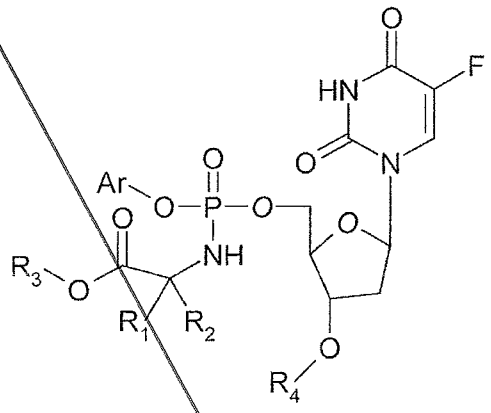
CLAIMS

1. A compound of formula (I):

I



wherein

Ar is a fused bicyclic aryl moiety or a monocyclic aryl moiety, either of which aryl moieties is carbocyclic or heterocyclic and is optionally substituted;

R_3 is alkyl, which is optionally substituted;

R_4 is H or alkoyl;

R_1 and R_2 are independently selected from the group consisting of H and alkyl, or R_1 and R_2 together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system, or one of R_1 and R_2 comprises an alkylene chain attached to N, the H atom attached to N is absent and one of R_1 and R_2 comprise H or alkyl, any of which said alkyl moieties or alkylene chains may be substituted;

or a pharmaceutically acceptable derivative or metabolite of formula I,

wherein the compound is not a compound having, in combination, Ar as unsubstituted phenyl, R_3 as CH_3, R_4 as H, one of R_1 and R_2 as H and one of R_1 and R_2 as CH_3.

2. The compound according to claim 1 wherein Ar is naphthyl.

3. The compound according to claim 2 wherein Ar is 1-naphthyl.

4. The compound according to claim 1 wherein Ar is phenyl.

5. The compound according to any one of claims 1 to 4 wherein Ar is substituted.

6. The compound according to any one of claims 1 to 5 wherein R_4 is selected from the group consisting of H and acetyl.

7. The compound according to claim 6 wherein R_4 is H.

8. The compound according to any one of claims 1 to 7 wherein R_3 is selected from the group consisting of benzyl and members of the group comprising C_1 to C_{10} alkyls.

9. The compound according to claim 8 wherein R_3 is ethyl, n-propyl, n-butyl, n-pentyl, or n-hexyl.

10. The compound according to claim 9 wherein R_3 is n-pentyl.

11. The compound according to any one of claims 1 to 10 wherein R_1 and R_2 are different and the stereochemistry at the asymmetric centre $-CR_1R_2$ corresponds to a member selected from the group consisting of an L-amino acid, a D-amino acid and mixtures of L and D amino acids.

12. The compound according to any one of claims 1 to 11 wherein R_1 and R_2 correspond to the moieties attached to the alpha C atom in a natural occurring alpha amino acid.

13. The compound of claim 12 wherein the natural occurring alpha amino acid is L-alanine.

14. The compound according to claim 1 wherein Ar is 1-naphthyl, R_3 is benzyl, and one of R_1 and R_2 is H, one of R_1 and R_2 is methyl and the C atom to which R_1 and R_2 are attached has L-chirality.

15. The compound according to claim 1 wherein Ar is 1-naphthyl, R_3 is n-pentyl, one of R_1 and R_2 is H, one of R_1 and R_2 is methyl and the C atom to which R_1 and R_2 are attached has L-chirality.

