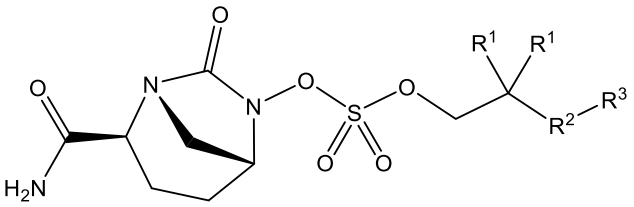
CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:

a β-lactam antibiotic or a pharmaceutically acceptable salt thereof; and

an avibactam derivative of Formula (1):



(1)

or a pharmaceutically acceptable salt thereof, wherein,

each R^1 is independently selected from C_{1-6} alkyl, or each R^1 and the geminal carbon atom to which they are bonded forms a C_{3-6} cycloalkyl ring, a C_{3-6} heterocycloalkyl ring, a substituted C_{3-6} cycloalkyl ring, or a substituted C_{3-6} heterocycloalkyl ring;

R^2 is selected from a single bond, C_{1-6} alkanediyl, C_{1-6} heteroalkanediyl, C_{5-6} cycloalkanediyl, C_{5-6} heterocycloalkanediyl, C_6 arenediyl, C_{5-6} heteroarenediyl, substituted C_{1-6} alkanediyl, substituted C_{1-6} heteroalkanediyl, substituted C_{5-6} cycloalkanediyl, substituted C_{5-6} heterocycloalkanediyl, substituted C_6 arenediyl, and substituted C_{5-6} heteroarenediyl;

R^3 is selected from C_{1-6} alkyl, –O–C(O)–R^4, –S–C(O)–R^4, –NH–C(O)–R^4, –O–C(O)–O–R^4, –S–C(O)–O–R^4, –NH–C(O)–O–R^4, –C(O)–O–R^4, –C(O)–S–R^4, –C(O)–NH–R^4, –O–C(O)–O–R^4, –O–C(O)–S–R^4, –O–C(O)–NH–R^4, –S–S–R^4, –S–R^4, –NH–R^4, –CH(–NH_2)(–R^4), C_{5-6} heterocycloalkyl, C_{5-6} heteroaryl, substituted C_{5-6} cycloalkyl, substituted C_{5-6} heterocycloalkyl, substituted C_{5-6} aryl, substituted C_{5-6} heteroaryl, and –CH=C(R^4)$_2$, wherein,

R^4 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} heteroalkyl, C_{5-8} cycloalkyl, C_{5-8} heterocycloalkyl, C_{5-10} cycloalkylalkyl, C_{5-10} heterocycloalkylalkyl, C_{6-8} aryl, C_{5-8} heteroaryl, C_{7-10} arylalkyl, C_{5-10} heteroarylalkyl, substituted C_{1-8} alkyl, substituted C_{1-8} heteroalkyl, substituted C_{5-8} cycloalkyl, substituted C_{5-8} heterocycloalkyl, substituted C_{5-10} cycloalkylalkyl, substituted C_{5-10} heterocycloalkylalkyl, substituted C_{6-8} aryl, substituted C_{5-8} heteroaryl, substituted C_{7-10} arylalkyl, and substituted C_{5-10} heteroarylalkyl;

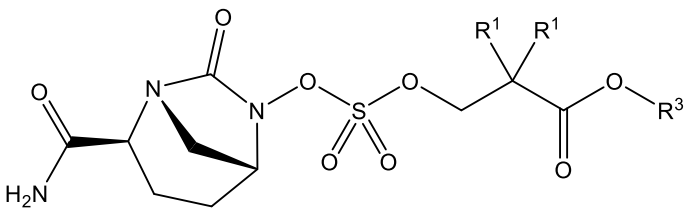
R^5 is selected from hydrogen, C_{1-6} alkyl, C_{5-8} cycloalkyl, C_{6-12} cycloalkylalkyl, C_{2-6} heteroalkyl, C_{5-8} heterocycloalkyl, C_{6-12} heterocycloalkylalkyl, substituted C_{1-6} alkyl, substituted C_{5-8} cycloalkyl, substituted C_{6-12} cycloalkylalkyl, substituted C_{2-6} heteroalkyl, substituted C_{5-8} heterocycloalkyl, and substituted C_{6-12} heterocycloalkylalkyl; and

R^6 is selected from hydrogen, C_{1-6} alkyl, C_{5-8} cycloalkyl, C_{6-12} cycloalkylalkyl, C_{2-6} heteroalkyl, C_{5-8} heterocycloalkyl, C_{6-12} heterocycloalkylalkyl, substituted C_{1-6} alkyl, substituted C_{5-8} cycloalkyl, substituted C_{6-12} cycloalkylalkyl, substituted C_{2-6} heteroalkyl, substituted C_{5-8} heterocycloalkyl, and substituted C_{6-12} heterocycloalkylalkyl.

