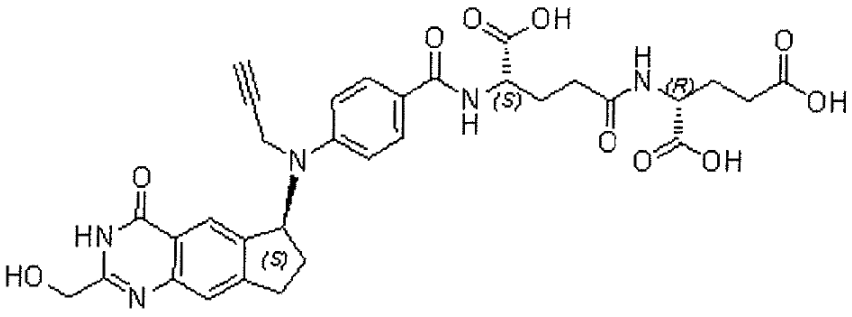
It will be realised by those skilled in the art that pharmaceuticals are expensive commodities and that it is desirable not to waste compound not required for a given treatment. As BTG945 is potentially toxic above the now taught doses it would be inappropriate for more than required to be provided in the clinical setting. Thus as a preferred dose per patient surface area is 6mg/m^2 or 12mg/m^2 and patients typically have surface area between lm^2 and 2.5m^2 in developed countries, with patients with unusually high BMI often capped at 2m^2, it can be seen that a novel preferred useable vial content, whether in dried solid or solution form, would be between 6mg to 24mg drug compound more preferred between lOmg and 24mg drug compound. Thus vials of drug content 6mg, 8mg, lOmg, 12mg, 14mg, 16mg, 18mg, 20mg and 24mg are disclosed as novel embodiments of the invention. Particularly those where drug is in the form of dried BTG945 salt and/or its dehydrate, or its simple solution in water or saline for injection.

The compound for the treatment of the invention may be synthesised as described in the aforementioned patent applications or as set out in more recent patent US8809526 (Onyx) and patent application US2013/0345423 (Onyx).

In another aspect the present invention provides a use of a compound of formula I

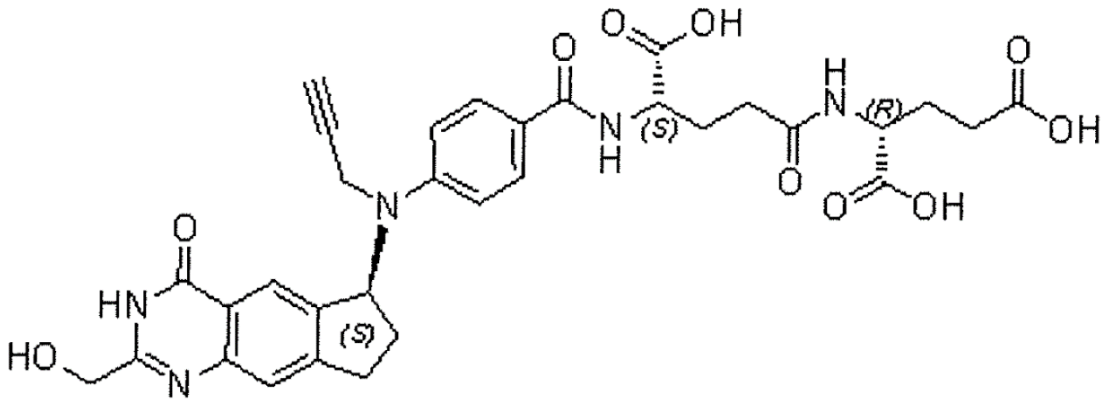


or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of cancer that carries α-folate receptors, wherein

(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy and

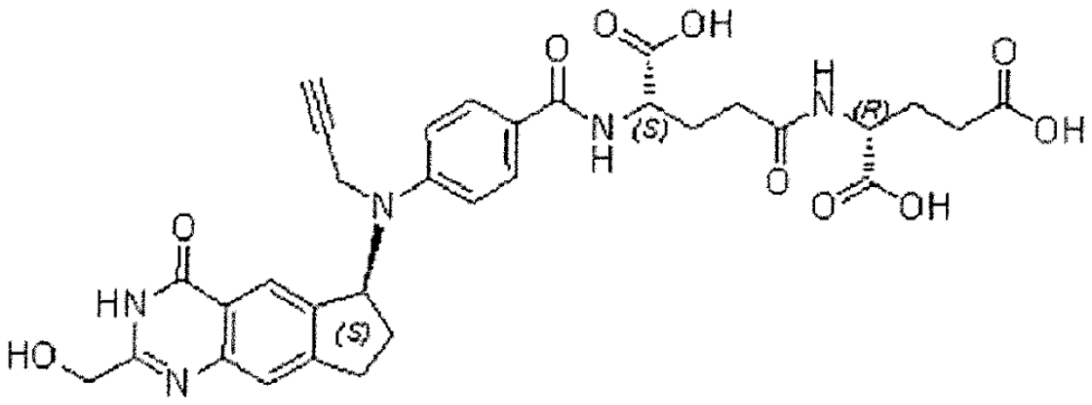
(ii) a dose of between 1mg/m^2 and 30mg/m^2 of compound per patient body surface area is to be administered per administration.

In another aspect the present invention provides a dosage form of a compound of formula I



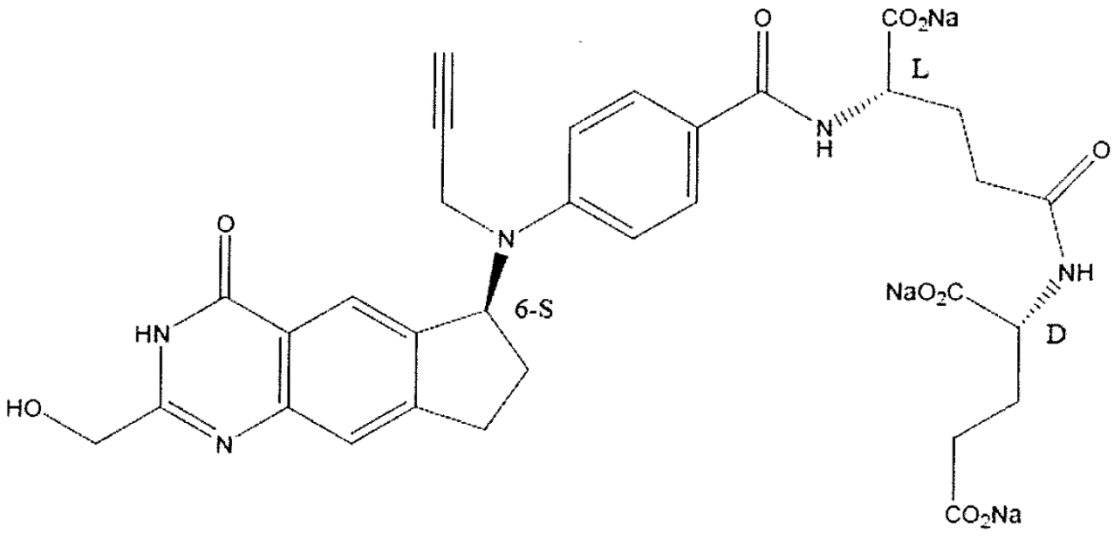
comprising a single dosage unit containing said compound or a pharmaceutically acceptable salt or ester thereof characterised in that the amount of said compound in the dosage unit is between 0.5mg and 40mg.

