While the underlying mechanism of observed ISRs is not clearly understood, and without intending to be bound by theory: The observed ISRs could be attributed to localized direct interaction of SCY-078 with the vascular endothelium at the injection site when SCY-078 is introduced into the bloodstream intravenously.

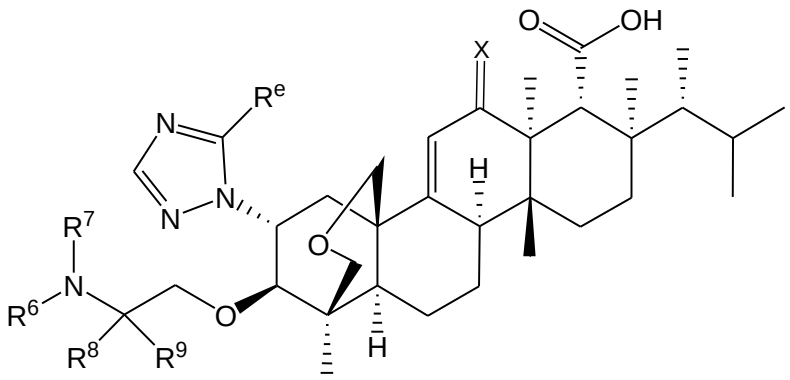
[0008] There is a need in the art to be able to administer SCY-078 and other enfumafungin derivative antifungals intravenously via a peripheral vein with fewer and/or less pronounced ISRs, and to enhance flexibility and convenience for caregivers and patients.

SUMMARY

[0008a] In a first aspect of the present disclosure, there is provided an injectable composition comprising:

an aqueous phase; and

one or more unilamellar vesicles that each comprise phospholipid and cholesterol, and that each encapsulate a compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof:



(**I**)

wherein:

X is O or H, H;

R^e is $C(O)NR^fR^g$ or a 6-membered ring heteroaryl group containing 1 or 2 nitrogen atoms wherein the heteroaryl group is optionally mono-substituted on a ring carbon with fluoro or chloro or on a ring nitrogen with oxygen;

R^f, R^g, R^6 and R^7 are each independently hydrogen or C_1-C_3 alkyl;

R^8 is C_1-C_4 alkyl, C_3-C_4 cycloalkyl or C_4-C_5 cycloalkyl-alkyl;

R^9 is methyl or ethyl; and

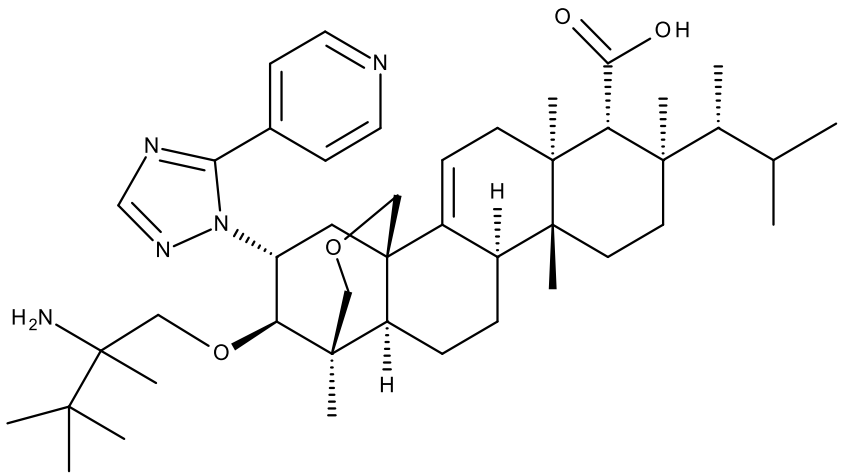
R^8 and R^9 are optionally taken together to form a 6-membered saturated ring containing 1 oxygen atom,

wherein the one or more unilamellar vesicles are hydrated in the aqueous phase.

