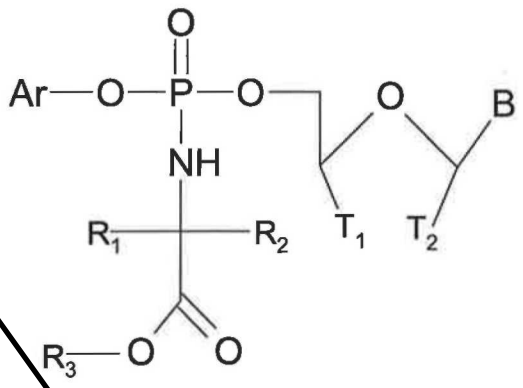
CLAIMS

1. A process for the preparation of a compound of Formula I, wherein Formula I is:

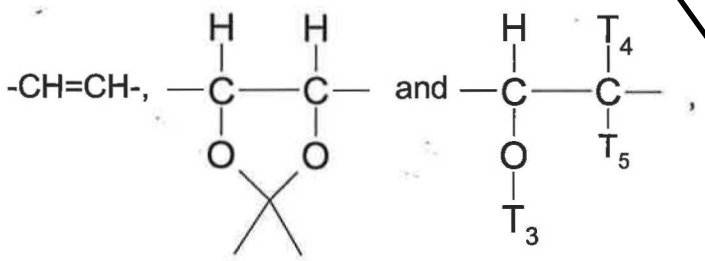


wherein:

Ar is selected from C_{6-30}aryl and C_{6-30}heteroaryl, each of which is optionally substituted;

R_1, R_2 and R_3 are, independently, selected from H and the group consisting of C_{1-20}alkyl, C_{2-20}alkenyl, C_{1-20}alkoxy, C_{1-20}alkoxyC_{1-20}alkyl, C_{1-20}alkoxyC_{6-30}aryl, C_{2-20}alkynyl, C_{3-20}cycloalkylC_{6-30}aryl, C_{6-30}aryloxy and C_{5-20}heterocyclyl, any of which is optionally substituted;

T_1 and T_2 are linked together and together are selected from the group consisting of:

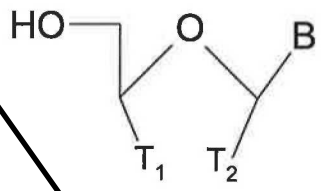


where T_3 is selected from the group consisting of H and –COOC_{1-6}alkyl and T_4 and T_5 are, independently, selected from the group consisting of H, F, Cl, Br, I, OH and methyl (CH_3);

and B is a heterocyclic moiety selected from optionally substituted purine and optionally substituted pyrimidine;

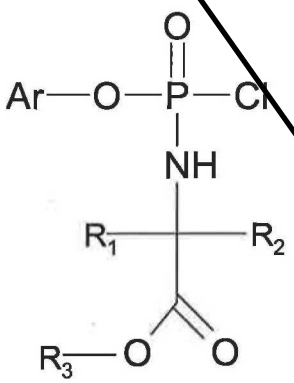
comprising the steps of:

(i) dissolving a compound of Formula II in a solvent selected from the group consisting of an ethereal solvent, acetonitrile and mixtures thereof and admixing the dissolved compound of Formula II with a base, wherein Formula II is:



where T_1, T_2 and B have the same meanings set out with respect to Formula I;

(ii) admixing the product of step (i) with a compound of Formula III, wherein Formula III is:



where Ar, R_1, R_2 and R_3 have the same meanings set out with respect to Formula I,

wherein step (ii) takes place in the presence of a catalyst comprising a metal salt wherein the metal salt is selected from the group consisting of metal salts of Cu, Fe, La and Yb; and

wherein the base employed in step (i) is selected from the group consisting of: $NR_4R_5R_6$, where R_4, R_5 and R_6 are selected, independently, from the group consisting of $C_{1\text{-}3}$alkyl and H, provided that at least two of R_4, R_5 and R_6 are, independently, $C_{1\text{-}3}$alkyl; and 1,8-diazabicyclo[5.4.0]undec-7-ene.