2. The pharmaceutical composition of claim 1, wherein the β-lactam antibiotic comprises an orally bioavailable β-lactam antibiotic or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition of claim 1, wherein the β-lactam antibiotic comprises ceftibuten or a pharmaceutically acceptable salt thereof.

4. The pharmaceutical composition of claim 1, wherein the avibactam derivative has the structure of Formula (1a):



(1a)

or a pharmaceutically acceptable salt thereof, wherein,

each R^1 is independently selected from C_{1-6} alkyl; and

R^3 is C_{1-6} alkyl.

5. The pharmaceutical composition of claim 1, wherein the avibactam derivative is selected from:

methyl 3-(((((1*R*,2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl)oxy)sulfonyl)oxy)-2,2-dimethylpropanoate;

ethyl 3-(((((1*R*,2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl)oxy)sulfonyl)oxy)-2,2-dimethylpropanoate;

propyl 3-(((((1*R*,2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl)oxy)sulfonyl)oxy)-2,2-dimethylpropanoate;

methyl 2-((((((1*R*,2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl)oxy)sulfonyl)oxy)methyl)-2-ethylbutanoate;

ethyl 2-((((((1*R*,2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl)oxy)sulfonyl)oxy)methyl)-2-ethylbutanoate;

propyl 2-((((((1*R*,2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl)oxy)sulfonyl)oxy)methyl)-2-ethylbutanoate;

methyl 2-((((((1*R*,2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl)oxy)sulfonyl)oxy)methyl)-2-propylpentanoate;

ethyl 2-((((((1*R*,2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl)oxy)sulfonyl)oxy)methyl)-2-propylpentanoate;

propyl 2-((((((1*R*,2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl)oxy)sulfonyl)oxy)methyl)-2-propylpentanoate;

a pharmaceutically acceptable salt of any of the foregoing; and

a combination of any of the foregoing.

6. The pharmaceutical composition of claim 1, wherein the avibactam derivative is ethyl 3-(((((1*R*,2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl)oxy)sulfonyl)oxy)-2,2-dimethylpropanoate (3), or a pharmaceutically acceptable salt thereof.

7. The pharmaceutical composition of claim 1, wherein the avibactam derivative is crystalline ethyl 3-(((((1*R*,2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl)oxy)sulfonyl)oxy)-2,2-dimethylpropanoate anhydrate characterized by an X-ray powder diffraction (XRPD) pattern having characteristic scattering angles (2θ) at least at 3.16°±0.2°, 6.37°±0.2°, 5.38°±0.2°, and 17.35°±0.2° at a Kα2/Kα1 (0.5) wavelength.

8. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises a weight ratio of avibactam equivalents to β-lactam antibiotic equivalents from 1:1 to 4:1.

9. The pharmaceutical composition of claim 1, wherein the bacterial infection is caused by Enterobacteriaceae bacteria.

10. The pharmaceutical composition of claim 1, wherein the bacterial infection is caused by bacteria that produce an extended-spectrum β-lactamase enzyme.

11. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises:

from 200 mg to 1,400 mg of the β-lactam antibiotic; and

from 200 mg to 1,400 mg of the avibactam derivative.

12. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises:

from 100 mg to 500 mg of ceftibuten or a pharmaceutically acceptable salt thereof; and

from 300 mg to 1,400 mg of the avibactam derivative or a pharmaceutically acceptable salt thereof.

13. The pharmaceutical composition of claim 1, wherein, following oral administration to a patient the composition provides a β-lactam antibiotic plasma concentration greater than 40% *f*T>MIC for a bacterial strain.

14. The pharmaceutical composition of claim 1, wherein, following oral administration to a patient, the composition provides an avibactam plasma concentration greater than 40% *f*T>C_t.

15. The pharmaceutical composition of claim 1, wherein, following oral administration to a patient, the composition provides an avibactam plasma concentration characterized by a *f*AUC:MIC ratio from 10 to 40.

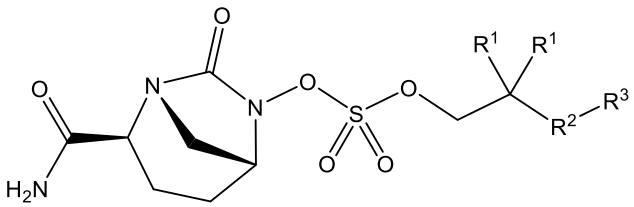
16. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises an oral formulation.

