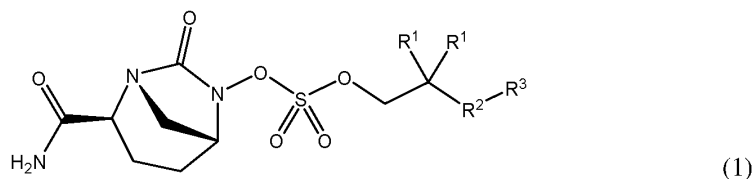


CLAIMS

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):



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;

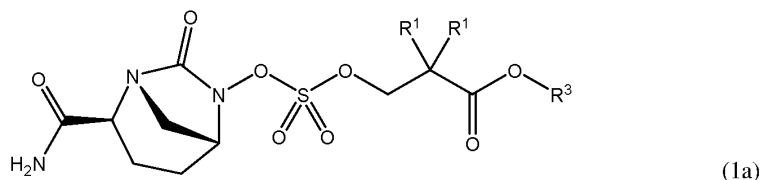
R^3 is selected from C_{1-6} alkyl, $-O-C(O)-R^4$, $-S-C(O)-R^4$, $-NH-C(O)-R^4$, $-O-C(O)-O-R^4$, $-S-C(O)-O-R^4$, $-NH-C(O)-O-R^4$, $-C(O)-O-R^4$, $-C(O)-S-R^4$, $-C(O)-NH-R^4$, $-O-C(O)-O-R^4$, $-O-C(O)-S-R^4$, $-O-C(O)-NH-R^4$, $-S-S-R^4$, $-S-R^4$, $-NH-R^4$, $-CH(-NH_2)(-R^4)$, C_{5-6} heterocycloalkyl, 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):



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 $3.16^\circ \pm 0.2^\circ$, $6.37^\circ \pm 0.2^\circ$, $5.38^\circ \pm 0.2^\circ$, and $17.35^\circ \pm 0.2^\circ$ at a $K\alpha_2/K\alpha_1$ (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% $fT > MIC$ for a bacterial strain.

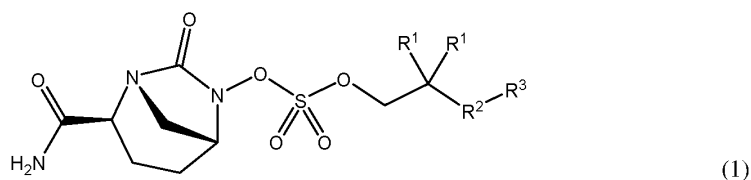
14. The pharmaceutical composition of claim 1, wherein, following oral administration to a patient, the composition provides an avibactam plasma concentration greater than 40% $fT > C_{tr}$.

15. The pharmaceutical composition of claim 1, wherein, following oral administration to a patient, the composition provides an avibactam plasma concentration characterized by a $fAUC:MIC$ 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. A method of treating a bacterial infection in a patient in need of such treatment comprising orally administering to the patient a therapeutically effective amount of:
a β -lactam antibiotic or a pharmaceutically acceptable salt thereof; and
an avibactam derivative of Formula (1):



or a pharmaceutically acceptable salt thereof, wherein,

each R¹ is independently selected from C₁₋₆ alkyl, or each R¹ and the geminal carbon atom to which they are bonded forms a C₃₋₆ cycloalkyl ring, a C₃₋₆ heterocycloalkyl ring, a substituted C₃₋₆ cycloalkyl ring, or a substituted C₃₋₆ heterocycloalkyl ring;

R² is selected from a single bond, C₁₋₆ alkanediyl, C₁₋₆ heteroalkanediyl, C₅₋₆ cycloalkanediyl, C₅₋₆ heterocycloalkanediyl, C₆ arenediyl, C₅₋₆ heteroarenediyl, substituted C₁₋₆ alkanediyl, substituted C₁₋₆ heteroalkanediyl, substituted C₅₋₆

cycloalkanediyl, substituted C₅₋₆ heterocycloalkanediyl, substituted C₆ arenediyl, and substituted C₅₋₆ heteroarenediyl;

R³ is selected from C₁₋₆ alkyl, -O-C(O)-R⁴, -S-C(O)-R⁴, -NH-C(O)-R⁴, -O-C(O)-O-R⁴, -S-C(O)-O-R⁴, -NH-C(O)-O-R⁴, -C(O)-O-R⁴, -C(O)-S-R⁴, -C(O)-NH-R⁴, -O-C(O)-O-R⁴, -O-C(O)-S-R⁴, -O-C(O)-NH-R⁴, -S-S-R⁴, -S-R⁴, -NH-R⁴, -CH(-NH₂)(-R⁴), C₅₋₆ heterocycloalkyl, C₅₋₆ heteroaryl, substituted C₅₋₆ cycloalkyl, substituted C₅₋₆ heterocycloalkyl, substituted C₅₋₆ aryl, substituted C₅₋₆ heteroaryl, and -CH=C(R⁴)₂, wherein,

R⁴ is selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ heteroalkyl, C₅₋₈ cycloalkyl, C₅₋₈ heterocycloalkyl, C₅₋₁₀ cycloalkylalkyl, C₅₋₁₀ heterocycloalkylalkyl, C₆₋₈ aryl, C₅₋₈ heteroaryl, C₇₋₁₀ arylalkyl, C₅₋₁₀ heteroarylalkyl, substituted C₁₋₈ alkyl, substituted C₁₋₈ heteroalkyl, substituted C₅₋₈ cycloalkyl, substituted C₅₋₈ heterocycloalkyl, substituted C₅₋₁₀ cycloalkylalkyl, substituted C₅₋₁₀ heterocycloalkylalkyl, substituted C₆₋₈ aryl, substituted C₅₋₈ heteroaryl, substituted C₇₋₁₀ arylalkyl, and substituted C₅₋₁₀ heteroarylalkyl;

R⁵ is selected from hydrogen, C₁₋₆ alkyl, C₅₋₈ cycloalkyl, C₆₋₁₂ cycloalkylalkyl, C₂₋₆ heteroalkyl, C₅₋₈ heterocycloalkyl, C₆₋₁₂ heterocycloalkylalkyl, substituted C₁₋₆ alkyl, substituted C₅₋₈ cycloalkyl, substituted C₆₋₁₂ cycloalkylalkyl, substituted C₂₋₆ heteroalkyl, substituted C₅₋₈ heterocycloalkyl, and substituted C₆₋₁₂ heterocycloalkylalkyl; and

R⁶ is selected from hydrogen, C₁₋₆ alkyl, C₅₋₈ cycloalkyl, C₆₋₁₂ cycloalkylalkyl, C₂₋₆ heteroalkyl, C₅₋₈ heterocycloalkyl, C₆₋₁₂ heterocycloalkylalkyl, substituted C₁₋₆ alkyl, substituted C₅₋₈ cycloalkyl, substituted C₆₋₁₂ cycloalkylalkyl, substituted C₂₋₆ heteroalkyl, substituted C₅₋₈ heterocycloalkyl, and substituted C₆₋₁₂ heterocycloalkylalkyl.

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

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