16. The compound according to claim 1 selected from the group comprising:

5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl(benzoxy-L-alaninyl)]phosphate (CPF 381)
5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl(ethoxy-L-alaninyl)] phosphate (CPF383)
5-Fluoro-2'deoxyuridine-5'-*O*-[phenyl(isopropoxy-L-alaninyl)] phosphate (CPF384)
5-Fluoro-2'deoxyuridine-5'-*O*-[phenyl (cyclohexoxy-L-alaninyl)] phosphate (CPF508)
5-Fluoro-2'deoxyuridine-5'-*O*-[*p*-nitro-phenyl(ethoxy-L-alaninyl)] phosphate (CPF430)
5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (benzoxy-L-alaninyl)] phosphate (CPF373)
5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (methoxy-L-alaninyl)] phosphate (CPF385)
5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (ethoxy-L-alaninyl)] phosphate (CPF386)

5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (isopropoxy-L-alaninyl)] phosphate (CPF387)

5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (cyclohexoxy-L-alaninyl)] phosphate (CPF509)

5-Fluoro-2'deoxyuridine-5'-*O*-[phenyl (benzoxy-α,α-dimethylglycine)] phosphate (CPF393)

5-Fluoro-2'deoxyuridine-5'-*O*-[phenyl (ethoxy-α,α-dimethylglycine)] phosphate (CPF394)

5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (benzoxy-α,α-dimethylglycine)] phosphate (CPF395)

5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (ethoxy-α,α-dimethylglycine)] phosphate (CPF396)

5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl(benzoxy-L-prolinyl)] phosphate (CPF583)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl(benzoxy-L-prolinyl)] phosphate (CPF577)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl(3,3-dimethyl-1-butoxy-L-alaninyl)] phosphate (CPF585)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(cyclobutoxy-L-alaninyl)] phosphate (CPF578)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(cyclopropylmethanoxy-L-alaninyl)] phosphate (CPF579)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(tetrahydropyroxy-L-alaninyl)] phosphate (CPF580)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(pentoxy-L-alaninyl)] phosphate (CPF581)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(cyclopentoxy-L-alaninyl)] phosphate (CPF582)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(2-indanoxy-L-alaninyl)] phosphate (CPF597)

5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl-(benzoxy-L-methioninyl)] phosphate (CPF586)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(benzoxy-L-phenylalaninyl)] phosphate (CPF587)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(2,2-dimethylpropoxy-L-alaninyl)] phosphate (CPF588)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(butoxy-L-alaninyl)] phosphate (CPF589)

17. The compound according to any one of claims 1 to 16 for use in a method of prophylaxis or treatment of cancer in homo sapiens.

18. The compound according to claim 17 wherein the cancer is selected from the group comprising leukemia, pancreatic, prostate, lung, breast and cervical cancer.

19. The compound according to claim 17 wherein the cancer is selected from the group comprising: oesophageal; gastrointestinal, including gastric, small intestine, colon and rectum, cancer; head and neck cancer; and ovarian cancer.

20. The compound according to any one of claims 17 to 19 for use in a method of prophylaxis or treatment of cancer in a patient who has developed or has the potential to develop resistance in tumour cells with respect to the activity of 5-fluoracil or 5-fluoro-2'-deoxyuridine in the prophylaxis or the treatment of cancer.

21. The compound according to any one of claims 17 to 20 for use in a method of prophylaxis or treatment of cancer in a patient with cells with a lowered level of nucleoside transporter proteins.

22. The compound according to any one of claims 17 to 21 for use in a method of prophylaxis or treatment of cancer in a patient with nucleoside kinase-deficient cells.

23. The compound according to any one of claims 17 to 22 for use in a method of prophylaxis or treatment of cancer in a patient with mycoplasma-infected cells.

24. The compound according to any one of claims 17 to 23 for use in a method of prophylaxis or treatment of cancer in a patient with cells with a raised level of thymidylate synthase (TS).

25. The compound according to any one of claims 17 to 24 for use in a method of prophylaxis or treatment of cancer in a patient to circumvent susceptibility to nucleoside degradation by catabolic enzymes.

26. The compound according to claim 25 wherein the catabolic enzymes are selected from the group comprising thymidine phosphorylase, uridine phosphorylase and deoxycytidine deaminase.

