DRUG COMPOUND AND PURIFICATION METHODS THEREOF

CROSS REFERENCE

[0001] This Application claims the benefit of U.S. Provisional Application No. 62/540,706, filed August 3, 2017, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] DNA methylation is a post replicative chemical modification of DNA. Different cancers can be stratified by their abnormal DNA methylation profiles (degree of global or specific DNA methylation) and the hypermethylation of specific genes can be associated with the prognosis for gastric, lung, esophageal, pancreatic, and colon cancer. DNA methylation patterns can also be used to predict response or resistance to therapy in glioma and melanoma. Azacitidine and decitabine are two FDA approved hypomethylating agents (HMAs) that exert their therapeutic effect by inhibiting DNA methylation levels.

[0003] Lyophilization, often referred to as freeze drying, is a method of dehydration in which a solvent-containing substrate is frozen and then subjected to a vacuum so that the solvent is removed by sublimation, i.e. direct conversion from the the solid frozen state into the gaseous state.

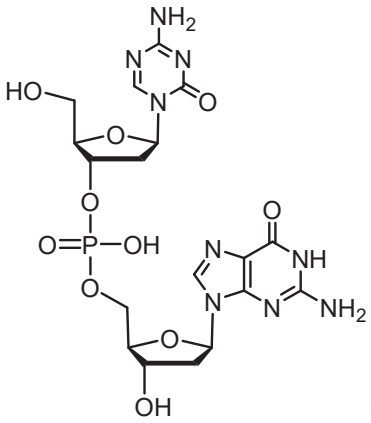
INCORPORATION BY REFERENCE

[0004] Each patent, publication, and non-patent literature cited in the application is hereby incorporated by reference in its entirety as if each was incorporated by reference individually.

SUMMARY OF THE DISCLOSURE

[0004a] In one aspect, provided herein is a method of preparing a lyophilized pharmaceutical product, the method comprising removing a portion of a solvent by a freeze-drying process from a solution, thereby generating the lyophilized pharmaceutical product, wherein the solution comprises:

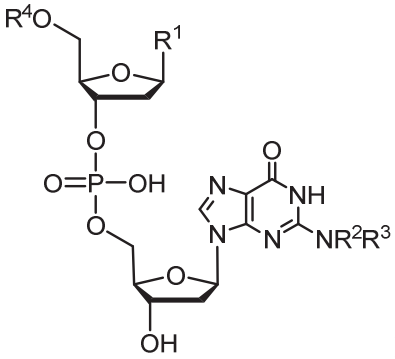
a) a compound of formula (1):



Formula (1), or a pharmaceutically acceptable salt thereof; and

b) the solvent, wherein the solvent comprises DMSO,

wherein the lyophilized pharmaceutical product comprises a compound of formula (2):



Formula (2), or a pharmaceutically-acceptable salt thereof, wherein:

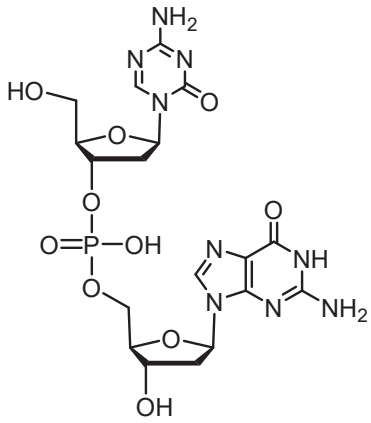
R^1 is a 4-amino-2H-1λ^2,3,5-triazin-2-one or a carbamide, each of which is independently substituted or unsubstituted;

each R^2 and R^3 is independently alkyl, which is substituted or unsubstituted; or hydrogen; and

R^4 is hydrogen or an acyl group, each of which is independently substituted or unsubstituted.

