OXAZOLIDINONE COMPOUNDS, LIPOSOME COMPOSITIONS COMPRISING OXAZOLIDINONE COMPOUNDS AND METHODS OF USE THEREOF

RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Patent Application No. 63/040,810, filed June 18, 2020, and U.S. Utility Patent Application No. 17/351,631, filed June 18, 2021, the entire contents of which are hereby incorporated herein by reference.

FIELD

[0002] The present disclosure relates to novel aminoalkyl oxazolidinone compounds, liposome compositions comprising novel aminoalkyl oxazolidinone compounds and use of the aminoalkyl oxazolidinone compounds in the treatment of Mycobacterium tuberculosis and other gram-positive bacterial infections.

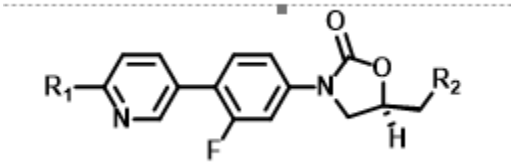
BACKGROUND

[0003] Mycobacteria is a genus of bacteria responsible for tuberculosis (TB). According to the World Health Organization, worldwide, TB is one of the top 10 causes of death and the leading cause of death from a single infectious agent. Rifampicin is the most effective first-line drug to treat TB. However, there is a growing number of cases infected with mycobacterium tuberculosis that is resistant to rifampicin. Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin.

SUMMARY

[0004] Compositions and methods for the treatment of tuberculosis, as well as other mycobacterial and gram positive bacterial infections are disclosed.

[0005] The disclosure provides a compound of Formula I or pharmaceutically acceptable salts thereof:

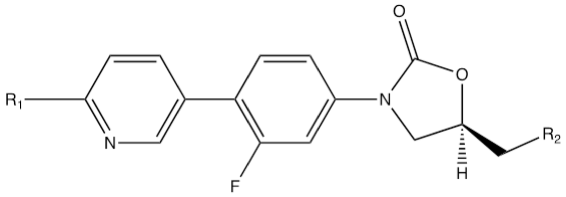


Formula I

wherein R_2 is an amine (NH_2) or an acetamide ($NHCOCH_3$), and

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

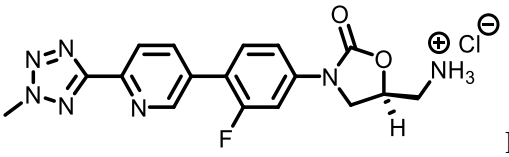
wherein

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

R_2 is an amine or an acetamide.

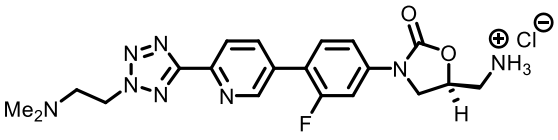
[0006] In some examples, the aminoalkyl is a dimethylaminoalkyl. In some examples, the aminoalkyl derivatives of oxazolidinone compounds include either an amine or acetamide group at the R_2 positions of the oxazolidinone ring and a dimethylaminoethyl group on the tetrazole ring.

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



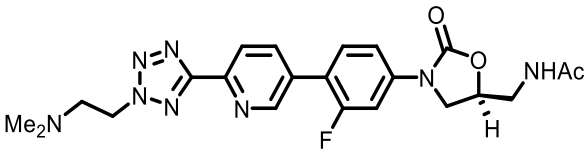
Formula 1a.

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



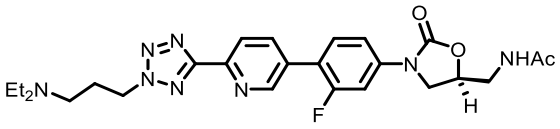
Formula 1b.

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



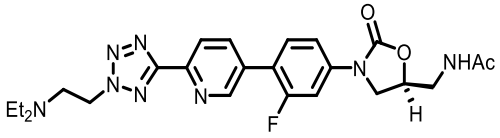
Formula 1c.

[0010] In some examples, a compound of Formula 1d or pharmaceutically acceptable salts thereof is provided:



Formula 1d

[0011] In some examples, a compound of Formula 1e is provided:



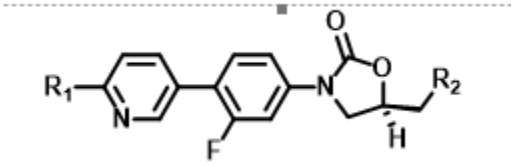
Formula 1e

[0012] In some examples, the compound has a Selectivity Index (SI) index for Erd/HepG2 and H37Rv/HepG2 ranges from 100 to 1700.