17. An oral formulation comprising the pharmaceutical composition of claim 1.

18. Use of ~~A method of treating a bacterial infection in a patient in need of such treatment comprising orally administering to the patent a therapeutically effective amount of:~~

a β-lactam antibiotic or a pharmaceutically acceptable salt thereof; and

an avibactam derivative of Formula (1):



(1)

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of bacterial infection, wherein,

each R^1 is independently selected from C_{1-6} alkyl, or each R^1 and the geminal carbon atom to which they are bonded forms a C_{3-6} cycloalkyl ring, a C_{3-6} heterocycloalkyl ring, a substituted C_{3-6} cycloalkyl ring, or a substituted C_{3-6} heterocycloalkyl ring;

R^2 is selected from a single bond, C_{1-6} alkanediyl, C_{1-6} heteroalkanediyl, C_{5-6} cycloalkanediyl, C_{5-6} heterocycloalkanediyl, C_6 arenediyl, C_{5-6} heteroarenediyl, substituted C_{1-6} alkanediyl, substituted C_{1-6} heteroalkanediyl, substituted C_{5-6}

cycloalkanediyl, substituted C_{5-6} heterocycloalkanediyl, substituted C_6 arenediyl, and substituted C_{5-6} heteroarenediyl;

R^3 is selected from C_{1-6} alkyl, –O–C(O)–R^4, –S–C(O)–R^4, –NH–C(O)–R^4, –O–C(O)–O–R^4, –S–C(O)–O–R^4, –NH–C(O)–O–R^4, –C(O)–O–R^4, –C(O)–S–R^4, –C(O)–NH–R^4, –O–C(O)–O–R^4, –O–C(O)–S–R^4, –O–C(O)–NH–R^4, –S–S–R^4, –S–R^4, –NH–R^4, –CH(–NH_2)(–R^4), C_{5-6} heterocycloalkyl, C_{5-6} heteroaryl, substituted C_{5-6} cycloalkyl, substituted C_{5-6} heterocycloalkyl, substituted C_{5-6} aryl, substituted C_{5-6} heteroaryl, and –CH=C(R^4)$_2$, wherein,

R^4 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} heteroalkyl, C_{5-8} cycloalkyl, C_{5-8} heterocycloalkyl, C_{5-10} cycloalkylalkyl, C_{5-10} heterocycloalkylalkyl, C_{6-8} aryl, C_{5-8} heteroaryl, C_{7-10} arylalkyl, C_{5-10} heteroarylalkyl, substituted C_{1-8} alkyl, substituted C_{1-8} heteroalkyl, substituted C_{5-8} cycloalkyl, substituted C_{5-8} heterocycloalkyl, substituted C_{5-10} cycloalkylalkyl, substituted C_{5-10} heterocycloalkylalkyl, substituted C_{6-8} aryl, substituted C_{5-8} heteroaryl, substituted C_{7-10} arylalkyl, and substituted C_{5-10} heteroarylalkyl;

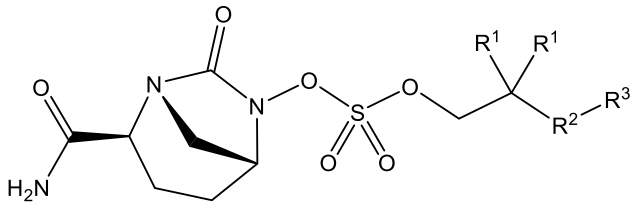
R^5 is selected from hydrogen, C_{1-6} alkyl, C_{5-8} cycloalkyl, C_{6-12} cycloalkylalkyl, C_{2-6} heteroalkyl, C_{5-8} heterocycloalkyl, C_{6-12} heterocycloalkylalkyl, substituted C_{1-6} alkyl, substituted C_{5-8} cycloalkyl, substituted C_{6-12} cycloalkylalkyl, substituted C_{2-6} heteroalkyl, substituted C_{5-8} heterocycloalkyl, and substituted C_{6-12} heterocycloalkylalkyl; and

R^6 is selected from hydrogen, C_{1-6} alkyl, C_{5-8} cycloalkyl, C_{6-12} cycloalkylalkyl, C_{2-6} heteroalkyl, C_{5-8} heterocycloalkyl, C_{6-12} heterocycloalkylalkyl, substituted C_{1-6} alkyl, substituted C_{5-8} cycloalkyl, substituted C_{6-12} cycloalkylalkyl, substituted C_{2-6} heteroalkyl, substituted C_{5-8} heterocycloalkyl, and substituted C_{6-12} heterocycloalkylalkyl.