[0008b] In another aspect of the present disclosure, there is provided an injectable composition comprising

an aqueous phase; and

one or more unilamellar vesicles that each comprise phospholipid and cholesterol, and that each encapsulate a compound of Formula (II) or a pharmaceutically acceptable salt or hydrate thereof:



(**II**)

which is (1*S*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*,14*R*,*15R*)-15-[[2-amino-2,3,3-trimethylbutyl]oxy]-8-[(1*R*)-1,2-dimethylpropyl]-14-[5-(4-pyridinyl)-*1H*-1,2,4-triazol-1-yl]-1,6,6a,7,8,9,10,10a,10b,11,12,12a-dodecahydro-1,6a,8,10a-tetramethyl-*4H*-1,4a-propano-*2H*-phenanthro[1,2-c]pyran-7-carboxylic acid,

wherein the concentration of the encapsulated compound of Formula (II) or a pharmaceutically acceptable salt or hydrate thereof in the injectable composition is from about 0.01 to about 50 mg/mL,

wherein the phospholipid comprises phosphatidylglycerol and phosphatidylcholine,

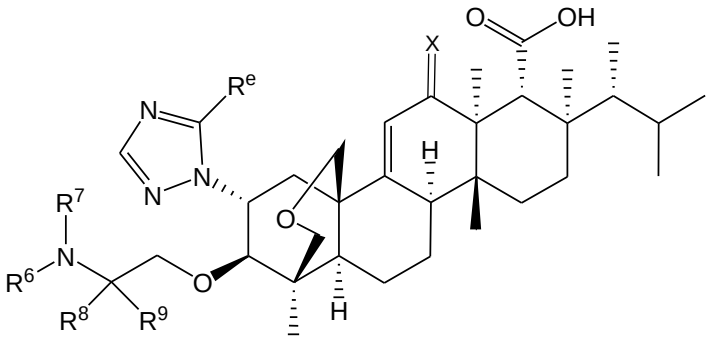
wherein the molar ratio of: the compound of Formula (II) or a pharmaceutically acceptable salt or hydrate thereof, to the phosphatidylglycerol, to the phosphatidylcholine, to the cholesterol, is 1 : 2 : 5 : 2.5,

wherein the aqueous phase comprises sugar and has a pH of from about 5.0 to about 7.0, and

wherein the one or more unilamellar vesicles are hydrated in the aqueous phase.

[0008c] In yet another aspect of the present disclosure, there is provided a use of the injectable composition disclosed herein, in the manufacture of a medicament for treating a fungal infection in a subject in need thereof, wherein the medicament is to be intravenously administered.

[0008d] In a further aspect of the present disclosure, there is provided a method of making an injectable composition comprising one or more unilamellar vesicles that each encapsulate a compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof



(**I**)

wherein:

X is O or H, H;

R^e is $C(O)NR^fR^g$ or a 6-membered ring heteroaryl group containing 1 or 2 nitrogen atoms wherein the heteroaryl group is optionally mono-substituted on a ring carbon with fluoro or chloro or on a ring nitrogen with oxygen;

R^f, R^g, R^6 and R^7 are each independently hydrogen or C_1-C_3 alkyl;

R^8 is C_1-C_4 alkyl, C_3-C_4 cycloalkyl or C_4-C_5 cycloalkyl-alkyl;

R^9 is methyl or ethyl; and

R^8 and R^9 are optionally taken together to form a 6-membered saturated ring containing 1 oxygen atom,

the method comprising:

a) dissolving phospholipid and cholesterol in an aliphatic alcohol having one to five carbon atoms to form a first solution;

b) dissolving the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof in the first solution to form a second solution;

c) mixing the second solution;

d) evaporating the solvent from the second solution to produce a phospholipid-cholesterol dispersion containing the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof;

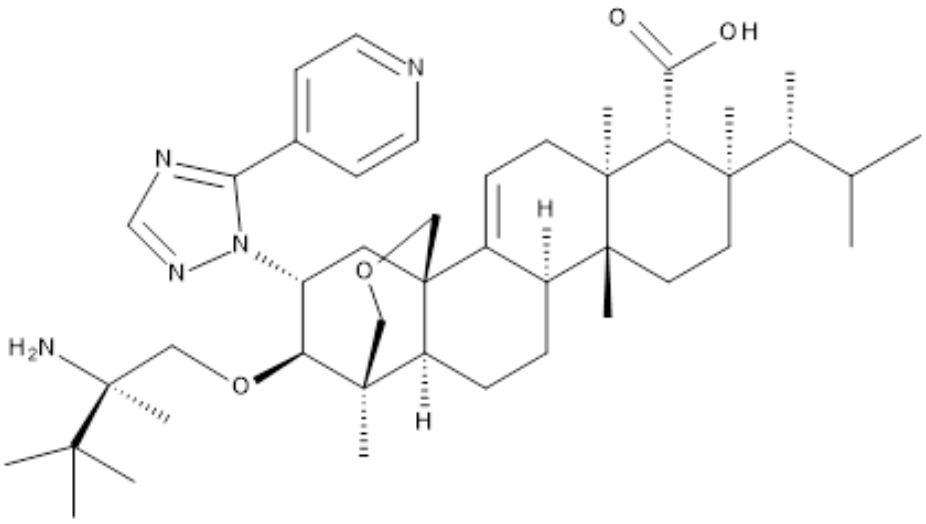
e) hydrating the phospholipid-cholesterol dispersion containing the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof with a sugar solution to produce a hydrated suspension; and

f) forming, from the hydrated suspension, one or more unilamellar vesicles that each comprise phospholipid and cholesterol and that encapsulate the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof.

