Claims

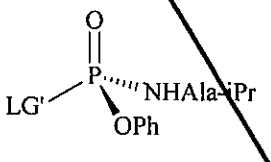
1. Crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate having XRPD 2θ-reflections (°) at about: 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3.

2. A composition comprising crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of claim 1.

3. A pharmaceutical composition comprising crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of claim 1 and a pharmaceutically acceptable medium.

4. Crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of claim 1 for use in the treatment of a hepatitis C virus infection.

5. A compound represented by the structural formula

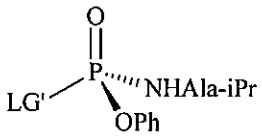


wherein LG' is a leaving group selected from the group consisting of benzo[d]thiazolide-2(3H)-thione, 2-nitrophenoxide, 2-chloro-4-nitrophenoxide and 2,4-dichlorophenoxide.

6. (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl)amino) propanoate.

7. Crystalline (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy) phosphoryl)amino)propanoate.

8. A process for preparing a compound a compound represented by the structural formula:



wherein LG' is a leaving group, which comprises:

crystallizing the compound from a composition comprising

a) a first composition;

b) a second leaving group precursor;

c) a non-nucleophilic base; and

d) a liquid composition;

wherein the first composition comprises the compound and its corresponding P-based diastereomer.

9. The process of claim 8, wherein the mole amount of the compound is greater than the mole amount of its corresponding P-based diastereomer.

10. The process of claim 8, wherein the second leaving group precursor is 2,4-dinitrophenol, 4-nitrophenol, 2-nitrophenol, 2-chloro-4-nitrophenol, 2,4-dichlorophenol, or pentafluorophenol.

11. The process of claim 8, wherein the amount of the second leaving group precursor ranges from about 0.01 mole equivalents to about 10 mole equivalents relative to the mole amount of the compound and its P-based diastereomer.

12. The process of claim 11, wherein the amount of the second leaving group precursor ranges from about 0.1 mole equivalents to about 1 mole equivalents relative to the mole amount of the compound and its P-based diastereomer.

13. The process of claim 8, wherein the crystallizing occurs at a temperature that ranges from about -10°C to about +40°C.

14. The process of claim 8, wherein the crystallizing occurs at about room temperature.

15. The process of claim 8, wherein the non-nucleophilic base is selected from among potassium carbonate, cesium carbonate, di-isopropylamine, di-isopropylethylamine, triethylamine, quinuclidine, naphthalene-1,8-diamine, 2,2,6,6-tetramethylpiperidine, 1,8-diazabicycloundec-7-ene, 4-dimethylamino-pyridine, pyridine, a 2,6-di-C_{1-6}-alkyl-pyridine, a 2,4,6-tri-C_{1-6}-alkyl-pyridine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4- diazabicyclo[2.2.2]octane, and mixtures thereof.

16. The process of claim 8, wherein the non-nucleophilic base is triethylamine.

17. The process of claim 8, wherein the non-nucleophilic base is present in an amount that ranges from about 0.01 mol equivalents to about 10 mol equivalents relative to the total mole amount of the compound and its P-based diastereomer.

18. The process of claim 8, wherein the non-nucleophilic base is present in an amount that ranges from about 0.1 mol equivalents to about 1 mol equivalents relative to the total mole amount of the compound and its P-based diastereomer.

19. The process of claim 8, wherein the solubility of the compound is less than the solubility of its corresponding P-based diastereomer in the liquid composition.

20. The process of claim 8, wherein the liquid composition comprises at least one of a solvent and an anti-solvent.

21. The process of claim 8, wherein the liquid composition comprises at least one of a C_1 to C_8 alcohol, a C_2 to C_8 ether, a C_3 to C_7 ketone, a C_3 to C_7 ester, a C_1 to C_2 chlorocarbon, a C_2 to C_7 nitrile, a C_5 to C_{12} saturated hydrocarbon, and a C_6 to C_{12} aromatic hydrocarbon.

