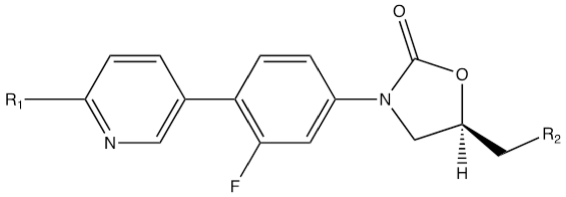
wherein R_1 is a tetrazole ring substituted at position 2' with an aminoalkyl.

[0005a] In one aspect, the present disclosure provides a compound of Formula I or a pharmaceutically acceptable salt thereof:



Formula I

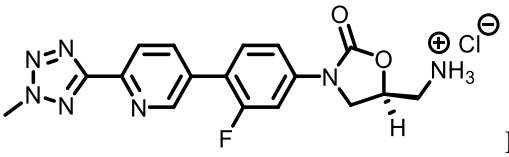
wherein

R_1 is a tetrazole ring substituted at position 2' with an aminoalkyl; and

R_2 is an NH_2 or an -$NHCOCH_3$.

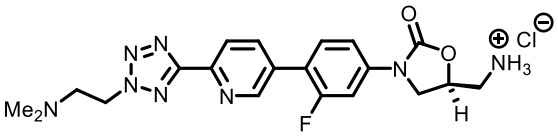
[0006] In some examples, the aminoalkyl is a dimethylaminoalkyl. In some examples, the aminoalkyl derivatives of oxazolidinone compounds include either an amine or acetamide group at the R_2 positions of the oxazolidinone ring and a dimethylaminoethyl group on the tetrazole ring.

[0007] In some examples, a compound of Formula 1a is provided:



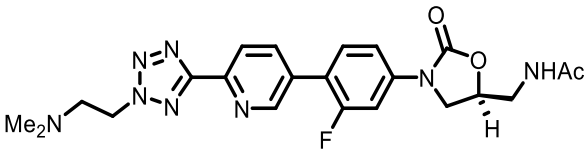
Formula 1a.

[0008] In some examples, a compound of Formula 1b is provided:



Formula 1b.

[0009] In some examples, a compound of Formula 1c or pharmaceutically acceptable salts thereof is provided:



Formula 1c.

phosphatidylcholine (HSPC). In some examples, the phosphatidylcholine to cholesterol molar ratios is from about 60:40 to 35:65. In some examples, the phosphatidylcholine to cholesterol molar ratio is from about 55:45 to about 35:65. In some examples, the phosphatidylcholine to cholesterol molar ratio is from about 50:50 to about 40:60.

[0026a] In another aspect, the present disclosure provides the liposomal composition, wherein the liposomal composition is an aqueous medium comprising the compound as described herein within liposome vesicles comprising a polyanion trapping agent, a phospholipid and cholesterol.

[0027] In some examples, the phosphatidylcholine to cholesterol molar ratio is from about 50:50 to about 45:55.

[0028] In some examples, the membrane further comprises a polymer-conjugated lipid.

[0029] In some examples, the liposome vesicle comprises HSPC, cholesterol and polymer-conjugated lipid in a about 55:45:2.75 molar ratio.

[0030] In some examples, the polymer-conjugated lipid is PEG(Mol. weight 2,000)-distearoylglycerol (PEG-DSG) or PEG(Mol. weight 2,000)-distearoylphosphatidylethanolamine (PEG-DSPE).

[0031] In some examples, the liposomes in the liposome composition have Z-average particle size from about 80 to about 130 nm.

[0032] In some examples, the composition is a liquid pharmaceutical formulation for parenteral administration.

[0033] The disclosure relates to a method of treating bacterial infection, the method comprising administering to a subject in need thereof a therapeutically effective amount of the liposomal composition provided herein.

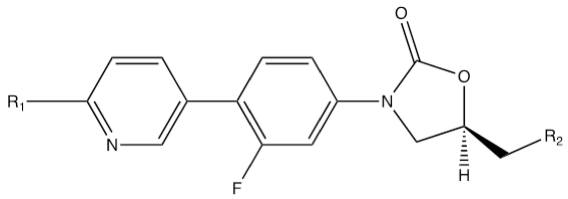
[0033a] In another aspect, the present disclosure provides the liposomal composition as described herein for use in therapy.

[0033b] In another aspect, the present disclosure provides use of the liposomal composition as described herein in the manufacture of a medicament for treating a gram positive bacterial infection.

CLAIMS

What is claimed is:

1. A compound of Formula I or a pharmaceutically acceptable salt thereof:



Formula I

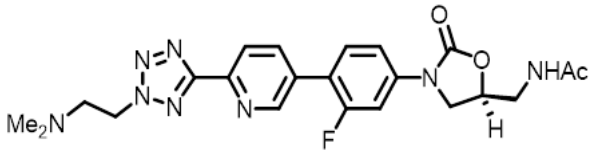
wherein

R_1 is a tetrazole ring substituted at position 2' with an aminoalkyl; and

R_2 is an NH_2 or an -$NHCOCH_3$.

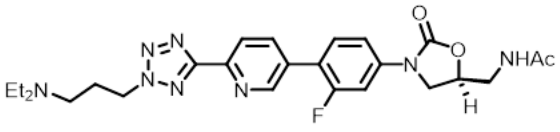
2. The compound of claim 1, wherein R_2 is -$NHCOCH_3$.