[0008e] In another aspect of the present disclosure, there is provided an injectable composition comprising

an aqueous phase; and

one or more unilamellar vesicles that each comprise phospholipid and cholesterol, and that each encapsulate a compound of Formula (IIa) or a pharmaceutically acceptable salt or hydrate thereof:



(**IIa**)

which is (1*S*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*,14*R*,*15R*)-15-[[(2*R*)-2-amino-2,3,3-trimethylbutyl]oxy]-8-[(1*R*)-1,2-dimethylpropyl]-14-[5-(4-pyridinyl)-*1H*-1,2,4-triazol-1-yl]-1,6,6a,7,8,9,10,10a,10b,11,12,12a-dodecahydro-1,6a,8,10a-tetramethyl-*4H*-1,4a-propano-*2H*-phenanthro[1,2-c]pyran-7-carboxylic acid,

wherein the one or more unilamellar vesicles are hydrated in the aqueous phase.

[0008f] In yet another aspect of the present disclosure, there is provided an injectable composition disclosed herein, for use in therapy.

[0009] The present disclosure provides injectable compositions of single bilayer vesicles or liposomes encapsulating an enfumafungin derived triterpenoid compound and hydrated in an aqueous phase, suitable for intravenous administration via a peripheral vein. The vesicles may be made of phospholipids and cholesterol. The pH of the aqueous phase is preferably from about 5.0 to about 7.0. A monosaccharide solution and a disaccharide solution are examples of the aqueous phase.

[0010] The injectable compositions preferably comprise SCY-078 or a salt thereof as the enfumafungin derivative.

[0011] The injectable compositions may be administered intravenously to treat and/or to prevent fungal infections, such as systemic fungal infections, including those caused by *Candida* species or *Aspergillus* species. With the injectable compositions of the present disclosure, local injection site reactions (including pain, irritation, inflammation, and phlebitis) after intravenous administration can be reduced in number and/or degree as compared with such reactions after intravenous administration of a non-liposomal composition containing the same active.

[0012] The present disclosure also provides methods of treating or preventing fungal infections in patients by intravenous administration of an injectable composition comprising single bilayer vesicles encapsulating an enfumafungin derived triterpenoid compound.

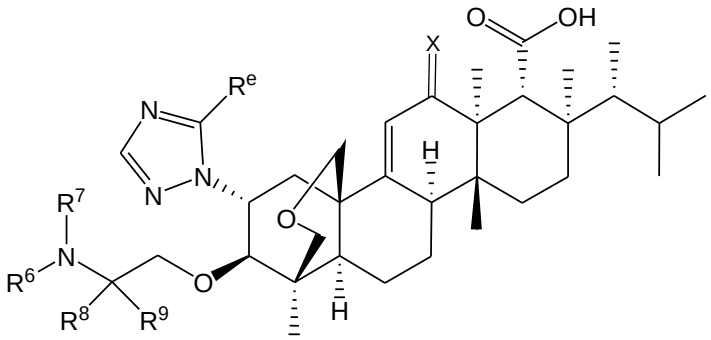
[0013] The present disclosure further provides methods of making compositions containing single bilayer liposomes encapsulating an enfumafungin derived triterpenoid compound, suitable for injection and for intravenous administration.

WHAT IS CLAIMED IS:

1. An injectable composition comprising:

an aqueous phase; and

one or more unilamellar vesicles that each comprise phospholipid and cholesterol, and that each encapsulate a compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof:



(**I**)

wherein:

X is O or H, H;

R^e is $C(O)NR^fR^g$ or a 6-membered ring heteroaryl group containing 1 or 2 nitrogen atoms wherein the heteroaryl group is optionally mono-substituted on a ring carbon with fluoro or chloro or on a ring nitrogen with oxygen;

R^f, R^g, R^6 and R^7 are each independently hydrogen or C_1-C_3 alkyl;

R^8 is C_1-C_4 alkyl, C_3-C_4 cycloalkyl or C_4-C_5 cycloalkyl-alkyl;

R^9 is methyl or ethyl; and

R^8 and R^9 are optionally taken together to form a 6-membered saturated ring containing 1 oxygen atom,

wherein the one or more unilamellar vesicles are hydrated in the aqueous phase.