22. The process of claim 8, wherein the liquid composition comprises at least one of a C_2 to C_8 ether, a C_3 to C_7 ester, a C_5 to C_{12} saturated hydrocarbon, and a C_6 to C_{12} aromatic hydrocarbon.

23. The process of claim 8, wherein the liquid composition comprises at least one of a C_2 to C_8 ether, a C_3 to C_7 ester, and a C_5 to C_{12} saturated hydrocarbon.

24. The process of claim 23, wherein the liquid composition comprises at least one of ethyl acetate, t-butyl-methylether, and hexane.

25. The process of claim 23, wherein the liquid composition comprises ethyl acetate and hexane.

26. The process of claim 23, wherein the liquid composition comprises t-butyl-methylether and hexane.

27. The process of claim 8, wherein the amount of liquid composition ranges from about 1 mL to about 10 mL for every gram of the first composition.

28. The process of claim 8, which further comprises adding crystalline compound to the composition.

29. The process of claim 8, which further comprises adding about 0.1 to about 1 wt. % of crystalline compound to the first composition.

30. The process of claim 8, which further comprises

a) reacting $PhOP(O)(LG)_2$ and ^{i}Pr-Ala-NH_2•HCl in the presence of a first base to obtain (PhO)P(O)(LG)(NHAla-^{i}Pr);

b) reacting (PhO)P(O)(LG)(NHAla-^{i}Pr) with a first leaving group precursor (LG'H) in the presence of a second base to obtain the composition comprising the compound and its P-based diastereomer;

wherein LG and LG', independent of each other, are leaving groups;

wherein the first leaving group precursor and the second leaving group precursor are the same or different; and

wherein the first base and the second base are the same or different.

31. A process for preparing crystalline (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate, which comprises:

crystallizing (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl) amino)propanoate from a second composition comprising

a) a first composition;

b) pentafluorophenol;

c) a non-nucleophilic base; and

d) a liquid composition;

wherein the first composition comprises (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate and (S)-isopropyl 2-(((R)-(perfluorophenoxy)(phenoxy)phosphoryl)amino) propanoate.

32. The process of claim 31, wherein the mole amount of the (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate is greater than the mole amount of (S)-isopropyl 2-(((R)-(perfluorophenoxy)(phenoxy)phosphoryl) amino)propanoate.

33. The process of claim 31, wherein the amount of pentafluorophenol ranges from about 0.01 mole equivalents to about 10 mole equivalents relative to the mole amount of (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl) amino)propanoate and (S)-isopropyl 2-(((R)-(perfluorophenoxy)(phenoxy) phosphoryl)amino)propanoate.

34. The process of claim 31, wherein the crystallizing occurs at a temperature that ranges from about -10°C to about +40°C.

35. The process of claim 31, wherein the crystallizing occurs at about room temperature.

36. The process of claim 31, wherein the non-nucleophilic base is selected from among potassium carbonate, cesium carbonate, di-isopropylamine, di-isopropylethylamine,

triethylamine, quinuclidine, naphthalene-1,8-diamine, 2,2,6,6-tetramethylpiperidine, 1,8-diazabicycloundec-7-ene, 4-dimethylamino-pyridine, pyridine, a 2,6-di-C_{1-6}-alkyl-pyridine, a 2,4,6-tri-C_{1-6}-alkyl-pyridine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4- diazabicyclo[2.2.2]octane, and mixtures thereof.

37. The process of claim 31, wherein the non-nucleophilic base is triethylamine.

38. The process of claim 31, wherein the non-nucleophilic base is present in an amount that ranges from about 0.1 to about 1 mol equivalents relative to the total mole amount of (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl) amino)propanoate and (S)-isopropyl 2-(((R)-(perfluorophenoxy)(phenoxy) phosphoryl)amino)propanoate.

39. The process of claim 31, wherein the solubility of (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate is less than the solubility of (S)-isopropyl 2-(((R)-(perfluorophenoxy)(phenoxy)phosphoryl)amino) propanoate in the liquid composition.