[0013] In some examples, the compound has a SI index for Erd/HepG2 and H37Rv/HepG2 ranges from 200 to 1700.

[0014] In some examples, the compound has a SI index for Erd/HepG2 and H37Rv/HepG2 ranges from 300 to 1700.

[0015] The disclosure provides a liposomal composition comprising liposome vesicles, the liposome vesicles comprising a compound of Formula I or pharmaceutically acceptable salts thereof therein



Formula I

wherein R_2 is an amine (NH_2) or an acetamide ($NHCOCH_3$), and

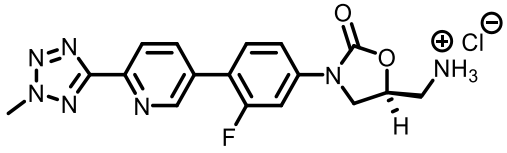
wherein R_1 is a tetrazole ring substituted at position 2' with an aminoalkyl.

[0015a] In another aspect, the present disclosure provides a liposomal composition comprising a compound as described herein.

[0016] 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.

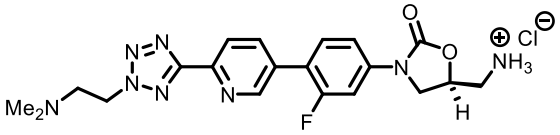
[0016a] In another aspect, the present disclosure provides the liposomal composition, comprising liposome vesicles, the liposome vesicles comprising the compound as described herein.

[0017] In some examples, a liposomal composition is provided comprising liposome vesicles, the liposome vesicles comprising a compound of Formula 1a:



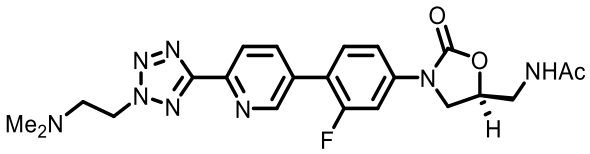
Formula 1a

[0018] In some examples, a liposomal composition is provided comprising liposomes vesicles, the liposome vesicles comprising a compound of Formula 1b:



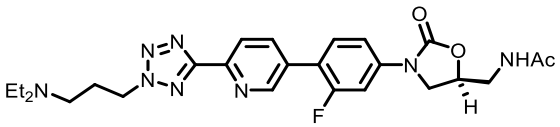
Formula 1b

[0019] In some examples, a liposomal composition is provided comprising liposomes vesicles, the liposome vesicles comprising a compound of Formula 1c or a pharmaceutically acceptable salt thereof:



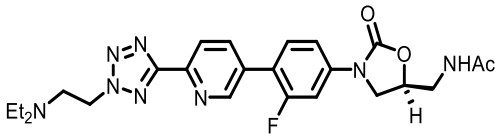
Formula 1c

[0020] In some examples, a liposomal composition is provided comprising liposomes vesicles, the liposome vesicles comprising a compound of Formula 1d:



Formula 1d

[0021] In some examples, a liposomal composition is provided comprising liposomes vesicles, the liposome vesicles comprising a compound of Formula 1e:



Formula 1e

[0022] In some examples, the liposome vesicles are in an aqueous medium.

[0023] In some examples, the compound is entrapped in the liposome vesicle with a trapping agent, wherein the trapping agent comprises a polyanion. In some examples, the trapping agent is triethylammonium sucrose octasulfate or ammonium sulfate. In some examples, the trapping agent is triethylammonium sucrose octasulfate. In some examples, the trapping agent is ammonium sulfate.

[0024] In some examples, the liposomal composition comprises a salt of the compound, wherein the salt is sulfate, citrate, sucrosofate, a salt with a phosphorylated or sulfated polyol, or a salt with a phosphorylated or sulfated polyanionic polymer. In some examples, the liposomal composition comprises a sulfate salt of the compound.

[0025] In some examples, the compound in the liposome vesicle has an aqueous solubility less than 1 mg/mL. In some examples, the compound in the liposome vesicle has an aqueous solubility less than 0.1 mg/mL.

[0026] In some examples, the liposome vesicle comprises a membrane comprising phosphatidylcholine and cholesterol. In some examples, the liposome vesicle comprises a membrane comprising phosphatidylcholine and cholesterol, wherein the membrane separates the inside of the liposome vesicles from the aqueous medium. In some examples, the phosphatidylcholine is distearoylphosphatidylcholine (DSPC) or hydrogenated soy

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 bacterial infection.