In another aspect the present invention provides a use of a compound chosen from formula I



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formula II



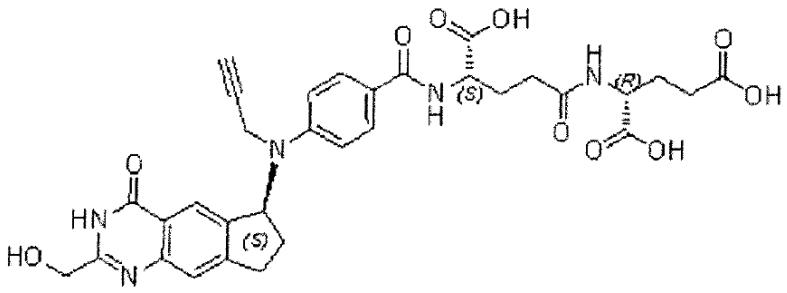
and pharmaceutically acceptable salts or esters thereof, in the manufacture of a medicament for the treatment of cancer that carries α-folate receptors, wherein

(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose of from 1mg/m^2 to 30mg/m^2 of compound per patient body surface area is to be administered per administration; and

(iii) the dose is to be administered intraperitoneally (IP).

In another aspect the present invention provides a use of a compound of formula I



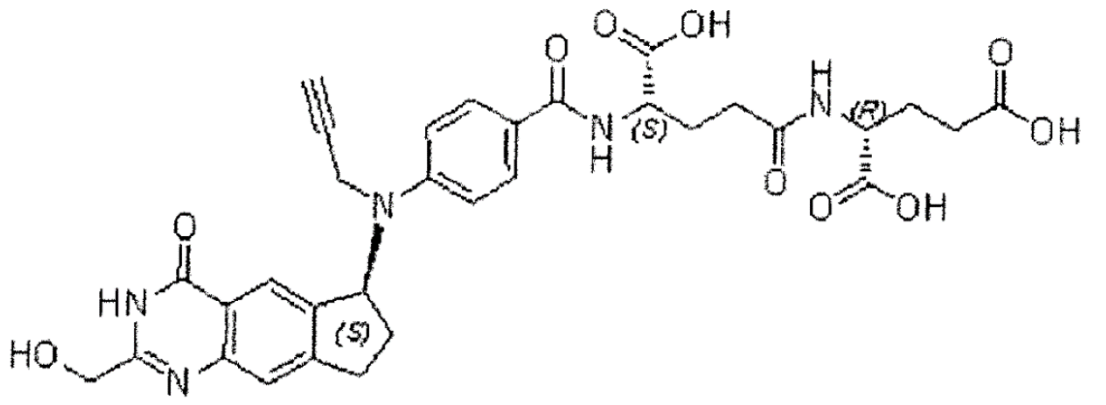
or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of cancer that carries α-folate receptors,

wherein the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

wherein a dose of from 1mg/m^2 to 30mg/m^2 of compound per patient body surface area is to be administered per administration; and

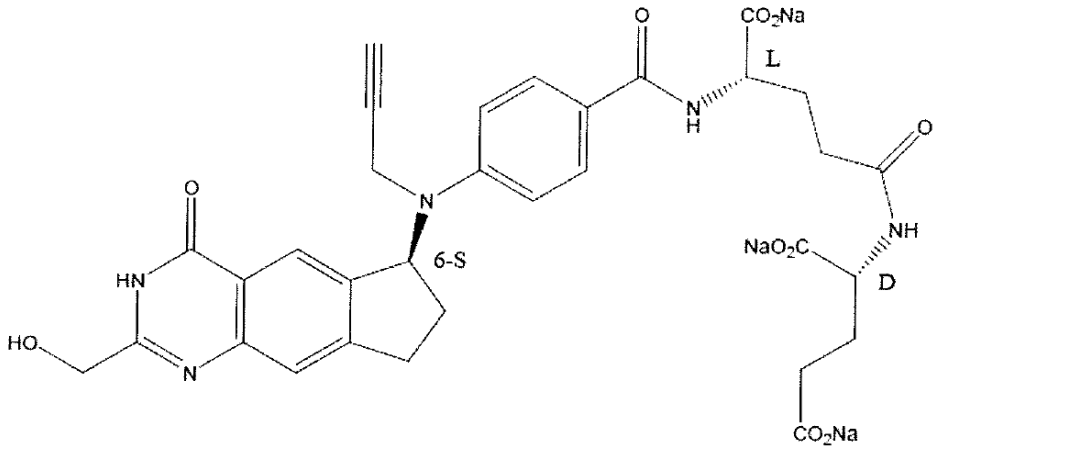
wherein the dose is to be administered intraperitoneally (IP).

In another aspect the present invention provides a use of a compound chosen from formula I



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formula II



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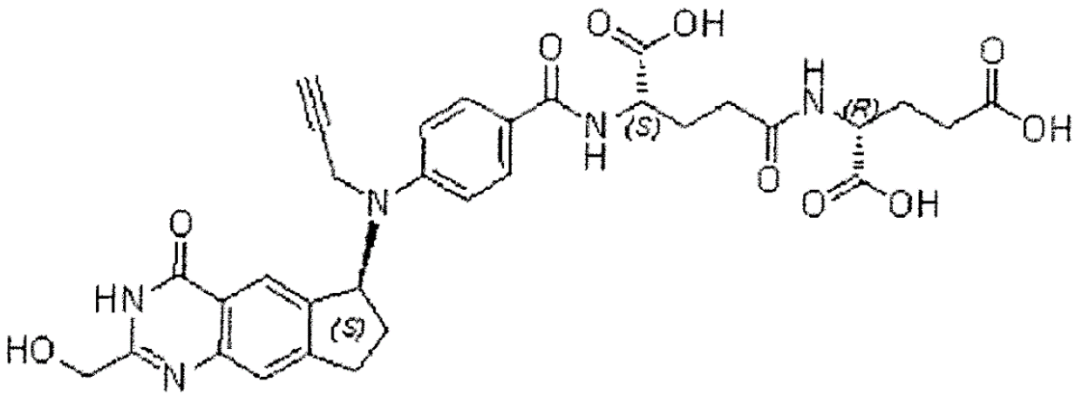
and pharmaceutically acceptable salts or esters thereof, in the manufacture of a medicament for the treatment of cancer that carries α-folate receptors, wherein

