~~31.~~1. ~~The compound of claim 1, wherein the~~A compound that is:



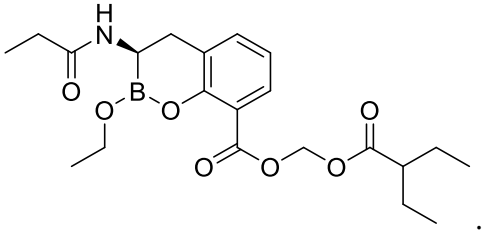
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

~~32.~~2. ~~The compound of claim 1, wherein the~~A compound that is:



or a pharmaceutically acceptable salt or solvate thereof.

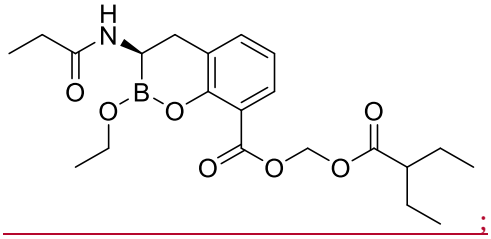
~~33.~~3. ~~The compound of claim 1, wherein the~~A compound that is:



~~34. A crystalline form of the compound of claim 33.~~

~~35. The crystalline form of claim 34, wherein the crystalline form has an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in FIG. 4.~~

~~36.~~4. ~~The~~ A crystalline form of the compound of claim 3~~4~~,



wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern comprising characteristic peaks at ~~about~~ 6.1 °±0.1° 2θ, ~~about~~ 9.9 °±0.1° 2θ, and ~~about~~ about 16.0 °±0.1° 2θ.

~~37.~~5. The crystalline form of claim ~~4~~36, wherein the X-ray powder diffraction (XRPD) pattern further comprises characteristic peaks at ~~about~~ 19.3 °±0.1° 2θ, ~~about~~ 6.8 °±0.1° 2θ, and ~~about~~ 17.9 °±0.1° 2θ.

~~38.~~6. The crystalline form of claim ~~4~~36 or ~~5~~37, wherein the X-ray powder diffraction (XRPD) pattern further comprises characteristic peaks at ~~about~~ 14.3 °±0.1° 2θ and ~~about~~ 21.2 °±0.1° 2θ.

~~39. The crystalline form of claim 34, wherein the crystalline form has a DSC thermogram substantially the same as shown in FIG. 6.~~

~~40.~~7. The crystalline form of claim ~~3~~44, wherein the crystalline form has a DSC thermogram with a broad endotherm having an onset at ~~about~~ 112.8 °C.

~~41. The crystalline form of claim 34, wherein the crystalline form has a ^{1}H spectrum substantially the same as shown in FIG. 1A.~~

~~42. The crystalline form of claim 34, wherein the crystalline form has a ^{13}C spectrum substantially the same as shown in FIG. 1B.~~

~~43. The crystalline form of claim 34, wherein the crystalline form has an FT-IR spectrum substantially the same as shown in FIG. 2.~~

~~44. The crystalline form of claim 34, wherein the crystalline form has a Raman spectrum substantially the same as shown in FIG. 3.~~

~~45. The crystalline form of claim 34, wherein the crystalline form has an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in FIG. 10.~~

~~46. The crystalline form of claim 34, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern comprising characteristic peaks at about 9.3 °±0.1° 2θ, about 12.9 °±0.1° 2θ, and about 21.5 °±0.1° 2θ.~~

~~47. The crystalline form of claim 46, wherein the X-ray powder diffraction (XRPD) pattern further comprises characteristic peaks at about 8.8 °±0.1° 2θ, about 14.6 °±0.1° 2θ, and about 17.3 °±0.1° 2θ.~~

~~48. The crystalline form of claim 34, wherein the crystalline form has a DSC thermogram substantially the same as shown in FIG. 11.~~

~~49. The crystalline form of claim 34, wherein the crystalline form has a DSC thermogram with a broad endotherm having an onset at about 116.9 °C.~~

~~50. The crystalline form of claim 34, wherein the crystalline form has an FT-Raman spectrum substantially the same as shown in FIG. 9A.~~

~~51.~~8. A pharmaceutical composition comprising a compound of any one of claims 1-7~~50~~, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

~~52.~~9. The pharmaceutical composition of claim 8~~51~~, further comprising a beta-lactam antibiotic.

~~53.~~10. The pharmaceutical composition of claim 9~~52~~, wherein the beta-lactam antibiotic is a penicillin, a cephalosporin, a carbapenem, a monobactam, or a combination thereof.

~~54.~~11. A compound of any one of claims 1-7~~50~~, for use in treating a bacterial infection in a subject, wherein the compound is to be administered in combination with a therapeutically effective amount of a beta-lactam antibiotic.

~~55.~~12. Use of compound of any one of claims 1-7~~50~~, in the manufacture of a medicament for treating a bacterial infection in a subject, wherein the compound is to be administered in combination with a therapeutically effective amount of a beta-lactam antibiotic.

~~56.~~13. The compound for use of claim 11~~54~~, or the use of claim 12~~55~~, wherein the beta-lactam antibiotic is ceftibuten, or a salt thereof.