2. The process of claim 1 wherein the catalyst is admixed with the nucleoside compound of Formula II, prior to the dissolution of the compound of Formula II in the solvent of step (i).

3. The process of claim 1 or claim 2 wherein the catalyst is a copper salt.

4. The process of claim 3 wherein the catalyst is selected from the group consisting of $Cu(OTf)_2$, CuCl, CuBr, CuI, $Cu(OAc)_2$ and $CuSO_4$, and preferably, is $Cu(OTf)_2$.

5. The process of claim 3 wherein the catalyst is selected from the group consisting of $Cu(OAc)_2$ and $Cu(OC(O)CF_3)_2$.

6. The process of claim 1 or claim 2 wherein the catalyst is a metal salt with a metal in an oxidation state of more than 1.

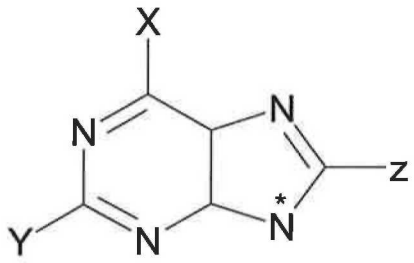
7. The process of claim 6 wherein the metal salt is an OTf salt.

8. The process of claim 7 wherein the metal salt is selected from the group consisting of $Cu(OTf)_2$, $Yb(OTf)_3$, $Fe(OTf)_3$ and $La(OTf)_3$ and, preferably, is $Cu(OTf)_2$.

9. The process of any one of claims 1 to 3 wherein the catalyst comprises a metal salt in which a metal component is in the form of a complex where a metal cation component is co-ordinated with one or more ligands.

10. The process of claim 9 wherein the metal salt is selected from the group consisting of $Cu(MeCN)_4 \cdot CF_3SO_3$ and $Cu(OTf) \cdot C_6H_6$.

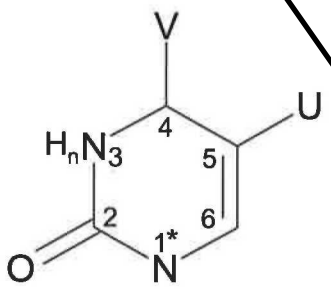
11. The process of any one of claims 1 to 10 wherein B in the compounds of Formulae I and II is the optionally substituted purine, where the N atom marked with * links directly to the C1 atom of the sugar moiety:



where each of X and Z is, independently, selected from H, OH, F, Cl, Br, I, OC_{1-6}alkyl, C_{1-6}alkyl and NR_7R_8, where each of R_7 and R_8 is, independently, selected from H and C_{1-6}alkyl; and

Y is selected from H, OH, OC_{1-6}alkyl, SH, SC_{1-6}alkyl, F, Cl, Br, I, C_{1-6}alkyl, C_{2-8}alkynyl and NR_9R_{10} where each of R_9 and R_{10} is, independently, selected from H and C_{1-6} alkyl.

12. The process of any one of claims 1 to 10 wherein B in the compounds of Formulae I and II is the optionally substituted pyrimidine , where the N atom marked with * links directly with the C1 atom of the sugar moiety:



where U is selected from the group consisting of H, C_{1-6}alkyl, F, Cl, Br and I; and

n is 0 or 1,

wherein

when n is 0, V is $-NH_2$ and a double bond exists between position 3 and position 4, and when n is 1, V is =O.

13. The process of any one of claims 1 to 12 wherein B comprises one or more members selected from the group consisting of: an NH moiety, where N is a heteroatom in an aromatic ring moiety of B, and one or more exocyclic heteroatoms selected from the group consisting of N, O, S and Cl directly linked to an aromatic ring moiety of B.

14. The process of any one of claims 1 to 13 wherein the compounds of Formulae I and II have T_1 and T_2 comprising T_3, T_4 and T_5.