(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose of from 1mg/m^2 to 30mg/m^2 of compound per patient body surface area is to be administered per administration; and

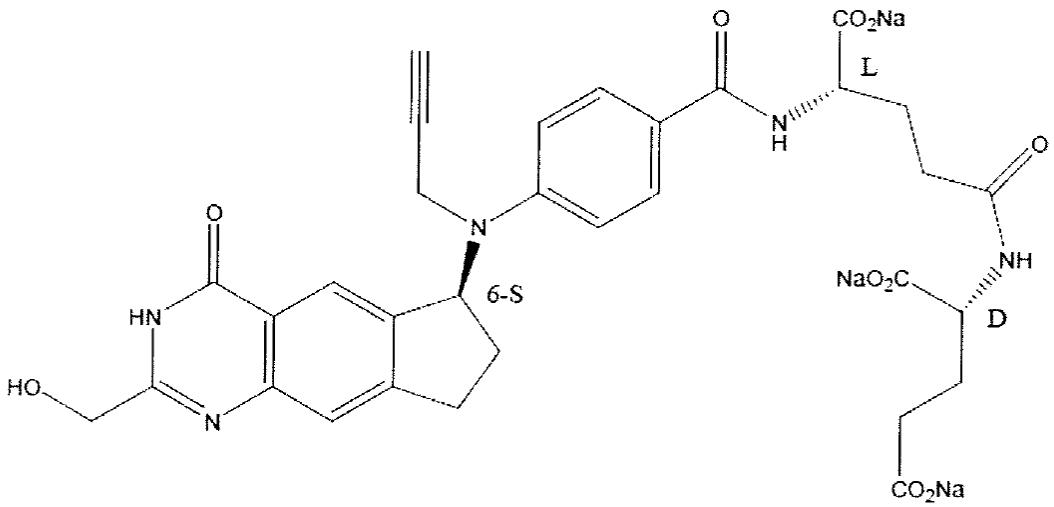
(iii) wherein at least one side effect associated with classical thymidylate synthase inhibitors or alpha folate receptor antibody drug conjugates is not observed

In another aspect the present invention provides a use of a compound chosen from formula I



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formula II



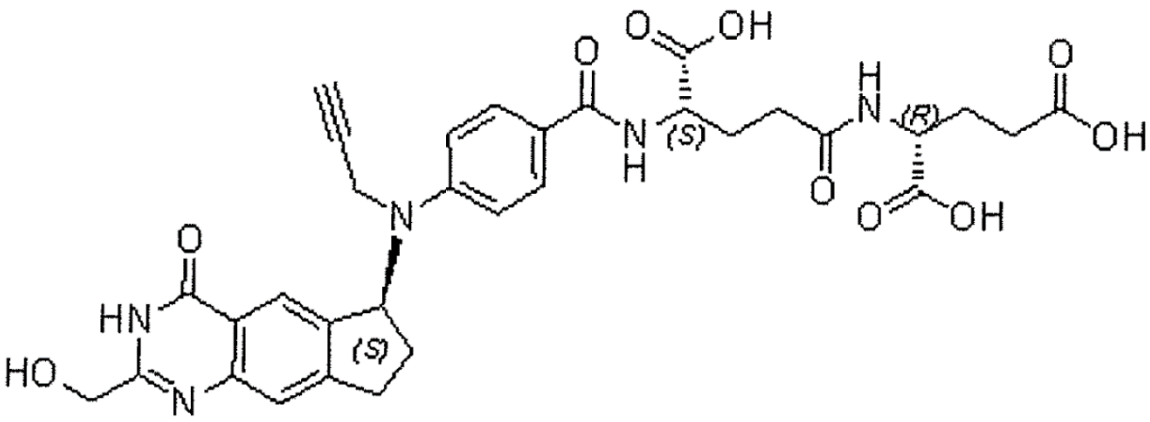
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and pharmaceutically acceptable salts or esters thereof, in the manufacture of a medicament for the treatment of cancer that carries α-folate receptors, wherein

(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose that achieves a concentration of 0.5 μM or greater of the compound for at least 72hrs is to be administered.

In another aspect the present invention provides a use of a pharmaceutical composition comprising a compound of formula I



or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of cancer that carries α-folate receptors, wherein

(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy and

(ii) a dose of between 1 mg/m^2 and 30mg/m^2 of compound per patient body surface area per administration.

FIGURES

Figures 1 to 5 show the clinical results of trial with the treatment of the present invention in humans.

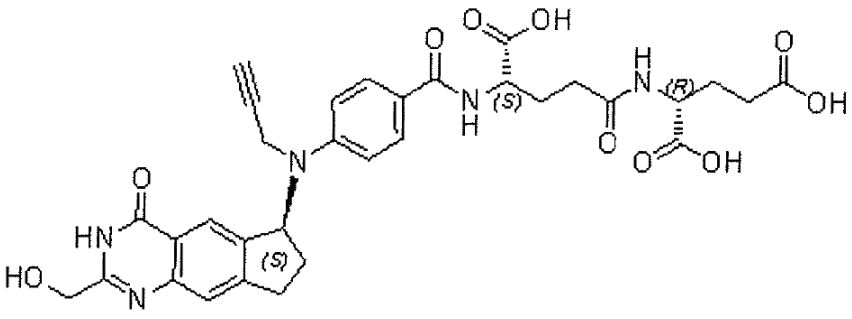
FIGURE 1: Shows the % change in tumours using RECIST criteria in patients in the dose escalation phase of the trial of Example 1 Weekly schedule is indicated by asterisk and an a-folate expressing tumour indicated by a cross.

FIGURE 2: Shows the % change in tumours as measured by CA125 level in escalation phase of the trial of example 1. Numbers represent dose mg/m2 and letters whether weekly (w) or fortnightly (f) and an a-folate expressing tumour indicated by a cross.

FIGURE 3: Shows the % change in tumours using RECIST criteria in patients in the expansion phase of the trial of Example 1 using 12mg/m^2 dose once every 14 days in 28 day cycles. An α-folate expressing tumour is indicated by a cross.