40. The process of claim 31, wherein the liquid composition comprises at least one of a solvent and an anti-solvent.

41. The process of claim 31, wherein the liquid composition comprises at least one of a C_1 to C_8 alcohol, a C_2 to C_8 ether, a C_3 to C_7 ketone, a C_3 to C_7 ester, a C_1 to C_2 chlorocarbon, a C_2 to C_7 nitrile, a C_5 to C_{12} saturated hydrocarbon, and a C_6 to C_{12} aromatic hydrocarbon.

42. The process of claim 31, wherein the liquid composition comprises at least one of a C_2 to C_8 ether, a C_3 to C_7 ester, a C_5 to C_{12} saturated hydrocarbon, and a C_6 to C_{12} aromatic hydrocarbon.

43. The process of claim 31, wherein the liquid composition comprises at least one of a C_2 to C_8 ether, a C_3 to C_7 ester, and a C_5 to C_{12} saturated hydrocarbon.

44. The process of claim 43, wherein the liquid composition comprises at least one of ethyl acetate, t-butyl-methylether, and hexane.

45. The process of claim 43, wherein the liquid composition comprises ethyl acetate and hexane.

46. The process of claim 43, wherein the liquid composition comprises t-butyl-methylether and hexane.

47. The process of claim 31, wherein the amount of liquid composition ranges from about 1 to about 10 mL for every gram of the first composition.

48. The process of claim 31, which further comprises adding crystalline (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate to the second composition.

49. The process of claim 31, which further comprises adding about 0.1 to about 1 wt. % of crystalline (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy) phosphoryl)amino)propanoate based on the total weight of (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate in the first composition.

50. Crystalline (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy) phosphoryl)amino)propanoate obtained by the process of claim 31.

51. A process for preparing (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, which comprises:

crystallizing (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl) amino)propanoate from a second composition comprising

a) a first composition;

b) pentafluorophenol;

c) a non-nucleophilic base; and

d) a liquid composition;

wherein the first composition comprises (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate and (S)-isopropyl 2-(((R)-(perfluorophenoxy)(phenoxy)phosphoryl)amino) propanoate.

52. A process for preparing (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, which comprises:

contacting (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl) amino)propanoate with a product obtained by reacting a t-butylmagnesium halide with 1-((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione.

53. The process of claim 52, wherein the contacting occurs in a medium having a temperature that ranges from about 0°C to about 40°C.

54. The process of claim 52, wherein the contacting occurs in a medium having a temperature that ranges from about 0°C to about 30°C.

55. The process of claim 52, wherein the mole ratio of t-butylmagnesium halide to 1-((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione ranges from about 2 to about 2.2.

56. The process of claim 52, wherein the mole ratio of t-butylmagnesium halide to 1-((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione is about 2.1.

57. The process of claim 52, wherein the t-butylmagnesium halide is t-butylmagnesium chloride.

58. A process for preparing substantially pure (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, which comprises:

obtaining (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate according to the process of claim 63 and

crystallizing the so-formed (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate.

59. The process of claim 31, wherein the non-nucleophilic base is present in an amount that ranges from about 0.01 mol equivalents to about 10 mol equivalents relative to the total mole amount of (S)-isopropyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl) amino)propanoate and (S)-isopropyl 2-(((R)-(perfluorophenoxy)(phenoxy) phosphoryl)amino)propanoate.

60. A process for preparing substantially pure (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, which comprises:

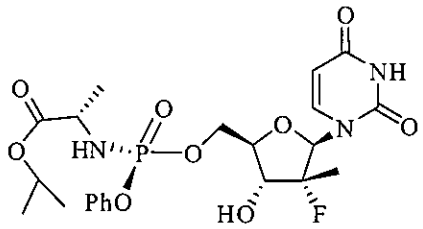
obtaining (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate according to the process of claim 64 and

crystallizing the so-formed (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate.

61. Crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of claim 1 for use in the treatment of a hepatitis C virus infection in a human.