[0004b] In one aspect, provided herein is a method of preparing a lyophilized pharmaceutical product, the method comprising removing a portion of a solvent by a freeze-drying process from a solution, thereby generating the lyophilized pharmaceutical product, wherein the solution comprises:

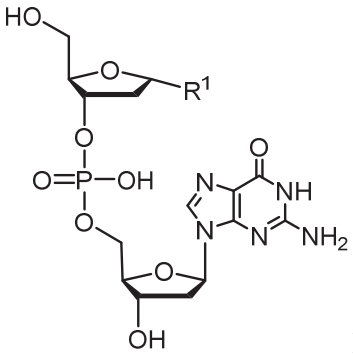
a) a compound of formula (1)



Formula (1), or a pharmaceutically acceptable salt thereof; and

b) the solvent, wherein the solvent comprises DMSO,

wherein the lyophilized pharmaceutical product comprises a compound of formula (3):

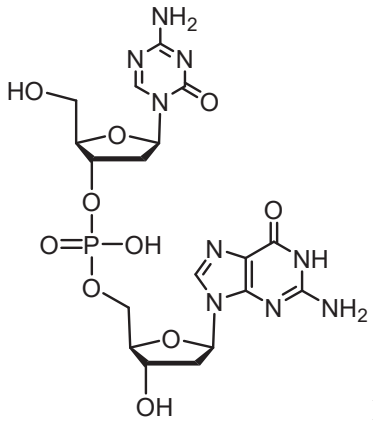


Formula (3),

or a pharmaceutically acceptable salt thereof, wherein R^1 is 4-amino-2H-1λ^2,3,5-triazin-2-one or a carbamide, each of which is independently substituted or unsubstituted.

[0004c] In one aspect, provided herein is method of preparing a lyophilized pharmaceutical product, the method comprising removing a portion of a solvent by a freeze-drying process from a solution, thereby generating the lyophilized pharmaceutical product, wherein the solution comprises:

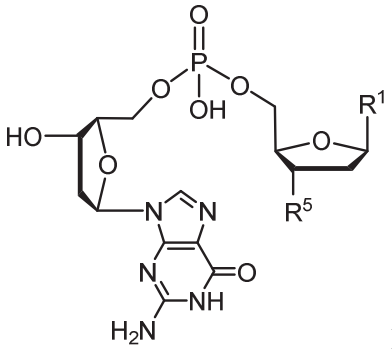
a) a compound of formula (1)



Formula (1), or a pharmaceutically acceptable salt thereof; and

b) the solvent, wherein the solvent comprises DMSO,

wherein the lyophilized pharmaceutical product comprises a compound of formula (4):

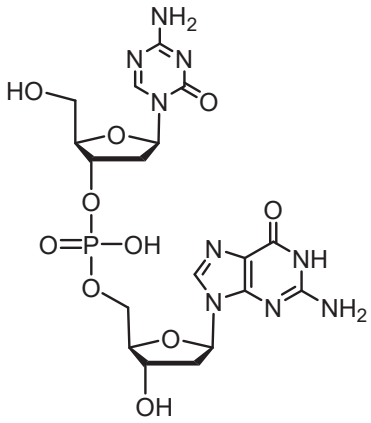


Formula (4),

or a pharmaceutically acceptable salt thereof, wherein R^1 is 4-amino-2H-1λ^2,3,5-triazin-2-one, which is substituted or unsubstituted; and R^5 is hydroxy or a nucleotide.

[0004d] In one aspect, provided herein is a method of preparing a lyophilized pharmaceutical product, the method comprising removing a portion of a solvent by a freeze-drying process from a solution, thereby generating the lyophilized pharmaceutical product, wherein the solution comprises:

a) a compound of formula (1):



Formula (1), or a pharmaceutically-acceptable salt thereof; and

b) the solvent, wherein the solvent comprises DMSO, wherein the freeze-drying process comprises:

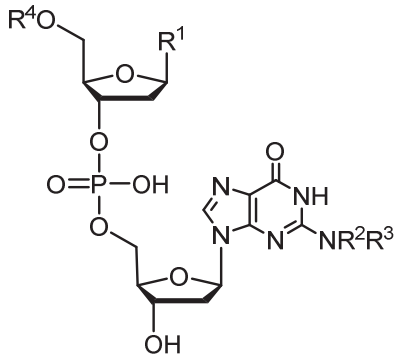
(i) a first freezing stage in which the solution is frozen by reducing a temperature of the solution to about -45 °C to form a frozen solution;

(ii) a first annealing stage in which the temperature of the solution is raised from about -45 °C to about 0 °C, wherein the solution remains frozen when the temperature of the solution is about 0 °C;

(iii) a second freezing stage in which the temperature of the solution is lowered from about 0 °C to about -45 °C;