CLAIMS

1. Use of a compound of formula I



or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of cancer that carries α-folate receptors, wherein

(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy and

(ii) a dose of between 1mg/m^2 and 30mg/m^2 of compound per patient body surface area is to be administered per administration.

2. A use as claimed in claim 1 characterised in that the cancer is platinum refractory or resistant.

3. A use as claimed in claim 1 characterised in that the cancer is selected from ovarian, endometrial, mesothelial, non-small cell lung and cancers derived from one of these.

4. A use as claimed in claim 1, 2 or 3 characterised in that is selected from those expressing α-folate receptors (FR-α).

5. A use as claimed in claim 4 characterised in that the cancer expresses higher than background non-cancerous tissue levels of α-folate receptors.

6. A use as claimed in any one of the preceding claims characterised in that the cancer is an ovarian cancer.

7. A use as claimed in claim any one of the preceding claims characterised in that the cancer is epithelial ovarian, fallopian tube or peritoneal cancer.

8. A use as claimed in claim 6 or claim 7 characterised in that the cancer is serous ovarian cancer.

9. A use as claimed in claim 8 characterised in that the cancer is High-Grade Serous Ovarian Cancer (HGSOC).

10. A use as claimed in any one of the preceding claims characterised in that the dose is to be administered intraperitoneally (IP) or intravenously (IV).

11. A use as claimed in any one of the preceding claims characterised in that the dose is 3mg/m^2 to 30mg/m^2 of compound per patient body surface area per administration.

12. A use as claimed in any one of the preceding claims characterised in that each dose is to be administered as individual infusions spaced between 10 and 28 days apart.

13. A use as claimed in claim 12 characterised in that the infusions are spaced between 10 and 21 days apart.

14. A use as claimed in claim 13 characterised in that the infusions are to be administered at dosing interval of about 14 days.

15. A use as claimed in claim 14 characterised in that a cumulative maximum of 150mg/m^2 of compound per patient body surface area is to be administered over the course of all the infusions.

16. A use as claimed in claim 15 characterised in that the maximum cumulative dose is 144mg/m^2.

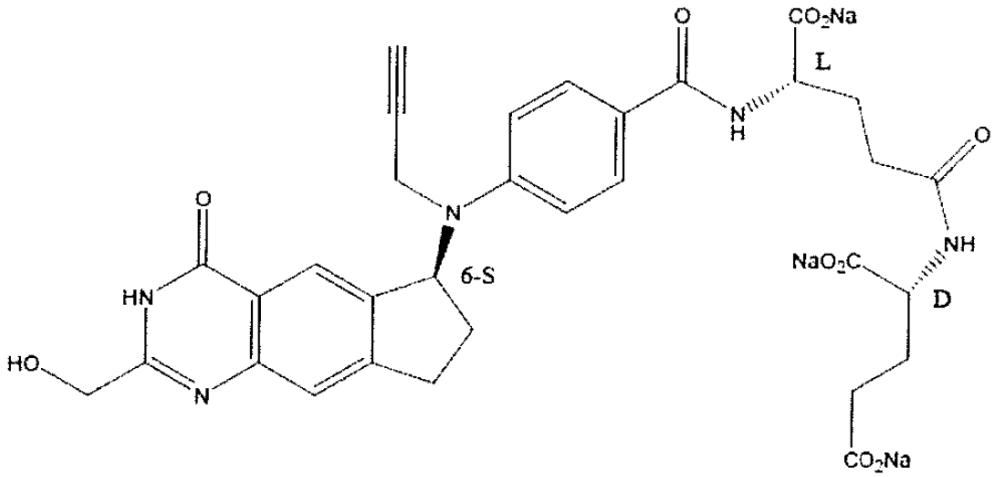
17. A use as claimed in any one of the preceding claims characterised in that an infusion of 1mg/m^2 to 20mg/m^2 is to be administered per administration.

18. A use as claimed in claim 17 characterised in that an infusion of 10mg/m^2 to 15mg/m^2 is to be administered per administration.

19. A use as claimed in claim 16 characterised in that an infusion of about 12mg/m^2 is to be administered per administration.

20. A use as claimed in any one of claims 1 to 19 characterised in that the dose is added to a saline drip.

21. A use as claimed in any one of the preceding claims characterised in that the compound is the trisodium salt of formula II



22. A use as claimed in any one of the preceding claims wherein the medicament is to be administered with a therapeutically effective amount of one or more further anticancer agents.

23. A use as claimed in claim 22, wherein the medicament I and the one or more further anticancer agents are to be administered separately.

24. A use as claimed in claim 22, wherein the administration of the medicament and the administration of the one or more further anticancer agents are separated by 12 hours.

25. A use as claimed in claim 22, wherein the administration of the medicament and the administration of the one or more further anticancer agents are separated by 24 hours.

26. A use as claimed in claim 22, wherein the administration of the medicament and the administration of the one or more further anticancer agents are separated by 36 hours.

27. A use as claimed in claim 22, wherein the administration of the medicament and the administration of the one or more further anticancer agents are separated by 38 hours.

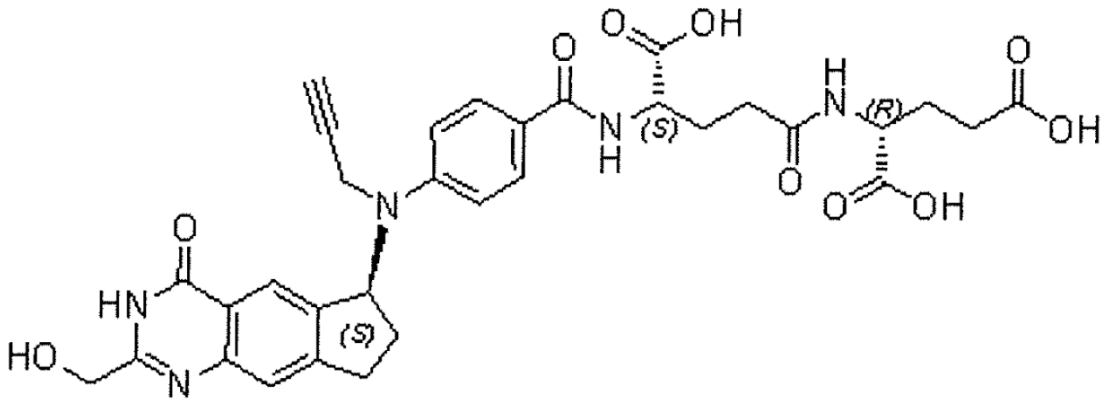
28. A use as claimed in claim 22, wherein the administration of the medicament and the administration of the one or more further anticancer agents are performed on alternate weeks of a 7 day dosing schedule.