27. The compound according to any one of claims 17 to 26 for use in conjunction with other anti-cancer therapy.

28. A method of propylaxis or treatment of cancer comprising administering to a homo sapiens patient in need of such treatment an effective dose of a compound according to any one of claims 1 to 16.

29. The method according to claim 28 wherein the cancer is selected from the group comprising leukemia, pancreatic, prostate, lung, breast and cervical cancer.

30. The method according to claim 28 wherein the cancer is selected from the group comprising: oesophageal; gastrointestinal, including gastric, small intestine, colon and rectum, cancer; head and neck cancer; and ovarian cancer.

31. The method according to any one of claims 28 to 30 in a patient who has developed or has the potential to develop resistance in tumour cells with respect to

the activity of 5-fluoracil or 5-fluoro-2'-deoxyuridine in a method of prophylaxis or treatment of cancer.

32. The method according to any one of claims 28 to 31 wherein the patient has cells with a lowered level of nucleoside transporter proteins.

33. The method according to any one of claims 28 to 32 wherein the patient has nucleoside kinase-deficient cells.

34. The method according to any one of claims 28 to 33 wherein the patient has mycoplasma-infected cells.

35. The method according to any one of claims 28 to 34 wherein the patient has cells with a raised level of thymidylate synthase (TS).

36. The method according to any one of claims 28 to 35 in a patient to circumvent susceptibility to nucleoside degradation by catabolic enzymes.

37. The method according to claim 36 wherein the catabolic enzymes are selected from the group comprising thymidine phosphorylase, uridine phosphorylase and deoxycytidine deaminase.

38. The method according to any one of claims 28 to 37 in conjunction with other cancer therapy.

39. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16 in combination with a pharmaceutically acceptable carrier, diluent or excipient.

40. A method of preparing a pharmaceutical composition comprising the step of combining a compound according to any one of claims 1 to 16 with a pharmaceutically acceptable excipient, carrier or diluent.

41. The compound according to claim 1 selected from the group comprising:

5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl(ethoxy-L-valinyl)] phosphate
5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl(benzoxy-L-leucinyl)] phosphate
5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl(benzoxy-L-isoleucinyl)] phosphate
5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl(benzoxy-L-phenylalaninyl)] phosphate
5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl(pentoxy-L-methioninyl)] phosphate
5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl(hexoxy-L-alaninyl)] phosphate
5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl(cyclohexoxy-L-valinyl)] phosphate
5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl(pentoxy-L-leucinyl)] phosphate
5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl(benzoxy-L-leucinyl)] phosphate
5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl(pentoxy-L-isoleucinyl)] phosphate
5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl(pentoxy-L-phenylalaninyl)] phosphate
5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl(benzoxy-L-methioninyl)] phosphate
5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl(pentoxy-α,α-dimethylglycine)] phosphate.

42. The compound according to claim 41 for use in a method of prophylaxis or treatment of cancer in homo sapiens.

43. The compound according to claim 42 wherein the cancer is selected from the group comprising leukemia, pancreatic, prostate, lung, breast and cervical cancer.

44. The compound according to claim 42 wherein the cancer is selected from the group comprising: oesophageal; gastrointestinal, including gastric, small intestine, colon and rectum, cancer; head and neck cancer; and ovarian cancer.

45. The compound according to any one of claims 42 to 44 for use in a method of prophylaxis or treatment of cancer in a patient who has developed or has the

potential to develop resistance in tumour cells with respect to the activity of 5-fluoracil or 5-fluoro-2'-deoxyuridine in the prophylaxis or the treatment of cancer.

46. The compound according to any one of claims 42 to 45 for use in a method of prophylaxis or treatment of cancer in a patient with cells with a lowered level of nucleoside transporter proteins.

47. The compound according to any one of claims 42 to 46 for use in a method of prophylaxis or treatment of cancer in a patient with nucleoside kinase-deficient cells.

48. The compound according to any one of claims 42 to 47 for use in a method of prophylaxis or treatment of cancer in a patient with mycoplasma-infected cells.