(iv) a primary drying stage in which the temperature of the solution is raised from about -45 °C to about -6 °C, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in a frozen state of the solution under reduced pressure to give a partially dried product; and

(v) a secondary drying stage in which the temperature of the solution is raised from about -6 °C to about 40 °C, wherein in the secondary drying stage the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized pharmaceutical product, wherein the lyophilized pharmaceutical product comprises a compound of formula (2):



Formula (2), or a pharmaceutically-acceptable salt thereof, wherein:

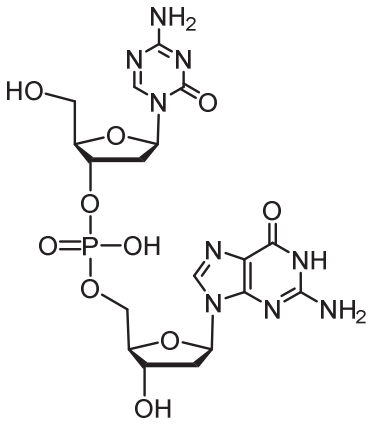
R^1 is 4-amino-2H-1λ^2,3,5-triazin-2-one or a carbamide, each of which is independently substituted or unsubstituted;

each R^2 and R^3 is independently alkyl, which is substituted or unsubstituted; or hydrogen; and

R^4 is hydrogen or an acyl group, each of which is independently substituted or unsubstituted.

[0005] In some embodiments, the disclosure provides a composition comprising:

a) a compound of the formula:



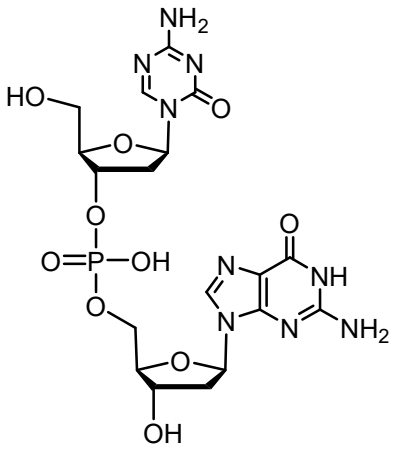
Formula (1),

CLAIMS

WHAT IS CLAIMED IS:

1. A method of preparing a lyophilized pharmaceutical product, the method comprising removing a portion of a solvent by a freeze-drying process from a solution, thereby generating the lyophilized pharmaceutical product, wherein the solution comprises:

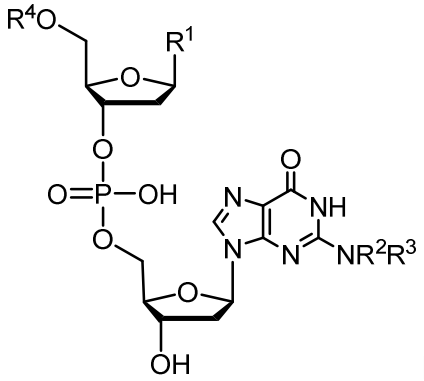
   a) a compound of formula (1):



Formula (1), or a pharmaceutically acceptable salt thereof; and

   b) the solvent, wherein the solvent comprises DMSO,

   wherein the lyophilized pharmaceutical product comprises a compound of formula (2):



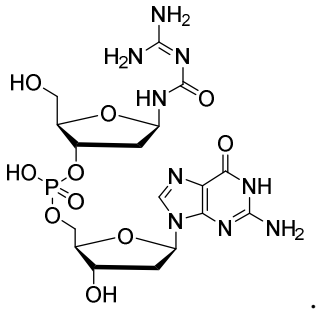
Formula (2), or a pharmaceutically-acceptable salt thereof, wherein:

R^1 is a 4-amino-2H-1λ^2,3,5-triazin-2-one or a carbamide, each of which is independently substituted or unsubstituted;

each R^2 and R^3 is independently alkyl, which is substituted or unsubstituted; or hydrogen; and

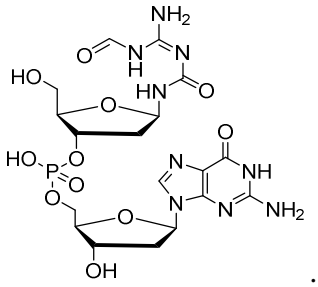
R^4 is hydrogen or an acyl group, each of which is independently substituted or unsubstituted.