29. A use as claimed in claim 22, wherein the administration of the medicament and the administration of the one or more further anticancer agents are to be performed on alternate weeks of a 14 day dosing schedule.

30. A use as claimed in claims 22 to 29 wherein the one or more further anticancer agents used in this combination therapy are selected from Cisplatin, Carboplatin, Doxorubicin, Bevacizumab Gemcitabine, Topetecan, Paclitaxel, Docetaxel, Etoposide, Nanoparticle albumin-bound paclitaxel, Lynparza (olaparib), Rubraca (rucaparib), Zejula (niraparib), Tecentriq (atezoizumab), Bavercio (avelumab).

31. A use as claimed in claims 22 to 29 wherein the medicament is to be administered together with bevacizumab in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan.

32. A dosage form of a compound of formula I



comprising a single dosage unit containing said compound or a pharmaceutically acceptable salt or ester thereof characterised in that the amount of said compound in the dosage unit is between 0.5mg and 40mg.

33. A dosage form as claimed in claim 32, containing from 0.5mg to 40mg of the compound of formula I or salt or ester thereof.

34. A dosage unit as claimed in claim 32 or 33 containing between 1mg and 30mg of the compound of formula I or salt or ester thereof.

35. A dosage unit as claimed in claim 32, 33, or 34 containing between 5mg and 26mg of the compound of formula I or a salt or ester thereof.

36. A dosage unit as claimed in claim 32, 33, 34, or 35 containing between 10 and 24mg of the compound or salt or ester of formula I.

37. A dosage form as claimed in any one of claims 32 to 36 characterised in that it comprises a container of the compound of formula I or its salt or ester.

38. A dosage form as claimed in claim 37 characterised in that it comprises the sodium salt, as a sterile solid or aqueous solution.

39. A dosage form as claimed in claim 38 characterised in that the aqueous solution is of compound in water for injection or saline.

40. A dosage form as claimed in any one of claims 32 to 39 characterised in that it is a vial containing an aqueous solution of the compound, salt or ester.

41. A dosage form as claimed in claim 40 containing from 1mg to 40mg of the compound of formula I or salt or ester thereof.

42. A dosage form as claimed in any one of claims 32 to 41 characterised in that it comprises a vial containing between 1 and 40mg of a compound of formula I or a salt or ester thereof in dried solid or aqueous solution form.

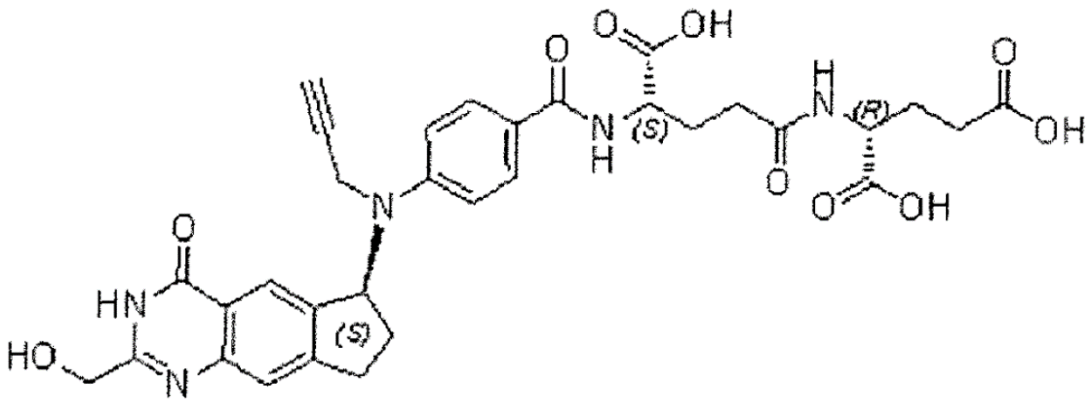
43. A dosage form as claimed in claim 42 containing from 5mg to 30mg of the compound of formula I or salt or ester thereof.

44. A dosage form as claimed in any one of claims 32 to 43 characterised in that it comprises a vial containing 5mg to 30mg of a compound of formula I or a salt or ester thereof in dried solid or aqueous solution form.

45. A dosage form as claimed in claim 44 containing from 10mg to 24mg of the compound of formula I or salt or ester thereof.

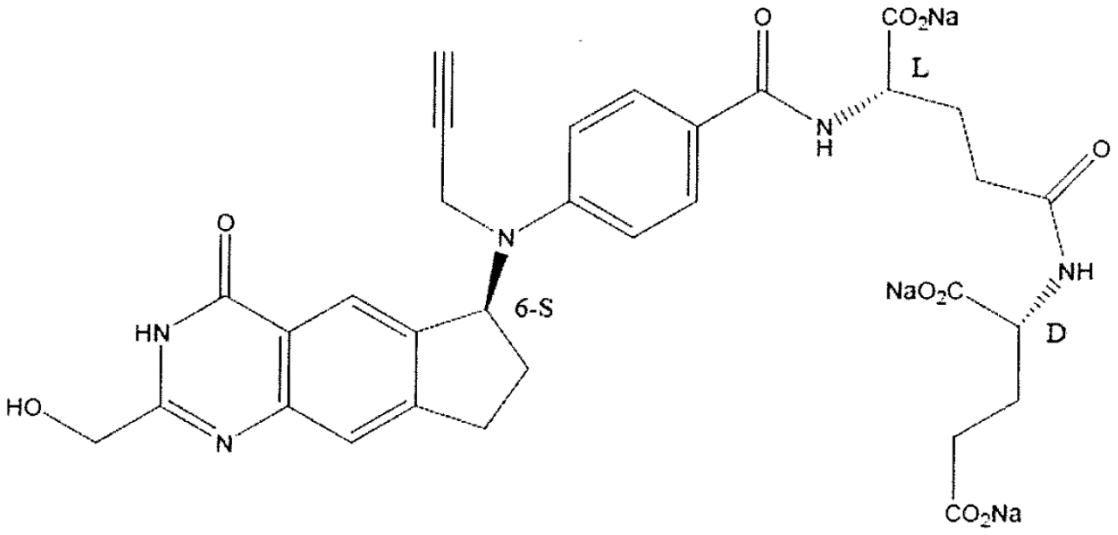
46. A dosage form as claimed in any one of claims 32 to 45 characterised in that it comprises a vial containing 10 to 24mg of a compound of formula I or a salt or ester thereof in dried solid or aqueous solution form.