2. The injectable composition according to claim 1, wherein the concentration of the encapsulated compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof in the injectable composition is from about 0.01 to about 50 mg/mL.

3. The injectable composition according to claim 1, wherein the aqueous phase comprises sugar.

4. The injectable composition according to claim 3, wherein the sugar is selected from monosaccharides, disaccharides, and combinations thereof.

5. The injectable composition according to claim 4, wherein the sugar is selected from sucrose, trehalose, lactose, glucose, fructose, and galactose, and combinations thereof.

6. The injectable composition according to claim 3, wherein the pH of the aqueous phase is in the range of from about 5.0 to about 7.0.

7. The injectable composition according to claim 1, wherein the one or more unilamellar vesicles comprise phosphatidylcholine, phosphatidic acid, phosphatidylserine, phosphatidylethanolamine, phosphatidylglycerol, or combinations thereof.

8. The injectable composition according to claim 1, wherein the one or more unilamellar vesicles comprise phosphatidylcholine and phosphatidylglycerol.

9. The injectable composition according to claim 8, wherein the phosphatidylcholine is selected from dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, egg phosphatidylcholine, soy phosphatidylcholine, dilauroyl phosphatidylcholine, and dimyristoyl phosphatidylcholine.

10. The injectable composition according to claim 8, wherein the phosphatidylglycerol is selected from dipalmitoyl phosphatidylglycerol, distearoyl phosphatidylglycerol, dilauroyl phosphatidylglycerol, and dimyristoyl phosphatidylglycerol.

11. The injectable composition according to claim 1, wherein the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof is present in the vesicles in an amount of about 5 to about 12 mole percent, the phospholipid is present in the vesicles in an amount of about 50 to about 80 mole percent, and the cholesterol is present in the vesicles in an amount of about 10 to about 30 mole percent.

12. The injectable composition according to claim 1, wherein the phospholipid comprises phosphatidylglycerol and phosphatidylcholine, and the molar ratio of: the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof, to the phosphatidylglycerol, to the phosphatidylcholine, to the cholesterol, is 1 : 2 : 5 : 2.5.

13. The injectable composition according to claim 1, wherein the average particle size of the one or more unilamellar vesicles is less than about 150 nm.

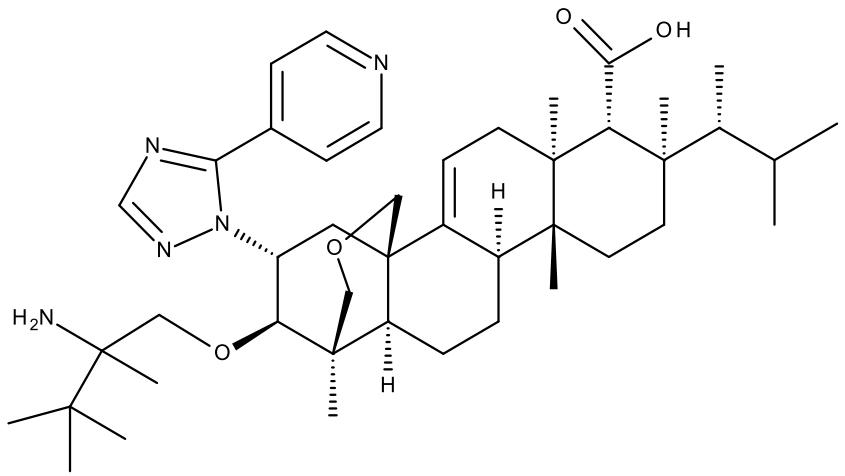
14. The injectable composition according to claim 13, wherein the average particle size of the one or more unilamellar vesicles is less than about 100 nm.

15. The injectable composition according to claim 14, wherein the average particle size of the one or more unilamellar vesicles is from about 70 to about 80 nm.