2. The method of claim 1, wherein the compound of formula (2) is



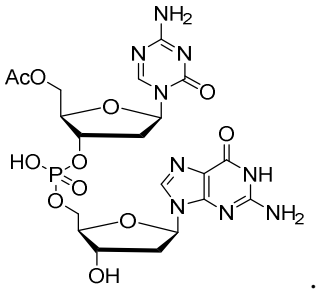
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3. The method of claim 1, wherein the compound of formula (2) is



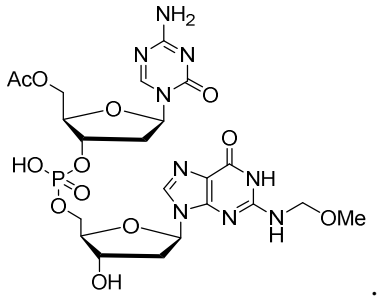
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4. The method of claim 1, wherein the compound of formula (2) is



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5. The method of claim 1, wherein the compound of formula (2) is



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6. The method of claim 1, wherein the freeze-drying process comprises:

   (a) a first freezing stage in which the solution is frozen by reducing a temperature of the solution to about -45 °C to form a frozen solution.

7. The method of claim 6, wherein the freeze-drying process further comprises:

   (b) a first warming stage in which the temperature of the solution is raised from about -45 °C to about 0 °C, wherein the solution remains frozen when the temperature of the solution is about 0 °C.

8. The method of claim 7, wherein the freeze-drying process further comprises:

   (c) a second freezing stage in which the temperature of the solution is lowered from about 0 °C to about -45 °C.

9. The method of claim 8, wherein the freeze-drying process further comprises:

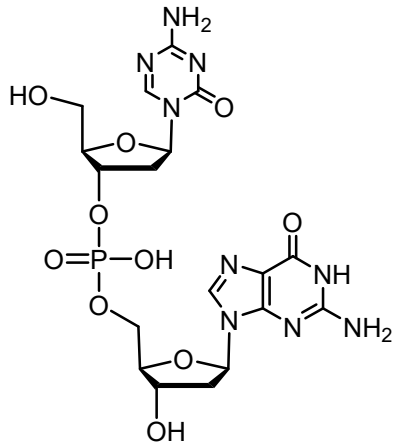
   (d) a primary drying stage in which the temperature of the solution is raised from about -45 °C to about -6 °C, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in a frozen state of the solution under reduced pressure to give a partially dried product.

10. The method of claim 9, wherein the freeze-drying process further comprises:

(e) a secondary drying stage in which the temperature of the solution is raised from about -6 °C to about 40 °C, wherein in the secondary drying stage the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized pharmaceutical product.

11. A method of preparing a lyophilized pharmaceutical product, the method comprising removing a portion of a solvent by a freeze-drying process from a solution, thereby generating the lyophilized pharmaceutical product, wherein the solution comprises:

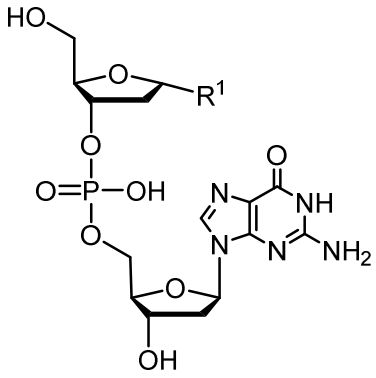
a) a compound of formula (1)



Formula (1), or a pharmaceutically acceptable salt thereof; and

b) the solvent, wherein the solvent comprises DMSO,

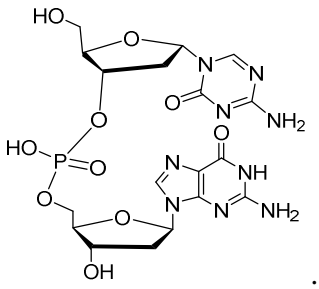
wherein the lyophilized pharmaceutical product comprises a compound of formula (3):



Formula (3),

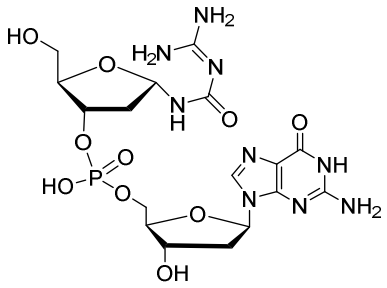
or a pharmaceutically acceptable salt thereof, wherein R^1 is 4-amino-2H-1λ^2,3,5-triazin-2-one or a carbamide, each of which is independently substituted or unsubstituted.