47. Use of a compound chosen from formula I



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formula II



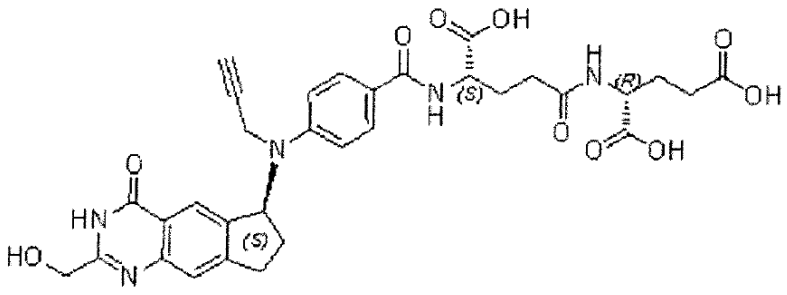
and pharmaceutically acceptable salts or esters thereof, in the manufacture of a medicament for the treatment of cancer that carries α-folate receptors, wherein

(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose of from 1mg/m^2 to 30mg/m^2 of compound per patient body surface area is to be administered per administration; and

(iii) the dose is to be administered intraperitoneally (IP).

48. Use of a compound of formula I



or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of cancer that carries α-folate receptors,

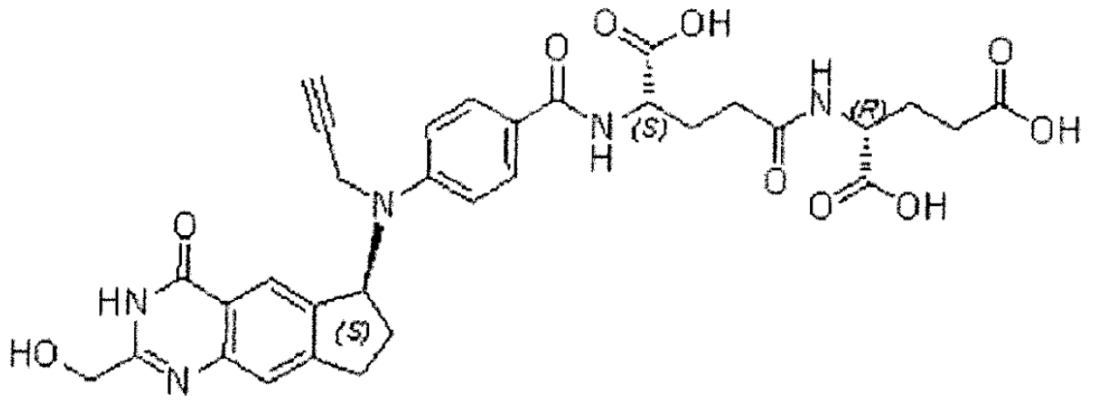
wherein the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

wherein a dose of from 1mg/m^2 to 30mg/m^2 of compound per patient body surface area is to be administered per administration; and

wherein the dose is to be administered intraperitoneally (IP).

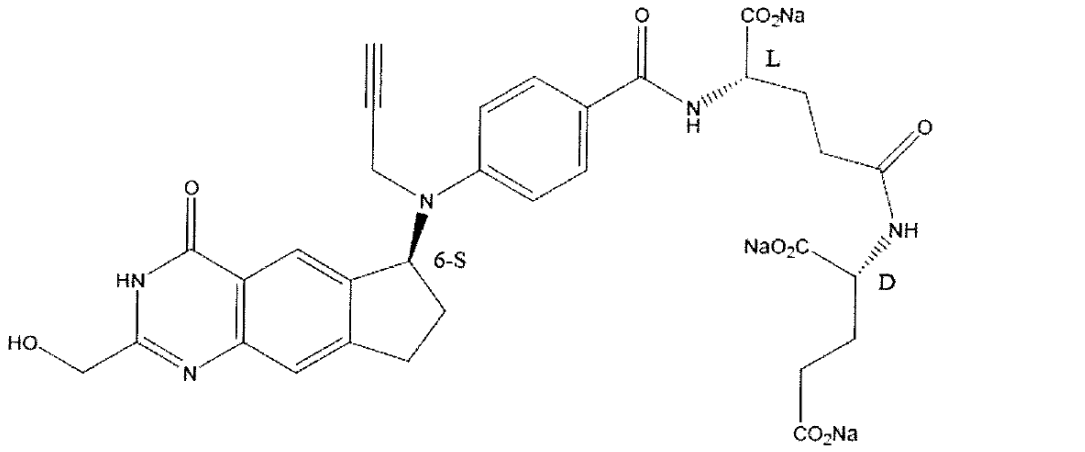
49. A use as claimed in claim 48 wherein the medicament is to be administered in combination with a therapeutically effective amount of one or more further anticancer agents.

50. Use of a compound chosen from formula I



,

formula II



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and pharmaceutically acceptable salts or esters thereof, in the manufacture of a medicament for the treatment of cancer that carries α-folate receptors, wherein

(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose of from 1mg/m^2 to 30mg/m^2 of compound per patient body surface area is to be administered per administration; and

(iii) wherein at least one side effect associated with classical thymidylate synthase inhibitors or alpha folate receptor antibody drug conjugates is not observed.

51. The use according to claim 50, wherein the at least one side effect is chosen from neutropenia, diarrhoea, hair loss, blurred vision or nausea.

52. A use as claimed in claim 50 or 51 characterised in that the cancer is selected from ovarian, endometrial, mesothelial, non-small cell lung and cancers derived from one of these.

53. A use as claimed in claim 50, 51, or 52 characterised in that it is selected from those expressing α-folate receptors (FR-α).

54. A use as claimed in claim 53 characterised in that the cancer expresses higher than background non-cancerous tissue levels of α-folate receptors.

55. A use as claimed in any one of claims 50 to 54 characterised in that the cancer is an ovarian cancer.

56. A use as claimed in any one of claims 50 to 55 characterised in that the cancer is epithelial ovarian, fallopian tube or peritoneal cancer.

57. A use as claimed in claim 55 or claim 56 characterised in that the cancer is serous ovarian cancer.

58. A use as claimed in claim 57 characterised in that the cancer is High-Grade Serous Ovarian Cancer (HGSOC).

59. A use as claimed in any one of claims 50 to 58 characterised in that the dose is to be administered intraperitoneally (IP) or intravenously (IV).

60. A use as claimed in any one of claims 50 to 59 characterised in that the dose is 3mg/m^2 to 30mg/m^2 of compound per patient body surface area per administration,

61. A use as claimed in any one claims 50 to 60 characterised in that each dose is to be administered as individual infusions spaced between 10 and 28 days apart.