15. The process of any one of claims 1 to 14 wherein the compounds of Formulae I and III have Ar as naphthyl or phenyl and, preferably, is naphthyl.

16. The process of any one of claims 1 to 15 wherein R_1 is selected from the group consisting of a tertiary alkyl moiety and benzyl.

17. The process of any one of claims 1 to 16 wherein at least one of R_2 and R_3 is a secondary or tertiary alkyl moiety.

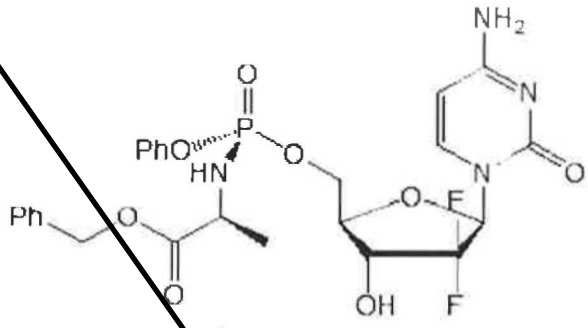
18. The process of any one of claims 1 to 17 wherein the ethereal solvent employed in step (i) is selected from the group consisting of 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane, diethyl ether, anisole, dimethoxybenzene and mixtures thereof.

19. The process of any one of claims 1 to 18 including further steps of removing the solvent and subjecting the residue to column chromatography.

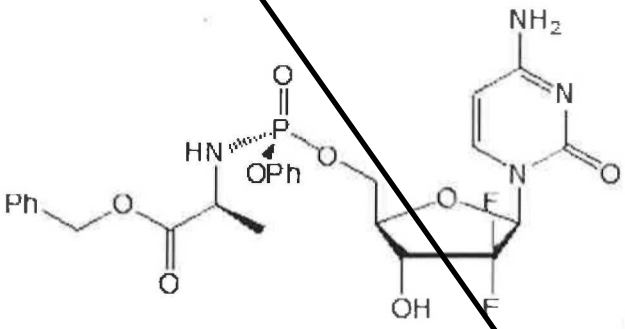
20. The process of any one of claims 1, 2, 3 and any one of claims 11 to 19 provided said claim of claims 11 to 19 is dependent on claim 3, wherein the metal salt is Cu(OAc).

21. The process of any one of claims 1, 2, 6 and any one of claims 11 to 19 provided said claim of claims 11 to 19 is dependent on claim 6, wherein the metal salt is selected from the group consisting of tris(acetylacetonato)iron(III) and bis(acetylacetonato)iron(II).

22. The product of any one of claims 1 to 21, wherein the product comprises a ratio of R_P enantiomer to S_P enantiomer that is greater than 2, more preferably greater than 5, even more preferably greater than 7.5;
wherein Rp is of a form gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*R*)-phosphate with a structure:

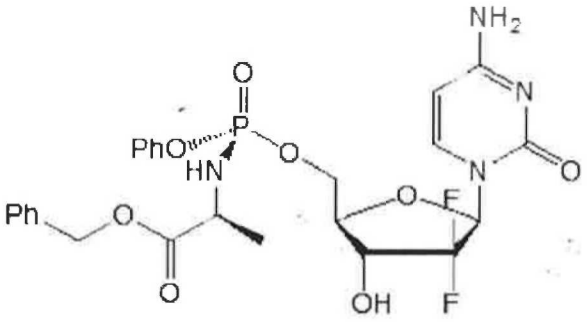


and wherein the Sp is of a form gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate with a structure:

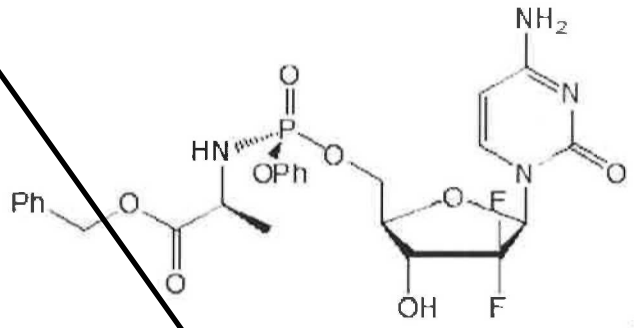


23. The product of any one of claims 1 to 21, wherein the product comprises a ratio of S_P enantiomer to R_P enantiomer that is greater than 2, more preferably greater than 5, even more preferably greater than 7.5;

wherein Rp is of a form gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*R*)-phosphate with a structure:



and wherein the Sp is of a form gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate with a structure:

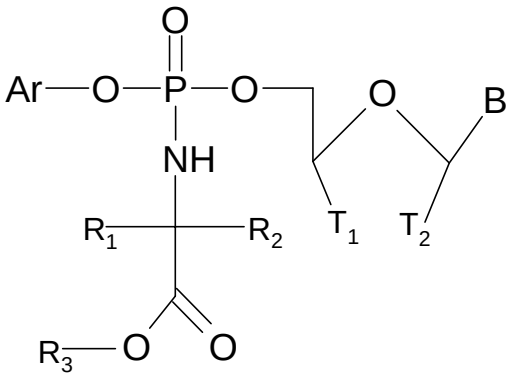


24. A pharmaceutical composition comprising the product of claim 22 or claim 23 together with pharmaceutical acceptable carrier, diluent or excipient.

25. The use of the pharmaceutical composition of claim 24 in the manufacture of a medicament for the treatment of a cancer or a viral infection, suitably in *homo sapiens*.

CLAIMS

1. A process for the preparation of a compound of Formula I, wherein Formula I is:

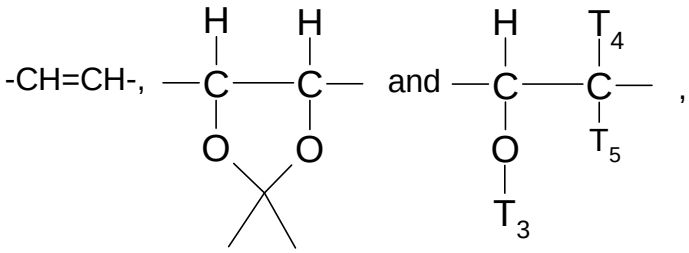


wherein:

Ar is selected from C_{6-30}aryl and C_{6-30}heteroaryl, each of which is optionally substituted;

R_1, R_2 and R_3 are, independently, selected from H and the group consisting of C_{1-20}alkyl, C_{2-20}alkenyl, C_{1-20}alkoxy, C_{1-20}alkoxyC_{1-20}alkyl, C_{1-20}alkoxyC_{6-30}aryl, C_{2-20}alkynyl, C_{3-20}cycloalkylC_{6-30}aryl, C_{6-30}aryloxy and C_{5-20}heterocyclyl, any of which is optionally substituted;

T_1 and T_2 are linked together and together are selected from the group consisting of:

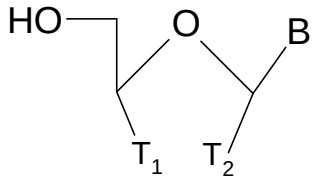


where T_3 is selected from the group consisting of H and –COOC_{1-6}alkyl and T_4 and T_5 are, independently, selected from the group consisting of H, F, Cl, Br, I, OH and methyl (CH_3);

and B is a heterocyclic moiety selected from optionally substituted purine and optionally substituted pyrimidine;

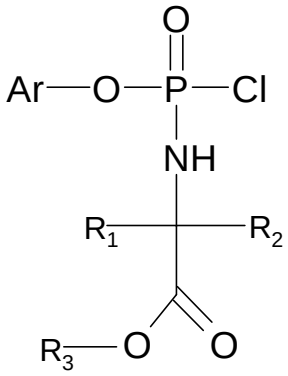
comprising the steps of:

(i) dissolving a compound of Formula II in a solvent selected from the group consisting of an ethereal solvent, acetonitrile and mixtures thereof and admixing the dissolved compound of Formula II with a base, wherein Formula II is:



where T_1, T_2 and B have the same meanings set out with respect to Formula I;

(ii) admixing the product of step (i) with a compound of Formula III, wherein Formula III is:



where Ar, R_1, R_2 and R_3 have the same meanings set out with respect to Formula I,

wherein step (ii) takes place in the presence of a catalyst comprising a metal salt wherein the metal salt is selected from the group consisting of metal salts of Cu, Fe, La and Yb; and

wherein the base employed in step (i) is selected from the group consisting of: $NR_4R_5R_6$, where R_4, R_5 and R_6 are selected, independently, from the group consisting of $C_{1\text{-}3}$alkyl and H, provided that at least two of R_4, R_5 and R_6 are, independently, $C_{1\text{-}3}$alkyl; and 1,8-diazabicyclo[5.4.0]undec-7-ene.

2. The process of claim 1 wherein the catalyst is admixed with the nucleoside compound of Formula II, prior to the dissolution of the compound of Formula II in the solvent of step (i).

3. The process of claim 1 or claim 2 wherein the catalyst is a copper salt.

4. The process of claim 3 wherein the catalyst is selected from the group consisting of $Cu(OTf)_2$, CuCl, CuBr, CuI, $Cu(OAc)_2$ and $CuSO_4$, and preferably, is $Cu(OTf)_2$.

5. The process of claim 3 wherein the catalyst is selected from the group consisting of $Cu(OAc)_2$ and $Cu(OC(O)CF_3)_2$.

6. The process of claim 1 or claim 2 wherein the catalyst is a metal salt with a metal in an oxidation state of more than 1.

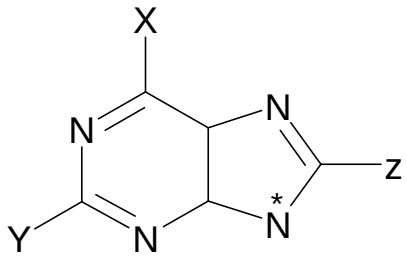
7. The process of claim 6 wherein the metal salt is an OTf salt.

8. The process of claim 7 wherein the metal salt is selected from the group consisting of $Cu(OTf)_2$, $Yb(OTf)_3$, $Fe(OTf)_3$ and $La(OTf)_3$ and, preferably, is $Cu(OTf)_2$.

9. The process of any one of claims 1 to 3 wherein the catalyst comprises a metal salt in which a metal component is in the form of a complex where a metal cation component is co-ordinated with one or more ligands.

10. The process of claim 9 wherein the metal salt is selected from the group consisting of $Cu(MeCN)_4 \cdot CF_3SO_3$ and $Cu(OTf) \cdot C_6H_6$.

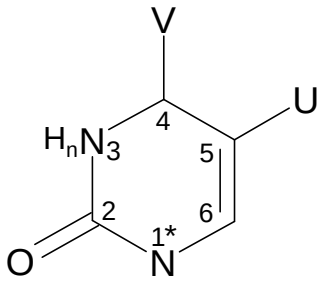
11. The process of any one of claims 1 to 10 wherein B in the compounds of Formulae I and II is the optionally substituted purine, where the N atom marked with * links directly to the C1 atom of the sugar moiety:



where each of X and Z is, independently, selected from H, OH, F, Cl, Br, I, OC_{1-6}alkyl, C_{1-6}alkyl and NR_7R_8, where each of R_7 and R_8 is, independently, selected from H and C_{1-6}alkyl; and

Y is selected from H, OH, OC_{1-6}alkyl, SH, SC_{1-6}alkyl, F, Cl, Br, I, C_{1-6}alkyl, C_{2-8}alkynyl and NR_9R_{10} where each of R_9 and R_{10} is, independently, selected from H and C_{1-6} alkyl.