[0034] In some examples, the bacterial infection is Mycobacterium tuberculosis infection. In some examples, the compound in the liposome vesicle has a minimum inhibitory concentration (MIC) ranging from about 0.01 µg/ml to about 0.25 µg/ml. In some examples, the compound in the liposome vesicle has a minimum inhibitory concentration (MIC) ranging from about 0.01 µg/ml to about 0.1 µg/ml.

[0035] In some examples, the liposomal composition is administered parenterally.

[0036] In some examples, the method comprises administering simultaneously or sequentially one of more additional active agent. In some examples, the one or more active agents comprise bedaquiline, pretomanid, pyrazinamide, moxifloxacin, a pharmaceutically acceptable salt thereof or a combination thereof.

[0037] In some examples, the liposomal composition is administered once a week to

once every six weeks.

[0038] In some examples, the percentage of compound remaining in blood is greater than 20 % of the administered amount at 6 hours following administration to the subject in need thereof. In some examples, the percentage of compound remaining in blood is greater than 10 % of the administered amount.

[0039] In another aspect, the present disclosure provides 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 as described herein 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] FIG. 1 is a graph showing the effect of pH on the liposome loading of compounds AKG-3, AKG-5, and AKG-16.

[0041] FIG. 2A and FIG. 2B are graphs showing the encapsulation of compounds AKG-3, AKG-5, and AKG-16 into liposomes with TEA-SOS trapping agent at different drug-to-lipid (DL) ratios FIG. 2A shows the effect of the added drug-to-lipid (DL0) ratio, in grams of the drug per mole of liposome phospholipid (PhL), on the liposome payload, expressed as post-load drug-to-lipid ratio (DL). FIG. 2B shows the effect the DL0 ratio (drug-to-lipid input ratio) on liposome loading efficiency, calculated as percent of post-load DL relative to DL0.

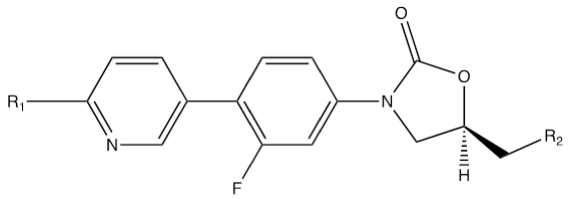
[0042] FIG. 3A, FIG. 3B FG. 3C, and FIG. 3D are graphs showing the encapsulation of compounds AKG-3, AKG-5, and AKG-16 into liposomes with 0.5M ammonium sulfate as a trapping agent at different DL ratios. FIG. 3A shows the effect the DL0 ratio on liposome payload for AKG-5, and AKG-16. FIG. 3B shows the effect the DL0 ratio on liposome loading efficiency for AKG-5, and AKG-16. FIG. 3C shows the effect the DL0 ratio on liposome payload for AKG-3. FIG. 3D shows the effect the DL0 ratio on liposome loading efficiency for AKG-3.

[0043] FIG. 4A and FIG. 4B are graphs showing the encapsulation of AKG-28 and AKG-38 with TEA-SOS and ammonium sulfate as trapping agents at different DL0 ratio. FIG. 4A shows the effect the DL0 ratio on liposome payload. FIG. 4B shows the effect the DL0 ratio on loading efficiency.

CLAIMS

What is claimed is:

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



Formula I

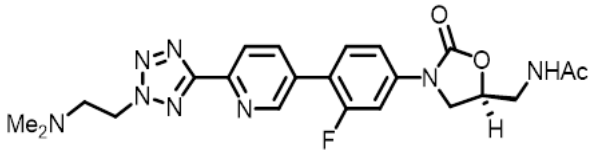
wherein

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

R_2 is an amine or an acetamide.

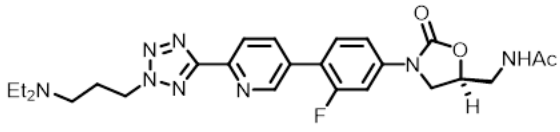
2. The compound of claim 1, wherein R_2 is $-NHCOCH_3$.

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



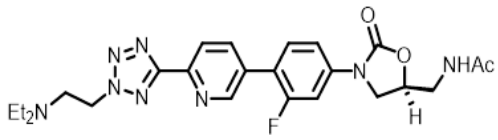
Formula 1c.

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 about 80 nm to about 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 about 80 nm to about 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 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.