49. The compound according to any one of claims 42 to 48 for use in a method of prophylaxis or treatment of cancer in a patient with cells with a raised level of thymidylate synthase (TS).

50. The compound according to any one of claims 42 to 49 for use in a method of prophylaxis or treatment of cancer in a patient to circumvent susceptibility to nucleoside degradation by catabolic enzymes.

51. The compound according to claim 50 wherein the catabolic enzymes are selected from the group comprising thymidine phosphorylase, uridine phosphorylase and deoxycytidine deaminase.

52. The compound according to any one of claims 42 to 51 for use in conjunction with other anti-cancer therapy.

53. A method of propylaxis or treatment of cancer comprising administering to a homo sapiens patient in need of such treatment an effective dose of a compound according to claim 41.

54. The method according to claim 53 wherein the cancer is selected from the group comprising leukemia, pancreatic, prostate, lung, breast and cervical cancer.

55. The method according to claim 53 wherein the cancer is selected from the group comprising: oesophageal; gastrointestinal, including gastric, small intestine, colon and rectum, cancer; head and neck cancer; and ovarian cancer.

56. The method according to any one of claims 53 to 55 in a patient who has developed or has the potential to develop resistance in tumour cells with respect to the activity of 5-fluoracil or 5-fluoro-2'-deoxyuridine in a method of prophylaxis or treatment of cancer.

57. The method according to any one of claims 53 to 56 wherein the patient has cells with a lowered level of nucleoside transporter proteins.

58. The method according to any one of claims 53 to 57 wherein the patient has nucleoside kinase-deficient cells.

59. The method according to any one of claims 53 to 58 wherein the patient has mycoplasma-infected cells.

60. The method according to any one of claims 53 to 59 wherein the patient has cells with a raised level of thymidylate synthase (TS).

61. The method according to any one of claims 53 to 60 in a patient to circumvent susceptibility to nucleoside degradation by catabolic enzymes.

62. The method according to claim 61 wherein the catabolic enzymes are selected from the group comprising thymidine phosphorylase, uridine phosphorylase and deoxycytidine deaminase.

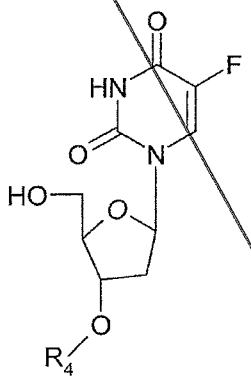
63. The method according to any one of claims 53 to 62 in conjunction with other cancer therapy.

64. A pharmaceutical composition comprising a compound according to claim 41 in combination with a pharmaceutically acceptable carrier, diluent or excipient.

65. A method of preparing a pharmaceutical composition comprising the step of combining a compound according to claim 41 with a pharmaceutically acceptable excipient, carrier or diluent.

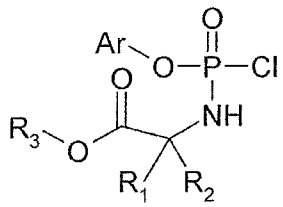
66. A process for the preparation of a compound of formula I according to claim 1, the process comprising reacting a compound of formula (II)

II



with a compound of formula (III)

III

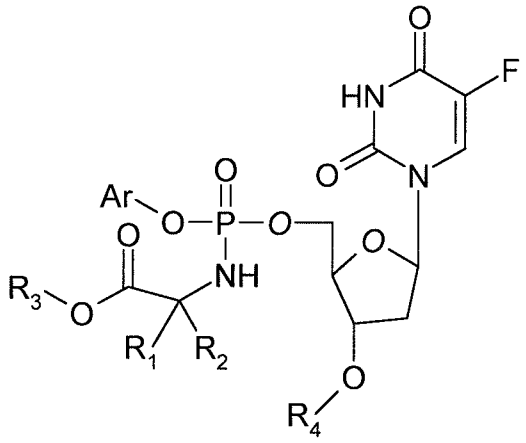


wherein Ar, R_3, R_4, R_1 and R_2 have the meanings described in claim 1.

