WHAT IS CLAIMED:

1. A process for preparing 5-azacytidine, or a ~~salt,~~ solvate, hydrate, or polymorph thereof, comprising the steps of reacting a silylated 5-azacytosine with a protected β-D-ribofuranose in the presence of a metallic Lewis acid to yield a protected 5-azacytidine, deprotecting the protected 5-azacytidine to yield 5-azacytidine, contacting the 5-azacytidine with an acid to yield a salt of 5-azacytidine, contacting the salt of 5-azacytidine with a base to yield 5-azacytidine, and ~~purifying~~ re-crystallizing the 5-azacytidine to yield 5-azacytidine, or a ~~salt,~~ solvate, hydrate, or polymorph thereof, that is ~~substantially~~ free of metal-based impurities.

2. The process of claim 1, wherein the total metal-based impurities in the purified 5-azacytidine, or ~~a salt,~~ solvate, hydrate, or polymorph thereof, are less than ~~about~~ 20 ppm w/w.

3. The process of claim 1, comprising the steps of:

(a) reacting 5-azacytosine with a silylating reagent to yield a silylated 5-azacytosine;

(b) reacting the silylated 5-azacytosine with an acyl protected β-D-ribofuranose in the presence of a metallic Lewis acid; and quenching the reaction with water and at least one neutralizing reagent to yield a protected 5-azacytidine;

(c) reacting the protected 5-azacytidine with a base, selected from the group consisting of alkoxide, ammonia, and tetra-substituted ammonium hydroxide, in an alcohol to yield 5-azacytidine; ~~and~~

(d) contacting the 5-azacytidine from step (c) with an acid in an organic solvent to yield a salt of 5-azacytidine~~.~~

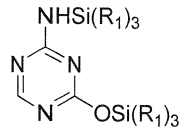
~~4. The process of claim 3, further comprising the step of:~~

(e) contacting the salt of 5-azacytidine from step (d) with a base in an organic solvent to yield 5-azacytidine free base~~.~~

~~5. The process of claim 4, further comprising the step of:~~

(f) re-crystallizing the 5-azacytidine from step (e).

~~6~~4. The process of ~~any one of claims 3 to 5~~claim 3, wherein the silylated 5-azacytosine is a compound of formula (A):



(A),

wherein each R_1 is independently optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, or optionally substituted C_6-C_{10} aryl.

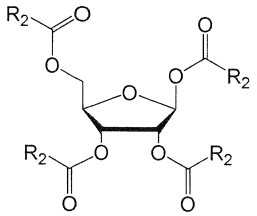
~~75~~75. The process of claim ~~64~~64, wherein R_1 is methyl.

~~86~~86. The process of any one of claims 3 to ~~75~~75, wherein the silylating reagent used in step (a) is a trimethylsilyl reagent.

~~97~~97. The process of any one of claims 3 to ~~86~~86, wherein the silylating reagent used in step (a) is hexamethyldisilazane.

~~108~~108. The process of any one of claims 3 to ~~97~~97, wherein the silylation reaction of step (a) is carried out in the presence of ammonium sulfate.

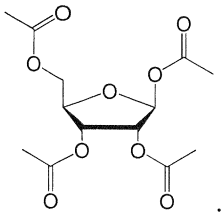
~~119~~119. The process of any one of claims 3 to ~~108~~108, wherein the protected β-D-ribofuranose is a compound of formula (B):



(B),

wherein each R_2 is independently hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, or optionally substituted C_6-C_{10} aryl.

~~1210~~1210. The process of any one of claims 3 to ~~108~~108, wherein the protected β-D-ribofuranose is:



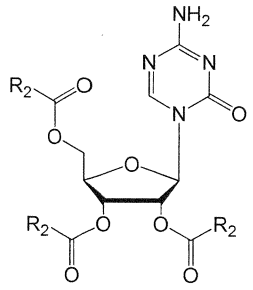
.

~~13~~11. The process of any one of claims 3 to ~~12~~10, wherein the metallic Lewis acid is stannic chloride or ferric chloride.

~~14~~12. The process of any one of claims 3 to ~~12~~10, wherein the metallic Lewis acid is stannic chloride.

~~15~~13. The process of any one of claims 3 to ~~12~~10, wherein the metallic Lewis acid is ferric chloride.

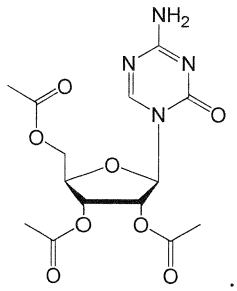
~~16~~14. The process of any one of claims 3 to ~~11~~9 and ~~13~~11 to ~~15~~13, wherein the protected 5-azacytidine is a compound of formula (C):



(C),

wherein each R_2 is independently hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, or optionally substituted C_6-C_{10} aryl.

~~17~~15. The process of any one of claims 3 to ~~15~~13, wherein the protected 5-azacytidine is:



~~18~~16. The process of any one of claims 3 to ~~17~~15, wherein the coupling reaction of step (b) is carried out in a solvent with low water solubility.

