Claims

1. A method of providing at least one diastereoisomer of gemcitabine-[phenyl-benzoxy-L-alaninyl)]-phosphate in a diastereoisomeric purity of greater than 85%, the method comprising the steps of:

suspending a mixture of gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*R*)-phosphate and gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate in a solvent or a mixture of solvents to form a slurry; and

filtering the slurry to provide solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-phosphate and a filtrate comprising gemcitabine-[phenyl-benzoxy-L-alaninyl)]-phosphate dissolved in the solvent or mixture of solvents;

wherein the solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-phosphate is gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*R*)-phosphate in a diastereoisomeric purity of greater than 85% and/or the filtrate comprises gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate in a diastereoisomeric purity of greater than 85%.

2. A method of claim 1, wherein the slurry is heated once formed; optionally to a temperature from 30°C to 80°C.

3. A method of claim 2, wherein the slurry is not cooled prior to filtration.

4. A method of any one of claims 1 to 3, further comprising the step of washing the solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-phosphate.

5. A method of any one of claims 1 to 4, wherein the method is a method of providing gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate in a diastereoisomeric purity of greater than 85%and wherein the method further comprises the step of removing the solvent(s) from the filtrate comprising gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate to obtain solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate in a diastereoisomeric purity of greater than 85%.

6. A method of claim 5, wherein the step of removing the solvent or mixture of solvents comprises:

removing a portion of the solvent or mixture of solvents from the filtrate comprising gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate by evaporation, e.g. by distillation or evaporation under reduced pressure, to provide a concentrated filtrate comprising solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate;

optionally agitating the concentrated filtrate; and

filtering the concentrated filtrate to obtain gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate as a solid in in a diastereoisomeric purity of greater than 85%.

7. A method of claim 5, wherein the step of removing the solvent or mixture of solvents comprises:

cooling the filtrate comprising gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate to provide a cooled filtrate comprising solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate;

optionally agitating the cooled filtrate; and

filtering the cooled filtrate to obtain gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate as a solid in in a diastereoisomeric purity of greater than 85%.

8. A method of claim 7, further comprising the step of adding seed material to the filtrate.

9. A method of claim 7 or claim 8, further comprising the step of adding additional solvent to the filtrate.

10. A method of any one of claims 7 to 9, further comprising washing the solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate in a diastereoisomeric purity of greater than 85%.

11. A method of any one of claims 1 to 4, wherein the method is a method of providing gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*R*)-phosphate in a diastereoisomeric purity of greater than 85%;

optionally wherein the method further comprises the steps:

suspending solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-phosphate obtained from the first filtration in a second solvent or a second mixture of solvents to form a second slurry; and

filtering the second slurry to provide solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*R*)-phosphate in a diastereoisomeric purity of greater than 85%.

12. A method of any one of claims 1 to 11, wherein the solvent is or the solvent mixture comprises a solvent selected from a polar protic solvent and a polar aprotic solvent.

13. A method of claim 12, wherein the solvent is or the solvent mixture comprises isopropyl alcohol.

14. A method of claim 13, wherein the solvent is isopropyl alcohol.

15. A method of claim 12, wherein the solvent is or the solvent mixture comprises acetonitrile.