CLAIMS

1. A compound of formula (I):

I



wherein

Ar is a fused bicyclic aryl moiety or a monocyclic aryl moiety, either of which aryl moieties is carbocyclic or heterocyclic and is optionally substituted;

R_3 is alkyl, which is optionally substituted;

R_4 is H or alkoyl;

R_1 and R_2 are independently selected from the group consisting of H and alkyl, or R_1 and R_2 together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system, or one of R_1 and R_2 comprises an alkylene chain attached to N, the H atom attached to N is absent and one of R_1 and R_2 comprise H or alkyl, any of which said alkyl moieties or alkylene chains may be substituted;

or a pharmaceutically acceptable derivative thereof wherein said pharmaceutically acceptable derivative is any pharmaceutically acceptable salt, hydrate, solvate, or crystalline form,

wherein the compound is not a compound having, in combination, Ar as unsubstituted phenyl, R_3 as CH_3, R_4 as H, one of R_1 and R_2 as H and one of R_1 and R_2 as CH_3.

2. The compound according to claim 1 wherein Ar is naphthyl and is preferably 1-naphthyl.

3. The compound according to claim 1 wherein Ar is phenyl.

4. The compound according to any one of claims 1 to 3 wherein Ar is substituted.

5. The compound according to any one of claims 1 to 4 wherein R_4 is selected from the group consisting of H and acetyl and is preferably H.

6. The compound according to any one of claims 1 to 5 wherein R_3 is selected from the group consisting of benzyl and members of the group comprising C_1 to C_{10} alkyls, is preferably n-propyl, n-butyl, n-pentyl, or n-hexyl, and is more preferably n-pentyl.

7. The compound according to any one of claims 1 to 6 wherein R_1 and R_2 correspond to the moieties attached to the alpha C atom in a natural occurring alpha amino acid and preferably the natural occurring alpha amino acid is L-alanine.

8. The compound according to claim 7 wherein Ar is 1-naphthyl and R_1 and R_2 correspond to the moieties attached to the alpha C atom in L-alanine.

9. The compound according to claim 1 wherein Ar is 1-naphthyl, R_3 is either benzyl or n-pentyl, and one of R_1 and R_2 is H, one of R_1 and R_2 is methyl and the C atom to which R_1 and R_2 are attached has L-chirality.

10. The compound according to claim 1 selected from the group comprising:

5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl(benzoxy-L-alaninyl)]phosphate (CPF 381)
5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl(ethoxy-L-alaninyl)] phosphate (CPF383)
5-Fluoro-2'deoxyuridine-5'-*O*-[phenyl(isopropoxy-L-alaninyl)] phosphate (CPF384)
5-Fluoro-2'deoxyuridine-5'-*O*-[phenyl (cyclohexoxy-L-alaninyl)] phosphate (CPF508)
5-Fluoro-2'deoxyuridine-5'-*O*-[*p*-nitro-phenyl(ethoxy-L-alaninyl)] phosphate (CPF430)
5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (benzoxy-L-alaninyl)] phosphate (CPF373)
5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (methoxy-L-alaninyl)] phosphate (CPF385)
5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (ethoxy-L-alaninyl)] phosphate (CPF386)
5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (isopropoxy-L-alaninyl)] phosphate (CPF387)
5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (cyclohexoxy-L-alaninyl)] phosphate (CPF509)
5-Fluoro-2'deoxyuridine-5'-*O*-[phenyl (benzoxy-α,α-dimethylglycine)] phosphate (CPF393)
5-Fluoro-2'deoxyuridine-5'-*O*-[phenyl (ethoxy-α,α-dimethylglycine)] phosphate (CPF394)
5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (benzoxy-α,α-dimethylglycine)] phosphate (CPF395)
5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (ethoxy-α,α-dimethylglycine)] phosphate (CPF396)
5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl(benzoxy-L-prolinyl)] phosphate (CPF583)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl(benzoxy-L-prolinyl)] phosphate (CPF577)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl(3,3-dimethyl-1-butoxy-L-alaninyl)] phosphate (CPF585)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(cyclobutoxy-L-alaninyl)] phosphate (CPF578)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(cyclopropylmethanoxy-L-alaninyl)] phosphate (CPF579)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(tetrahydropyroxy-L-alaninyl)] phosphate (CPF580)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(pentoxy-L-alaninyl)] phosphate (CPF581)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(cyclopentoxy-L-alaninyl)] phosphate (CPF582)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(2-indanoxy-L-alaninyl)] phosphate (CPF597)