3. The compound of claim 1, wherein the compound is the compound of Formula 1c or a pharmaceutically acceptable salt thereof:



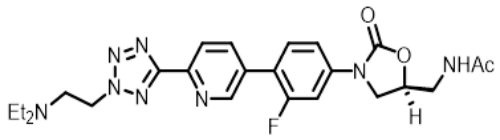
Formula 1c.

4. The compound of claim 1, wherein the compound is the compound of Formula 1d or a pharmaceutically acceptable salt thereof:



Formula 1d.

5. The compound of claim 1, wherein the compound is the compound of Formula 1e or a pharmaceutically acceptable salt thereof:



Formula 1e.

6. A liposomal composition comprising a compound of any one of claims 1-5.

7. The liposomal composition, comprising liposome vesicles, the liposome vesicles comprising the compound of any one of claims 2-5.

8. The liposomal composition, wherein the liposomal composition is an aqueous medium comprising the compound of any one of claims 2-5 within liposome vesicles comprising a polyanion trapping agent, a phospholipid and cholesterol.

9. The liposomal composition of claim 8, wherein the polyanion trapping agent is triethylammonium sucrose octasulfate (TEA-SOS) or ammonium sulfate (AS).

10. The liposomal composition of claim 8, wherein the pharmaceutically acceptable salt of the compound of Formula I is a sulfate salt encapsulated within the liposome vesicles.

11. The liposomal composition of claim 8, wherein the phospholipid is a phosphatidylcholine.

12. The liposomal composition of claim 11, wherein the phosphatidylcholine is distearoylphosphatidylcholine (DSPC) or hydrogenated soy phosphatidylcholine (HSPC).

13. The liposomal composition of claim 11, wherein the cholesterol in the liposomal composition is in an amount of 50 mol% to 65 mol% of the total phosphatidylcholine and cholesterol in the liposomal composition.

14. The liposomal composition of claim 11, wherein the phosphatidylcholine to cholesterol

molar ratio is 45:55 of the total phosphatidylcholine and cholesterol in the liposomal composition.

15. The liposomal composition of claim 7, wherein the liposomal composition further comprises a polymer-conjugated lipid.

16. The liposomal composition of claim 15, wherein the polymer-conjugated lipid is PEG(Mol. weight 2,000)-distearoylglycerol (PEG-DSG) or PEG(Mol. weight 2,000)-distearoylphosphatidylethanolamine (PEG-DSPE).

17. The liposomal composition of claim 11, wherein the liposome vesicles comprise

a. a sulfate salt of the compound of Formula I encapsulated within the liposome vesicles;

b. cholesterol in an amount of 50 mol% to 65 mol% of the total phosphatidylcholine and cholesterol in the liposomal composition; and

c. a polymer-conjugated lipid.

18. The liposomal composition of claim 17, wherein the liposomal composition comprises liposome vesicles encapsulating the sulfate salt of the compound of Formula I, and the liposome vesicles comprise phosphatidylcholine HSPC, cholesterol and polymer-conjugated lipid in a 45:55:2.25 molar ratio.

19. The liposomal composition of claim 17, wherein the polymer-conjugated lipid is PEG-lipid in an amount of 0.5 mol% to 10 mol% of the phosphatidylcholine.

20. The liposomal composition of claim 19, wherein the polymer-conjugated lipid is PEG-lipid in an amount of 5 mol% of the phosphatidylcholine.

21. The liposomal composition of claim 19, wherein the liposomal composition has

a. a Z-average particle size from 80 nm to 130 nm; and

b. a polydispersity index (PDI) of less than 0.1.

22. The liposomal composition of claim 19, wherein the liposomal composition has a drug-to-lipid ratio of the sulfate salt of the compound of Formula I to phospholipid ranging from 400 g/mol to 800 g/mol in the liposomal composition.

23. The liposomal composition of claim 18, wherein

a. the polymer-conjugated lipid is PEG(Mol. weight 2,000)-distearoylphosphatidylethanolamine (PEG-DSPE);

b. the liposomal composition has a Z-average particle size from 80 nm to 130 nm;

c. the liposomal composition has a polydispersity index (PDI) of less than 0.1; and

d. the liposomal composition has a drug-to-lipid ratio of the sulfate salt of the compound of Formula I to phospholipid ranging from 400 g/mol to 800 g/mol in the liposomal composition.

24. The liposomal composition of any one of claims 6 to 23 for use in therapy.

25. Use of the liposomal composition of any one of claims 6 to 23 in the manufacture of a medicament for treating a gram positive bacterial infection.

26. A method of making a liposomal composition comprising the steps of:
(i) preparing liposomes comprising phospholipid, cholesterol, and PEG-lipid, and having an interior space containing a trapping agent, in a medium substantially free from the trapping agent;
(ii) contacting the liposomes with a compound of any one of claims 1 to 5 in an aqueous medium to effect encapsulation of the compound in the liposomes;
(iii) removing unencapsulated compound; and
(iv) providing the liposomes in a physiologically acceptable medium suitable for parenteral use.

27. The method of claim 26, wherein the trapping agent of step (i) is ammonium sulfate, and the concentration of the trapping agent in the interior space of the liposomes is more than 0.25 M prior to drug loading in step (ii).

28. The method of claim 27, wherein the concentration of the trapping agent in the interior

space of the liposomes of step (i) is 0.5 M.

29. The method of claim 26 wherein the drug-to-lipid ratio at step (ii) is in the range from 400 g/mol to 1400 g/mol phospholipid.