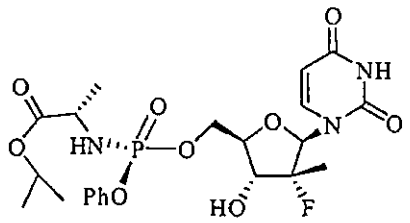
Claims

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:

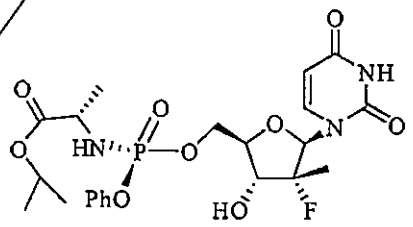


S_P-4

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.

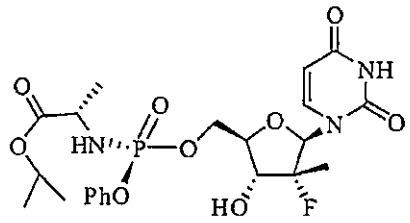
6. A pharmaceutical composition comprising crystalline (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate of any one of claims 1-4 and a pharmaceutically acceptable medium.

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.

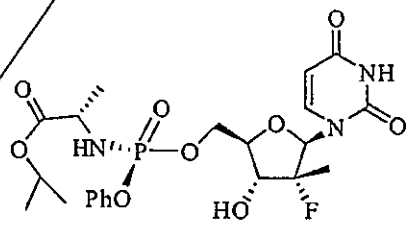
10. The process according to claim 9 further comprising:

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

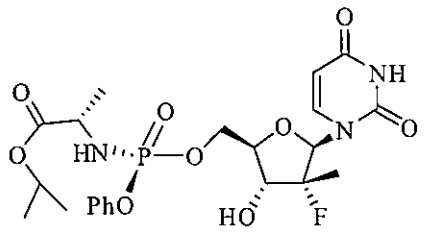
in water to provide a suspension.

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

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

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 (± 0.2°) at 6.1 and 12.7.

2. 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 1 further having XRPD 2θ-reflections (± 0.2°) at 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. 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 1 or 2 having XRPD 2θ-reflections (± 0.2°) at 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 (± 0.2°) at 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 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 another antiviral agent.

10. The pharmaceutical composition of claim 9, wherein the another antiviral agent is an HCV NS3 inhibitor.

11. The pharmaceutical composition of claim 9, wherein the another antiviral agent is an HCV NS5A inhibitor.

12. 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 combination with another antiviral agent.

13. 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 combination with another antiviral agent, wherein the another antiviral agent is an HCV NS3 inhibitor.

14. 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 combination with another antiviral agent, wherein the another antiviral agent is an HCV NS5A inhibitor.