16. An injectable composition comprising

an aqueous phase; and

one or more unilamellar vesicles that each comprise phospholipid and cholesterol, and that each encapsulate a compound of Formula (II) or a pharmaceutically acceptable salt or hydrate thereof:



(**II**)

which is (1*S*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*,14*R*,*15R*)-15-[[2-amino-2,3,3-trimethylbutyl]oxy]-8-[(1*R*)-1,2-dimethylpropyl]-14-[5-(4-pyridinyl)-*1H*-1,2,4-triazol-1-yl]-1,6,6a,7,8,9,10,10a,10b,11,12,12a-dodecahydro-1,6a,8,10a-tetramethyl-*4H*-1,4a-propano-*2H*-phenanthro[1,2-c]pyran-7-carboxylic acid,

wherein the concentration of the encapsulated compound of Formula (II) or a pharmaceutically acceptable salt or hydrate thereof in the injectable composition is from about 0.01 to about 50 mg/mL,

wherein the phospholipid comprises phosphatidylglycerol and phosphatidylcholine,

wherein the molar ratio of: the compound of Formula (II) or a pharmaceutically acceptable salt or hydrate thereof, to the phosphatidylglycerol, to the phosphatidylcholine, to the cholesterol, is 1 : 2 : 5 : 2.5,

wherein the aqueous phase comprises sugar and has a pH of from about 5.0 to about 7.0, and

wherein the one or more unilamellar vesicles are hydrated in the aqueous phase.

17. The injectable composition according to claim 16, wherein the one or more unilamellar vesicles encapsulate the citrate salt of the compound of Formula (II).

18. Use of the injectable composition according to claim 1, in the manufacture of a medicament for treating a fungal infection in a subject in need thereof, wherein the medicament is to be intravenously administered.

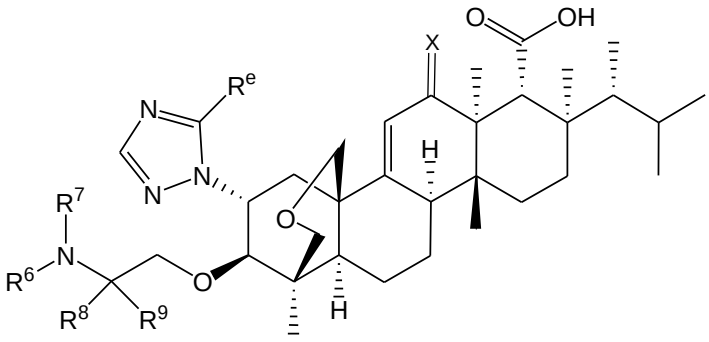
19. The use according to claim 18, wherein the subject is a human.

20. The use according to claim 18, wherein the fungal infection is caused by *Candida* spp.

21. The use according to claim 18, wherein the fungal infection is caused by *Aspergillus* spp.

22. Use of the injectable composition according to claim 16, in the manufacture of a medicament for treating a fungal infection in a subject in need thereof, wherein the medicament is to be intravenously administered.

23. A method of making an injectable composition comprising one or more unilamellar vesicles that each encapsulate a compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof



(**I**)

wherein:

X is O or H, H;

R^e is $C(O)NR^fR^g$ or a 6-membered ring heteroaryl group containing 1 or 2 nitrogen atoms wherein the heteroaryl group is optionally mono-substituted on a ring carbon with fluoro or chloro or on a ring nitrogen with oxygen;

R^f, R^g, R^6 and R^7 are each independently hydrogen or C_1-C_3 alkyl;

R^8 is C_1-C_4 alkyl, C_3-C_4 cycloalkyl or C_4-C_5 cycloalkyl-alkyl;

R^9 is methyl or ethyl; and

R^8 and R^9 are optionally taken together to form a 6-membered saturated ring containing 1 oxygen atom,

the method comprising:

a) dissolving phospholipid and cholesterol in an aliphatic alcohol having one to five carbon atoms to form a first solution;

b) dissolving the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof in the first solution to form a second solution;

c) mixing the second solution;

d) evaporating the solvent from the second solution to produce a phospholipid-cholesterol dispersion containing the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof;

e) hydrating the phospholipid-cholesterol dispersion containing the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof with a sugar solution to produce a hydrated suspension; and

f) forming, from the hydrated suspension, one or more unilamellar vesicles that each comprise phospholipid and cholesterol and that encapsulate the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof.

24. The method according to claim 23, wherein the aliphatic alcohol is selected from methanol or ethanol.

25. The method according to claim 23, wherein the sugar solution comprises sugar selected from monosaccharides, disaccharides, and combinations thereof.

26. The method according to claim 25, wherein the sugar is selected from sucrose, trehalose, lactose, glucose, fructose, and galactose, and combinations thereof.

27. The method according to claim 23, wherein about 90% or more of the amount of the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof present during step (b) is encapsulated during step (f) in the one or more unilamellar vesicles.