62. A use as claimed in claim 61 characterised in that the infusions are spaced between 10 and 21 days apart.

63. A use as claimed in claim 62 characterised in that the infusions are to be administered at dosing interval of about 14 days.

64. A use as claimed in claim 63 characterised in that a cumulative maximum of 150mg/m^2 of compound per patient body surface area over the course of all the infusions.

65. A use as claimed in claim 64 characterised in that the maximum cumulative dose is 144mg/m^2.

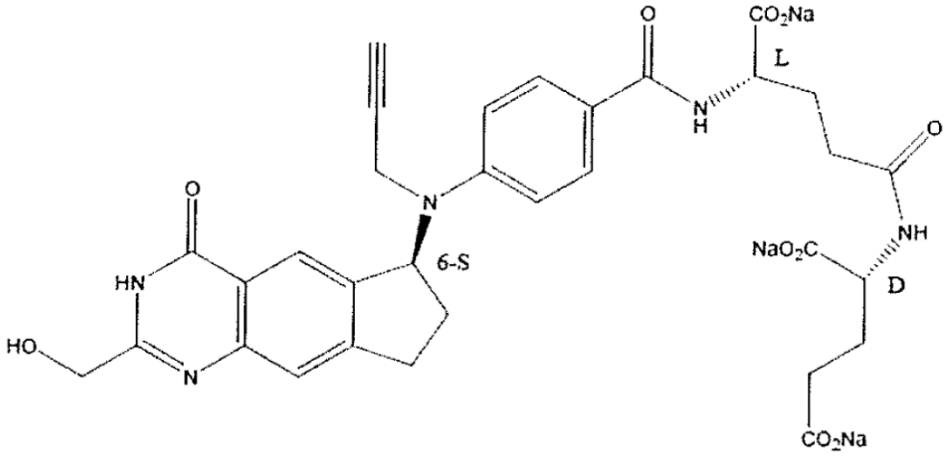
66. A use as claimed in any one of claims 50 to 65 characterised in that an infusion of 1mg/m^2 to 20mg/m is to be administered per administration.

67. A use as claimed in claim 66 characterised in that an infusion of 10mg/m^2 to 15mg/m^2 is to be administered per administration.

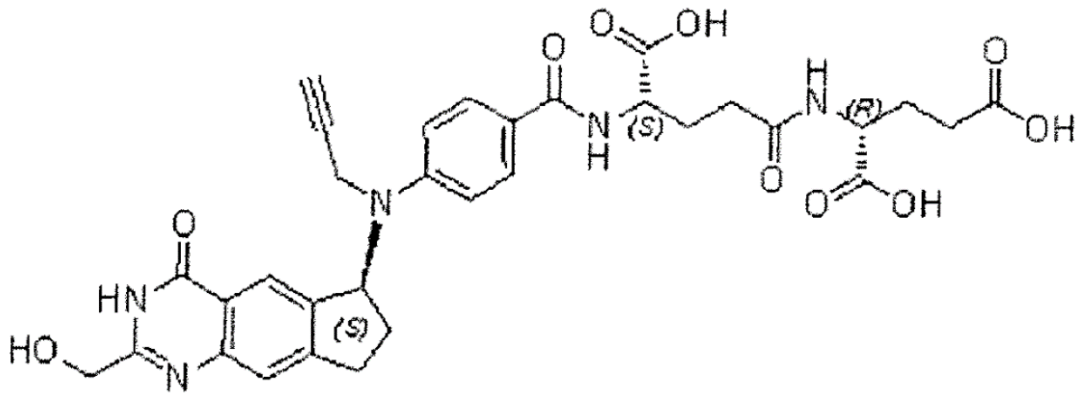
68. A use as claimed in claim 65 characterised in that an infusion of about 12mg/m^2 is to be administered per administration.

69. A use as claimed in any one of claims 50 to 68 characterised in that the dose is added to a saline drip.

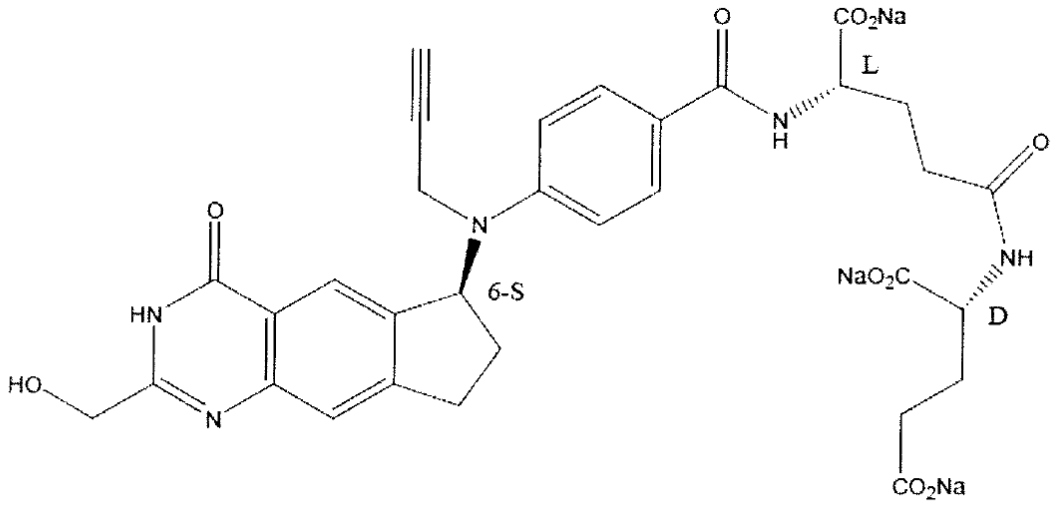
70. A use as claimed in any one of claims 50 to 69 characterised in that the compound is the trisodium salt of formula II



71. Use of a compound chosen from formula I



formula II



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and pharmaceutically acceptable salts or esters thereof, in the manufacture of a medicament for the treatment of cancer that carries α-folate receptors, wherein

(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose that achieves a concentration of 0.5 μM or greater of the compound for at least 72hrs is to be administered.

72. The use according to claim 71, wherein a dose that achieves a concentration of 0.7 μM or greater of the compound for at least 36hrs is to be administered.

73. The use according to claim 71, wherein a dose that achieves a concentration of 0.9 μM or greater of the compound for at least 24hrs is to be administered.

74. A use as claimed in claim 71, 72, or 73 characterised in that the cancer is selected from ovarian, endometrial, mesothelial, non-small cell lung and cancers derived from one of these.

75. A use as claimed in claim 71, 72, 73, or 74 characterised in that it is selected from those expressing α-folate receptors (FR-α).