5-Fluoro-2'-deoxyuridine-5'-*O*-[phenyl-(benzoxy-L-methioninyl)] phosphate (CPF586)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(benzoxy-L-phenylalaninyl)] phosphate (CPF587)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(2,2-dimethylpropoxy-L-alaninyl)] phosphate (CPF588)

5-Fluoro-2'-deoxyuridine-5'-*O*-[1-naphthyl-(butoxy-L-alaninyl)] phosphate (CPF589)

and a pharmaceutically acceptable derivative of any thereof wherein said pharmaceutically acceptable derivative is any pharmaceutically acceptable salt, hydrate, solvate, or crystalline form.

11. A compound according to claim 10 which is 5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (benzoxy-L-alaninyl)] phosphate (CPF373) or a pharmaceutically acceptable derivative thereof wherein said pharmaceutically acceptable derivative is any pharmaceutically acceptable salt, hydrate, solvate, or crystalline form.

12. A compound according to claim 11 which is 5-Fluoro-2'deoxyuridine-5'-*O*-[1-naphthyl (benzoxy-L-alaninyl)] phosphate (CPF373).

13. The compound according to any one of claims 1 to 12 for use in a method of prophylaxis or treatment of cancer in homo sapiens, preferably wherein the cancer is selected from the group comprising leukemia, pancreatic, prostate, lung, breast and cervical cancer.

14. The compound for use according to claim 13 in a method of prophylaxis or treatment of cancer in a patient:

(i) who has developed or has the potential to develop resistance in tumour cells with respect to the activity of 5-fluoracil or 5-fluoro-2'-deoxyuridine in the prophylaxis or the treatment of cancer;

(ii) with cells with a lowered level of nucleoside transporter proteins;

(iii) with nucleoside kinase-deficient cells;

(iv) with mycoplasma-infected cells; and/or

(v) with cells with a raised level of thymidylate synthase (TS).

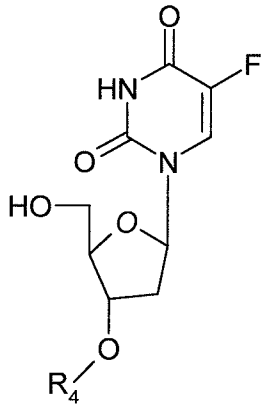
15. The compound for use according to any one of claims 13 to 14 in conjunction with other anti-cancer therapy.

16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12 in combination with a pharmaceutically acceptable carrier, diluent or excipient.

17. A method of preparing a pharmaceutical composition comprising the step of combining a compound according to any one of claims 1 to 12 with a pharmaceutically acceptable excipient, carrier or diluent.

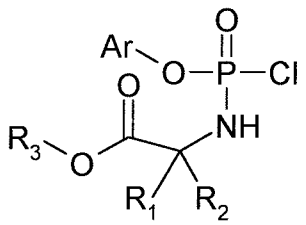
18. A process for the preparation of a compound of formula I according to claim 1, the process comprising reacting a compound of formula (II)

II



with a compound of formula (III)

III



wherein Ar, R_3, R_4, R_1 and R_2 have the meanings described in claim 1.