~~19~~17. The process of claim ~~18~~16, wherein the solvent with low water solubility is dichloromethane.

~~20~~18. The process of any one of claims 3 to ~~19~~17, wherein the coupling reaction of step (b) is carried out at a temperature of between ~~about~~ 0°C and ~~about~~ 5°C.

~~21~~19. The process of any one of claims 3 to ~~20~~18, wherein the neutralizing reagent in step (b) is a carbonate or bicarbonate salt.

~~22~~20. The process of any one of claims 3 to ~~20~~18, wherein the neutralizing reagent in step (b) is sodium bicarbonate.

~~23~~21. The process of any one of claims 3 to ~~22~~20, wherein the reaction of step (b) is quenched at a temperature of less than ~~about~~ 10°C.

~~24~~22. The process of any one of claims 3 to ~~23~~21, wherein the base in step (c) is an alkoxide.

~~25~~23. The process of claim ~~24~~22, wherein the alkoxide is sodium methoxide.

~~26~~24. The process of any one of claims 3 to ~~25~~23, wherein the alcohol in step (c) is methanol.

~~27~~25. The process of any one of claims 3 to ~~26~~24, wherein the acid used in step (d) is hydrochloric acid, hydrobromic acid, sulfuric acid, or methanesulfonic acid.

~~28~~26. The process of any one of claims 3 to ~~26~~24, wherein the acid used in step (d) is hydrochloric acid.

~~29~~27. The process of any one of claims 3 to ~~28~~26, wherein the organic solvent used in step (d) is an alcohol.

~~30~~28. The process of any one of claims 3 to ~~29~~27, wherein the organic solvent used in step (d) is methanol.

~~31~~29. The process of any one of claims 3 to ~~30~~28, wherein the salt of 5-azacytidine formed in step (d) is 5-azacytidine mono-hydrochloride salt.

~~32~~30. The process of any one of claims ~~4 to 31~~3 to 29, wherein the base used in step (e) is an organic base.

~~33~~31. The process of claim ~~32~~30, wherein the organic base is triethylamine.

~~34~~32. The process of any one of claims ~~4 to 33~~3 to 31, wherein the organic solvent used in step (e) is an alcohol.

~~35~~33. The process of any one of claims ~~4 to 34~~3 to 32, wherein the organic solvent used in step (e) is methanol.

~~36~~34. The process of any one of claims ~~5 to 35~~3 to 33, wherein step (f) comprises the steps of:

(1) dissolving 5-azacytidine from step (e) in dimethylsulfoxide at a temperature sufficient to allow the 5-azacytidine to dissolve; and optionally filtering the solution to remove insoluble particles;
(2) adding an anti-solvent to the solution of step (1); and
(3) cooling the mixture of step (2) wherein 5-azacytidine re-crystallizes.

~~37~~35. The process of claim ~~36~~34, wherein the anti-solvent of step (f)(2) is an alcohol.

~~38~~36. The process of claim ~~36 or 37~~34 or 35, wherein the anti-solvent of step (f)(2) is methanol.

~~39~~37. The process of any one of claims ~~36 to 38~~34 to 36, wherein step (f) further comprises the steps of:
(4) collecting the re-crystallized 5-azacytidine from step (3) by filtration; and

(5) drying the 5-azacytidine from step (4) under vacuum.

~~40~~38. ~~A~~ The process of any one of claims 3 to 39, wherein the salt of 5-azacytidine formed in step (d), is selected from the group consisting of hydrochloride salt, hydrobromide salt, a mesylate salt and sulfate salt.

~~41~~39. The ~~salt~~ process of claim ~~40~~38, wherein the salt is a mono-hydrochloride salt of 5-azacytidine.

~~42~~40. The ~~salt~~ process of claim ~~40~~38, wherein the salt is a mono-hydrobromide salt of 5-azacytidine.

~~43~~41. The ~~salt~~ process of claim ~~40~~38, wherein the salt is a hemisulfate salt of 5-azacytidine, which is a methanol solvate.

~~44~~42. The ~~salt~~ process of claim ~~40~~38, wherein the salt is a mesylate salt of 5-azacytidine.

~~45~~43. The ~~salt~~ process of any one of claims ~~40 to 44~~38 to 42, wherein the salt is ~~substantially~~ free of impurities.

~~46~~44. The ~~salt~~ process of any one of claims ~~40 to 45~~38 to 42, wherein the salt is ~~substantially~~ crystalline.

~~47. 5-Azacytidine, or a salt, solvate, hydrate, or polymorph thereof, prepared by the process of any one of claims 1 to 39.~~

~~48. 5-Azacytidine, or a salt, solvate, hydrate, or polymorph thereof, obtainable from the process of any one of claims 1 to 39.~~

~~49. The 5-azacytidine, or a salt, solvate, or hydrate thereof, which is substantially crystalline.~~