28. The method according to claim 23, wherein about 95% or more of the amount of the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof present during step (b) is encapsulated during step (f) in the one or more unilamellar vesicles.

29. The method according to claim 23, wherein the compound of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof is present in the vesicles in an amount of from about 5 to about 12 mole percent.

30. The method according to claim 23, wherein the phospholipid comprises phosphatidylglycerol and phosphatidylcholine, and wherein the molar ratio of: the compound

of Formula (I) or a pharmaceutically acceptable salt or hydrate thereof, to the phosphatidylglycerol, to the phosphatidylcholine, to the cholesterol, is 1 : 2 : 5 : 2.5.

31. The method according to claim 23, wherein during step (f), sonication, microfluidic mixing, homogenization, or a combination thereof is used to form the one or more unilamellar vesicles.

32. The method according to claim 23, further comprising sterilizing the one or more unilamellar vesicles produced in step (f).

33. The method according to claim 23, further comprising lyophilizing the one or more unilamellar vesicles produced in step (f).

34. The method according to claim 23, wherein the average particle size of the one or more unilamellar vesicles is less than about 150 nm.

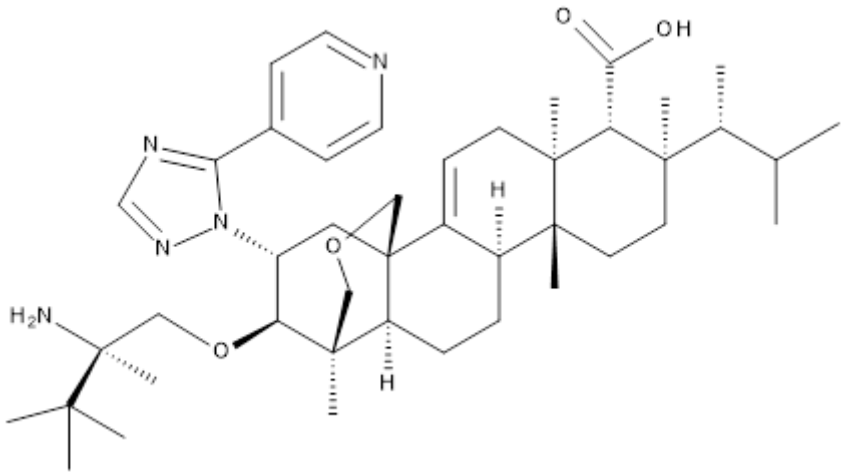
35. The method according to claim 34, wherein the average particle size of the one or more unilamellar vesicles is less than about 100 nm.

36. The method according to claim 35, wherein the average particle size of the one or more unilamellar vesicles is from about 70 to about 80 nm.

37. An injectable composition comprising

an aqueous phase; and

one or more unilamellar vesicles that each comprise phospholipid and cholesterol, and that each encapsulate a compound of Formula (IIa) or a pharmaceutically acceptable salt or hydrate thereof:



(**IIa**)

which is (1*S*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*,14*R*,*15R*)-15-[[(2*R*)-2-amino-2,3,3-trimethylbutyl]oxy]-8-[(1*R*)-1,2-dimethylpropyl]-14-[5-(4-pyridinyl)-*1H*-1,2,4-triazol-1-yl]-1,6,6a,7,8,9,10,10a,10b,11,12,12a-dodecahydro-1,6a,8,10a-tetramethyl-*4H*-1,4a-propano-*2H*-phenanthro[1,2-c]pyran-7-carboxylic acid,

wherein the one or more unilamellar vesicles are hydrated in the aqueous phase.

38. The injectable composition according to claim 37, wherein the one or more unilamellar vesicles encapsulate the compound of Formula (IIa).

39. The injectable composition according to claim 37, wherein the one or more unilamellar vesicles encapsulate a pharmaceutically acceptable salt of the compound of Formula (IIa).

40. The injectable composition according to claim 37, wherein the one or more unilamellar vesicles encapsulate the citrate salt of the compound of Formula (IIa).

41. Use of the injectable composition according to claim 37, in the manufacture of a medicament for treating a fungal infection in a subject in need thereof, wherein the medicament is to be intravenously administered.

42. The use according to claim 41, wherein the fungal infection is caused by *Candida* spp.

43. The use according to claim 41, wherein the fungal infection is candidemia.

44. The use according to claim 41, wherein the fungal infection is caused by *Aspergillus* spp.

45. The use according to claim 41, wherein the fungal infection is invasive aspergillosis.

46. The injectable composition according to any one of claim 1, 16 or 37, for use in therapy.