Claims

1. Crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate represented by the formula S_P-**4**:

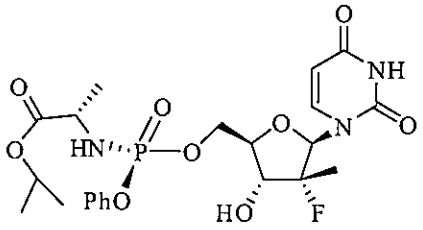


S_P-**4**

having XRPD 2θ-reflections (°) at about: 6.1 and 12.7.

2. Crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of claim 1 further having XRPD 2θ-reflections (°) at about: 8.2, 10.4, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3.

3. Crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate represented by the formula S_P-**4**:



S_P-**4**

having XRPD 2θ-reflections (°) at about 6.08, 8.2, 10.38, 10.85, 12.17, 12.7, 13.73, 14.1, 15.91, 16.83, 17.17, 17.66, 17.95, 18.79, 19.1, 19.41, 19.8, 20.11, 20.82, 21.81, 22.03, 23.03, 23.26, 23.64, 23.89, and 24.73.

4. The crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of claim 3, wherein the XRPD 2θ-reflections (°) at about 6.08, 8.2, 10.38, 10.85, 12.17, 12.7, 13.73, 14.1, 15.91, 16.83, 17.17, 17.66, 17.95, 18.79, 19.1, 19.41, 19.8, 20.11, 20.82, 21.81, 22.03, 23.03, 23.26, 23.64, 23.89, and 24.73 have intensities (%) of 66.7, 62.1, 29.8, 10.4, 12.0, 66.4, 14.9, 13.8, 3.1, 8.7, 19.7, 56.2, 37.7, 59.0, 14.3, 37.2, 46.0, 68.8, 100.0, 36.8, 7.4, 14.2, 21.6, 6.3, 7.0, and 3.3, respectively.

5. A composition comprising crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of any one of claims 1-4.

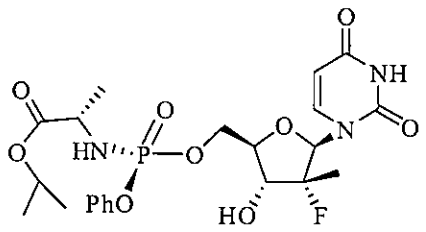
6. A pharmaceutical composition comprising crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of any one of claims 1-4 and a pharmaceutically acceptable medium.

7. Crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of any one of claims 1-4 for use in the treatment of a hepatitis C virus infection.

8. Crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of any one of claims 1-4 for use in the treatment of a hepatitis C virus infection in a human.

9. A process for preparing crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of any one of claims 1-4 comprising:

exposing a second crystalline compound represented by the formula S_P-**4**:



S_P-4

having XRPD 2θ-reflections (°) at about

(1) 5.2, 7.5, 9.6, 16.7, 18.3, 22.2, or

(2) 5.0, 7.3, 9.4, and 18.1

to atmospheric humidity to provide a first composition.

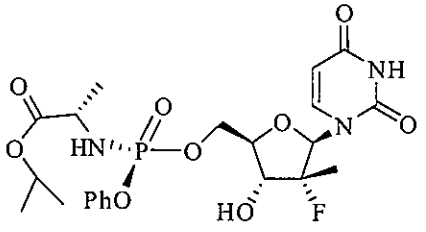
10. The process according to claim 9 further comprising:

grinding the first composition into a powder; and

allowing the powder to stand in an open vessel.

11. A process for preparing crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of any one of claims 1-4 comprising:

suspending a second crystalline compound represented by the formula S_P-4:



S_P-4

having XRPD 2θ-reflections (°) at about

(a) 5.2, 7.5, 9.6, 16.7, 18.3, 22.2, or

(b) 5.0, 7.3, 9.4, and 18.1

in water to provide a suspension.

12. The process according to claim 11 further comprising heating the suspension.

13. The process according to claim 12 further comprising cooling the suspension.