12. The process of any one of claims 1 to 10 wherein B in the compounds of Formulae I and II is the optionally substituted pyrimidine , where the N atom marked with * links directly with the C1 atom of the sugar moiety:



where U is selected from the group consisting of H, C_{1-6}alkyl, F, Cl, Br and I; and

n is 0 or 1,

wherein

when n is 0, V is $-NH_2$ and a double bond exists between position 3 and position 4, and when n is 1, V is =O.

13. The process of any one of claims 1 to 12 wherein B comprises one or more members selected from the group consisting of: an NH moiety, where N is a heteroatom in an aromatic ring moiety of B, and one or more exocyclic heteroatoms selected from the group consisting of N, O, S and Cl directly linked to an aromatic ring moiety of B.

14. The process of any one of claims 1 to 13 wherein the compounds of Formulae I and II have T_1 and T_2 comprising T_3, T_4 and T_5.

15. The process of any one of claims 1 to 14 wherein the compounds of Formulae I and III have Ar as naphthyl or phenyl and, preferably, is naphthyl.

16. The process of any one of claims 1 to 15 wherein R_1 is selected from the group consisting of a tertiary alkyl moiety and benzyl.

17. The process of any one of claims 1 to 16 wherein at least one of R_2 and R_3 is a secondary or tertiary alkyl moiety.

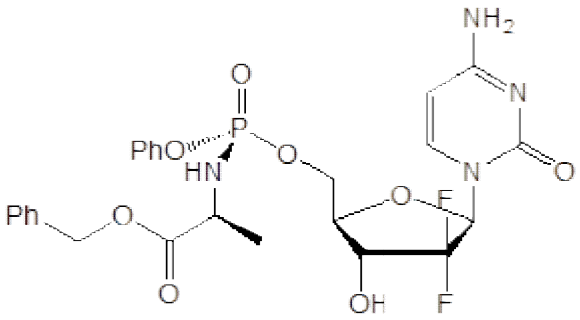
18. The process of any one of claims 1 to 17 wherein the ethereal solvent employed in step (i) is selected from the group consisting of 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane, diethyl ether, anisole, dimethoxybenzene and mixtures thereof.

19. The process of any one of claims 1 to 18 including further steps of removing the solvent and subjecting the residue to column chromatography.

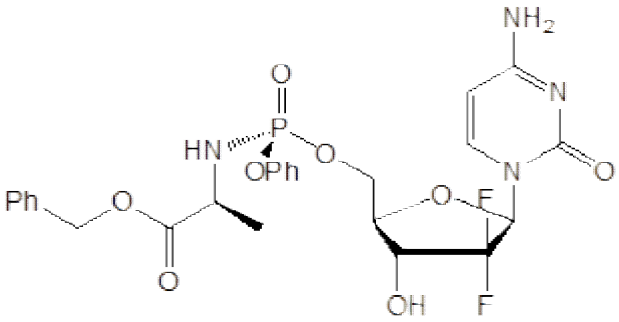
20. The process of any one of claims 1, 2, 3 and any one of claims 11 to 19 provided said claim of claims 11 to 19 is dependent on claim 3, wherein the metal salt is Cu(OAc).

21. The process of any one of claims 1, 2, 6 and any one of claims 11 to 19 provided said claim of claims 11 to 19 is dependent on claim 6, wherein the metal salt is selected from the group consisting of tris(acetylacetonato)iron(III) and bis(acetylacetonato)iron(II).

22. The product of any one of claims 1 to 21, wherein the product comprises a ratio of S_P enantiomer to R_P enantiomer that is greater than 2, more preferably greater than 5, even more preferably greater than 7.5;
wherein Rp is of a form gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*R*)-phosphate with a structure:



and wherein the Sp is of a form gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate with a structure:



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23. A pharmaceutical composition comprising the product of claim 22 together with pharmaceutical acceptable carrier, diluent or excipient.

24. The use of the pharmaceutical composition of claim 23 in the manufacture of a medicament for the treatment of a cancer, suitably in *homo sapiens*.