12. The method of claim 11, wherein the compound of formula (3) is



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13. The method of claim 11, wherein the compound of formula (3) is



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14. The method of claim 11, wherein the freeze-drying process comprises:

(a) a first freezing stage in which the solution is frozen by reducing a temperature of the solution to about -45 °C to form a frozen solution.

15. The method of claim 14, wherein the freeze-drying process further comprises:

(b) a first warming stage in which the temperature of the solution is raised from about -45 °C to about 0 °C, wherein the solution remains frozen when the temperature of the solution is about 0 °C.

16. The method of claim 15, wherein the freeze-drying process further comprises:

(c) a second freezing stage in which the temperature of the solution is lowered from about 0 °C to about -45 °C.

17. The method of claim 16, wherein the freeze-drying process further comprises:

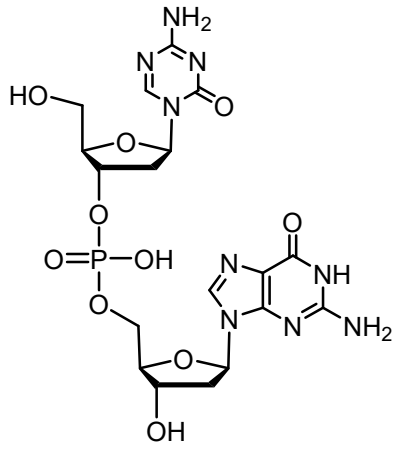
(d) a primary drying stage in which the temperature of the solution is raised from about -45 °C to about -6 °C, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in a frozen state of the solution under reduced pressure to give a partially dried product.

18. The method of claim 17, wherein the freeze-drying process further comprises:

(e) a secondary drying stage in which the temperature of the solution is raised from about -6 °C to about 40 °C, wherein in the secondary drying stage the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized pharmaceutical product.

19. A method of preparing a lyophilized pharmaceutical product, the method comprising removing a portion of a solvent by a freeze-drying process from a solution, thereby generating the lyophilized pharmaceutical product, wherein the solution comprises:

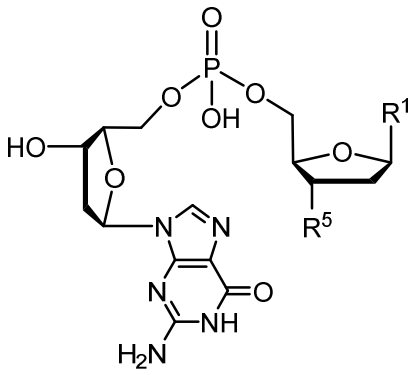
a) a compound of formula (1)



Formula (1), or a pharmaceutically acceptable salt thereof; and

b) the solvent, wherein the solvent comprises DMSO,

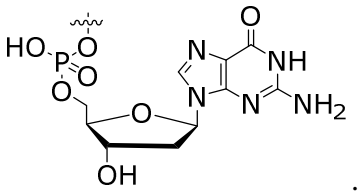
wherein the lyophilized pharmaceutical product comprises a compound of formula (4):



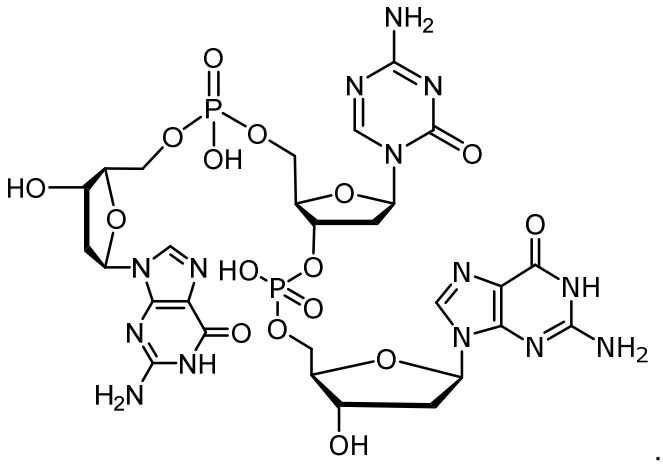
Formula (4),

or a pharmaceutically acceptable salt thereof, wherein R^1 is 4-amino-2H-1λ^2,3,5-triazin-2-one, which is substituted or unsubstituted; and R^5 is hydroxy or a nucleotide.