19. The ~~method~~ use of claim 18, wherein the bacterial infection is caused by bacteria that produce a β-lactamase enzyme.

20. The ~~method~~ use of claim 18, wherein the bacterial infection is caused by an Enterobacteriaceae bacteria.

21. A β-lactam antibiotic or a pharmaceutically acceptable salt thereof; and an avibactam derivative of Formula (1):



(1)

or a pharmaceutically acceptable salt thereof, for use in the treatment of bacterial infection, wherein,

each R^1 is independently selected from C_{1-6} alkyl, or each R^1 and the geminal carbon atom to which they are bonded forms a C_{3-6} cycloalkyl ring, a C_{3-6} heterocycloalkyl ring, a substituted C_{3-6} cycloalkyl ring, or a substituted C_{3-6} heterocycloalkyl ring;

R^2 is selected from a single bond, C_{1-6} alkanediyl, C_{1-6} heteroalkanediyl, C_{5-6} cycloalkanediyl, C_{5-6} heterocycloalkanediyl, C_6 arenediyl, C_{5-6} heteroarenediyl, substituted C_{1-6} alkanediyl, substituted C_{1-6} heteroalkanediyl, substituted C_{5-6} cycloalkanediyl, substituted C_{5-6} heterocycloalkanediyl, substituted C_6 arenediyl, and substituted C_{5-6} heteroarenediyl;

R^3 is selected from C_{1-6} alkyl, $–O–C(O)–R^4$, $–S–C(O)–R^4$, $–NH–C(O)–R^4$, $–O–C(O)–O–R^4$, $–S–C(O)–O–R^4$, $–NH–C(O)–O–R^4$, $–C(O)–O–R^4$, $–C(O)–S–R^4$, $–C(O)–NH–R^4$, $–O–C(O)–O–R^4$, $–O–C(O)–S–R^4$, $–O–C(O)–NH–R^4$, $–S–S–R^4$, $–S–R^4$, $–NH–R^4$, $–CH(–NH_2)(–R^4)$, C_{5-6} heterocycloalkyl, C_{5-6} heteroaryl, substituted C_{5-6} cycloalkyl, substituted C_{5-6} heterocycloalkyl, substituted C_{5-6} aryl, substituted C_{5-6} heteroaryl, and $–CH=C(R^4)_2$, wherein,

R^4 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} heteroalkyl, C_{5-8} cycloalkyl, C_{5-8} heterocycloalkyl, C_{5-10} cycloalkylalkyl, C_{5-10} heterocycloalkylalkyl, C_{6-8} aryl, C_{5-8} heteroaryl, C_{7-10} arylalkyl, C_{5-10} heteroarylalkyl, substituted C_{1-8} alkyl, substituted C_{1-8} heteroalkyl, substituted C_{5-8} cycloalkyl, substituted C_{5-8} heterocycloalkyl, substituted C_{5-10} cycloalkylalkyl, substituted C_{5-10} heterocycloalkylalkyl, substituted C_{6-8} aryl, substituted C_{5-8} heteroaryl, substituted C_{7-10} arylalkyl, and substituted C_{5-10} heteroarylalkyl;

R^5 is selected from hydrogen, C_{1-6} alkyl, C_{5-8} cycloalkyl, C_{6-12} cycloalkylalkyl, C_{2-6} heteroalkyl, C_{5-8} heterocycloalkyl, C_{6-12} heterocycloalkylalkyl, substituted C_{1-6} alkyl, substituted C_{5-8} cycloalkyl, substituted C_{6-12} cycloalkylalkyl, substituted C_{2-6} heteroalkyl, substituted C_{5-8} heterocycloalkyl, and substituted C_{6-12} heterocycloalkylalkyl; and

R^6 is selected from hydrogen, C_{1-6} alkyl, C_{5-8} cycloalkyl, C_{6-12} cycloalkylalkyl, C_{2-6} heteroalkyl, C_{5-8} heterocycloalkyl, C_{6-12} heterocycloalkylalkyl, substituted C_{1-6} alkyl, substituted C_{5-8} cycloalkyl, substituted C_{6-12} cycloalkylalkyl, substituted C_{2-6}

heteroalkyl, substituted C_{5-8} heterocycloalkyl, and substituted C_{6-12} heterocycloalkylalkyl.