76. A use as claimed in claim 75 characterised in that the cancer expresses higher than background non-cancerous tissue levels of α-folate receptors.

77. A use as claimed in any one of claims 71 to 76 characterised in that the cancer is an ovarian cancer.

78. A use as claimed in any one of claims 71 to 77 characterised in that the cancer is epithelial ovarian, fallopian tube or peritoneal cancer.

79. A use as claimed in claim 77 or claim 78 characterised in that the cancer is serous ovarian cancer.

80. A use as claimed in claim 79 characterised in that the cancer is High-Grade Serous Ovarian Cancer (HGSOC).

81. A use as claimed in any one of claims 71 to 80 characterised in that the dose is to be administered intraperitoneally (IP) or intravenously (IV).

82. A use as claimed in any one of claims 71 to 81 characterised in that the dose is 3mg/m^2 to 30mg/m^2 of compound per patient body surface area per administration,

83. A use as claimed in any one claims 71 to 82 characterised in that each dose is to be administered as individual infusions spaced between 10 and 28 days apart.

84. A use as claimed in claim 83 characterised in that the infusions are spaced between 10 and 21 days apart.

85. A use as claimed in claim 84 characterised in that the infusions are to be administered at dosing interval of about 14 days.

86. A use as claimed in claim 85 characterised in that a cumulative maximum of 150mg/m^2 of compound per patient body surface area is to be administered over the course of all the infusions.

87. A use as claimed in claim 86 characterised in that the maximum cumulative dose is 144mg/m^2.

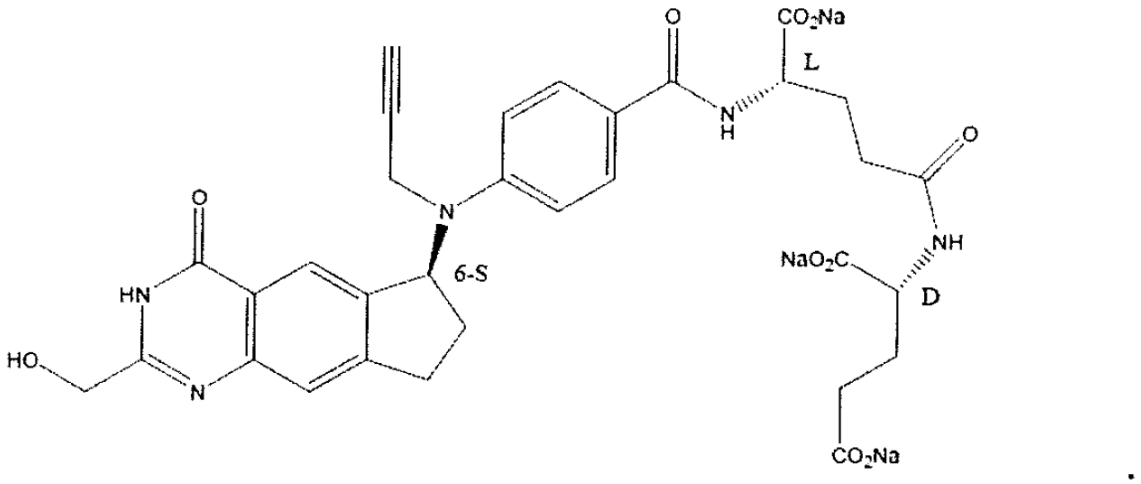
88. A use as claimed in any one of claims 71 to 87 characterised in that an infusion of 1mg/m^2 to 20mg/m^2 is to be administered per administration.

89. A use as claimed in claim 88 characterised in that an infusion of 10mg/m^2 to 15mg/m^2 is to be administered per administration.

90. A use as claimed in claim 87 characterised in that an infusion of about 12mg/m^2 is to be administered per administration.

91. A use as claimed in any one of claims 71 to 90 characterised in that the dose is added to a saline drip.

92. A use as claimed in any one of claims 71 to 91 characterised in that the compound is the trisodium salt of formula II



93. A use as claimed in Claim 1 wherein a dosage regimen to be administered is selected from the group

• a dose of 1 to 10mg/m^2 to be administered in a 28 day cycle at 7 day intervals on day 1, 8, 15 and 22.

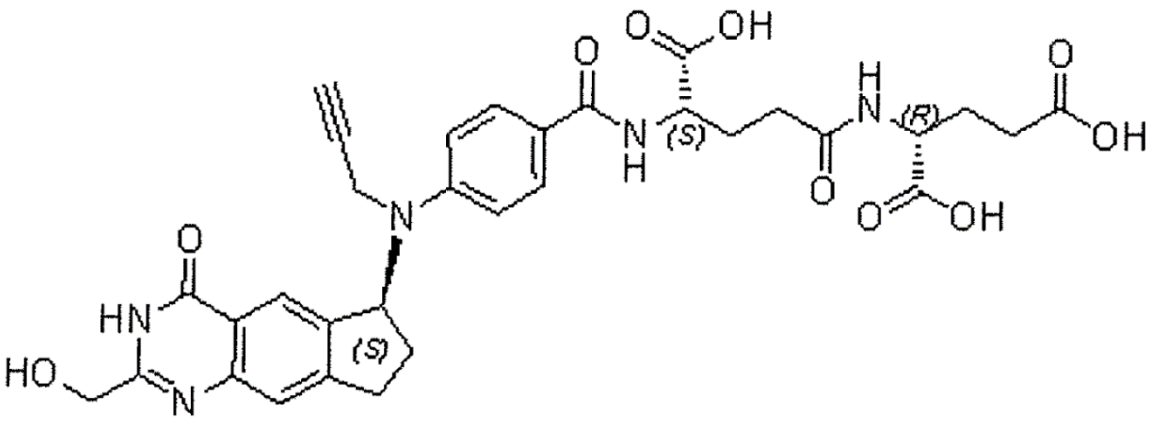
• a dose of 6 to 14mg/m^2 to be administered in a 28 day cycle at 14 day intervals on day 1 and 15

• a dose of 10 to 30mg/m^2 to be administered in a 21 day cycle on day 1.

94. A use as claimed in Claim 93 wherein the dosage regimen is a dose of 10 to 14mg/m^2 to be administered in a 28 day cycle at 14 day intervals on day 1 and 15.

95. A use as claimed in Claim 93 wherein the dosage regimen is a dose of 10 to 14mg/m^2 to be administered in a 21 day cycle on day 1.

96. Use of a pharmaceutical composition comprising a compound of formula I



or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of cancer that carries α-folate receptors, wherein

(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy and

(ii) a dose of between 1 mg/m^2 and 30mg/m^2 of compound per patient body surface area per administration.