20. The method of claim 19, wherein the nucleotide has the formula:



21. The method of claim 19, wherein the compound of formula (4) is



22. The method of claim 19, wherein the freeze-drying process comprises:

(a) a first freezing stage in which the solution is frozen by reducing a temperature of the solution to about -45 °C to form a frozen solution.

23. The method of claim 22, wherein the freeze-drying process further comprises:

(b) a first warming stage in which the temperature of the solution is raised from about -45 °C to about 0 °C, wherein the solution remains frozen when the temperature of the solution is about 0 °C.

24. The method of claim 23, wherein the freeze-drying process further comprises:

(c) a second freezing stage in which the temperature of the solution is lowered from about 0 °C to about -45 °C.

25. The method of claim 24, wherein the freeze-drying process further comprises:

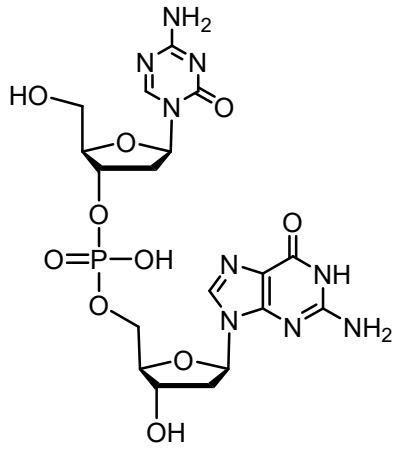
(d) a primary drying stage in which the temperature of the solution is raised from about -45 °C to about -6 °C, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in a frozen state of the solution under reduced pressure to give a partially dried product.

26. The method of claim 25, wherein the freeze-drying process further comprises:

(e) a secondary drying stage in which the temperature of the solution is raised from about -6 °C to about 40 °C, wherein in the secondary drying stage the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized pharmaceutical product.

27. A method of preparing a lyophilized pharmaceutical product, the method comprising removing a portion of a solvent by a freeze-drying process from a solution, thereby generating the lyophilized pharmaceutical product, wherein the solution comprises:

a) a compound of formula (1):



Formula (1), or a pharmaceutically-acceptable salt thereof; and

b) the solvent, wherein the solvent comprises DMSO, wherein the freeze-drying process comprises:

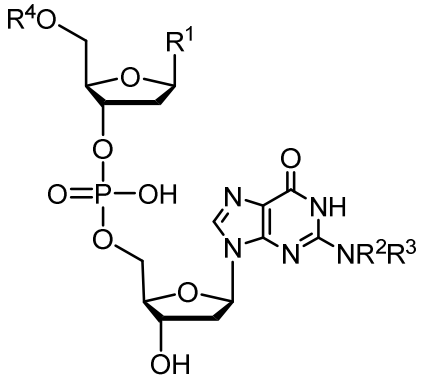
(i) a first freezing stage in which the solution is frozen by reducing a temperature of the solution to about -45 °C to form a frozen solution;

(ii) a first annealing stage in which the temperature of the solution is raised from about -45 °C to about 0 °C, wherein the solution remains frozen when the temperature of the solution is about 0 °C;

(iii) a second freezing stage in which the temperature of the solution is lowered from about 0 °C to about -45 °C;

(iv) a primary drying stage in which the temperature of the solution is raised from about -45 °C to about -6 °C, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in a frozen state of the solution under reduced pressure to give a partially dried product; and

(v) a secondary drying stage in which the temperature of the solution is raised from about -6 °C to about 40 °C, wherein in the secondary drying stage the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized pharmaceutical product, wherein the lyophilized pharmaceutical product comprises a compound of formula (2):



Formula (2), or a pharmaceutically-acceptable salt thereof, wherein:

R^1 is 4-amino-2H-1λ^2,3,5-triazin-2-one or a carbamide, each of which is independently substituted or unsubstituted.

each R^2 and R^3 is independently alkyl, which is substituted or unsubstituted; or hydrogen; and

R^4 is hydrogen or an acyl group, each of which is independently substituted or unsubstituted.