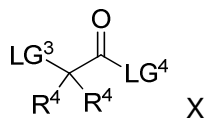
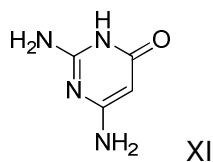


or a suitably protected derivative thereof, wherein R¹, R² and n are as defined herein,
with a compound of formula X

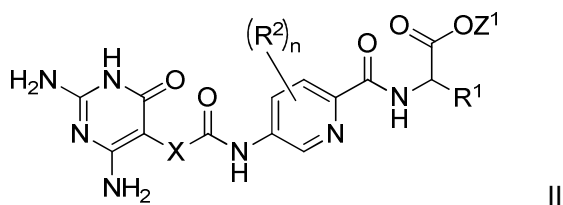


wherein each R⁴ is as defined herein and each of LG³ and LG⁴ independently represents
5 a suitable leaving group, and a compound of formula XI



or a suitably protected derivative thereof, under conditions known to those skilled in the
art.

10 A further aspect is a compound of formula II



wherein R¹, R², X and n are as defined herein and Z¹ represents

- (a) C₁₋₆ alkyl optionally substituted with one or more phenyl, or
- (b) phenyl.

15

In another aspect, there is provided a compound as described herein for use as a
pharmaceutical.

In yet another aspect, there is provided a pharmaceutical composition comprising a
20 compound as described herein, and optionally one or more pharmaceutically-acceptable
excipient.

In a further aspect, there is provided a compound as described herein for use in the
treatment or prophylaxis of a disease or disorder where modulation of
25 methylenetetrahydrofolate dehydrogenase/cyclohydrolase 2 (MTHFD2) activity exerts a
therapeutic effect.

In another aspect, there is provided a use of a compound as described herein for the
manufacture of a medicament for the treatment or prophylaxis of a disease or disorder

where modulation of methylenetetrahydrofolate dehydrogenase/cyclohydrolase 2 (MTHFD2) activity exerts a therapeutic effect.

In yet another aspect, there is provided a combination product comprising (I) a compound as described herein; and (II) one or more other therapeutic agent that is useful in the treatment of a disease or disorder where modulation of methylenetetrahydrofolate dehydrogenase/cyclohydrolase 2 (MTHFD2) activity exerts a therapeutic effect, wherein each of components (I) and (II) is formulated in admixture, optionally with one or more pharmaceutically-acceptable excipient.

In a further aspect, the present disclosure provides a kit-of-parts comprising: (a) a pharmaceutical formulation as described herein; and (b) one or more other therapeutic agent that is useful in the treatment of a disease or disorder where modulation of methylenetetrahydrofolate dehydrogenase/cyclohydrolase 2 (MTHFD2) activity exerts a therapeutic effect, optionally in admixture with one or more pharmaceutically-acceptable excipient, which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

Further aspects and embodiments are as described herein below.

Brief description of the drawings

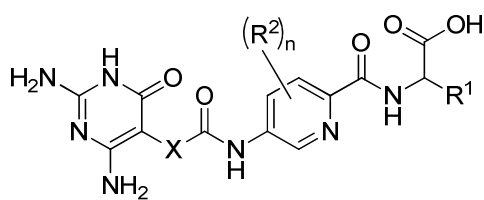
Figure 1 is a semilogarithmic graph showing the viability, compared to untreated cells, of (A) resting T cells or (B) activated T cells upon 7 days of treatment with either Example 4 (solid lines) or azathioprine (dashed lines) at various concentrations (in M).

Figure 2 is a Western blot image showing expression levels of MTHFD2 and actin in resting versus activated primary T cells (PTC) from 2 donors (D1 and D2) and HL-60 cancer cells.

Figure 3 is a bar chart representing the intensity of the MTHFD2 Western blot bands obtained for the resting and activated primary T cells from donors D1 and D2, respectively, and for the HL-60 cancer cells.

Claims

1. A compound of formula I



5 or a pharmaceutically-acceptable salt thereof, wherein:

R¹ represents

- (i) C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl each optionally substituted by one or more groups independently selected from oxy and A¹,
- 10 (ii) aryl optionally substituted by one or more groups independently selected from oxy and A²,
- (iii) heteroaryl optionally substituted by one or more groups independently selected from oxy and A³,
- (iv) heterocyclyl optionally substituted by one or more groups independently selected
- 15 from oxy and A⁴, or
- (v) -(CH₂)₂C(O)-G;

each R² independently represents

- (i) halo, -NO₂, -CN, -R^{1a}, -OR^{1b}, -S(O)_pR^{1c}, -S(O)_q(R^{1d})(R^{1e}), -N(R^{1f})S(O)_rR^{1g}, -N(R^{1h})(R¹ⁱ),
- 20 -C(O)OR^{1j}, or -C(O)N(R^{1k})(R^{1l}),
- (ii) aryl optionally substituted by one or more groups independently selected from oxy and A⁵,
- (iii) heteroaryl optionally substituted by one or more groups independently selected from oxy and A⁶, or
- 25 (iv) heterocyclyl optionally substituted by one or more groups independently selected from oxy and A⁷;

n represents 0 to 3;

30 X represents -N(R³)- or -C(R⁴)₂-;

R³ represents H or C₁₋₃ alkyl optionally substituted by one or more fluoro;

each R⁴ independently represents H, fluoro or C₁₋₃ alkyl optionally substituted by one or more fluoro;

G represents -OH, or a mono- or poly-glutamic acid group;

5

each of A¹ to A⁷ independently represents

(i) halo, -NO₂, -CN, -R^{2a}, -OR^{2b}, -S(O)_pR^{2c}, -S(O)_qN(R^{2d})(R^{2e}), -N(R^{2f})S(O)_rR^{2g},
-N(R^{2h})(R²ⁱ), -C(O)OR^{2j}, or -C(O)N(R^{2k})(R^{2l}),

(ii) aryl optionally substituted by one or more groups independently selected from oxy
10 and B¹,

(iii) heteroaryl optionally substituted by one or more groups independently selected from
oxy and B², or

(iv) heterocyclyl optionally substituted by one or more groups independently selected
from oxy and B³;

15

each R^{1a} and R^{2a} independently represents

(i) C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein each such alkyl, alkenyl or alkynyl group
is optionally substituted by one or more groups independently selected from oxy and D¹;

(ii) aryl optionally substituted by one or more groups independently selected from oxy
20 and D²,

(iii) heteroaryl optionally substituted by one or more groups independently selected from
oxy and D³, or

(iv) heterocyclyl optionally substituted by one or more groups independently selected
from oxy and D⁴;

25

each R^{1b} to R^{1l} and R^{2b} to R^{2l} independently represents H or

(i) C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein each such alkyl, alkenyl or alkynyl group
is optionally substituted by one or more groups independently selected from oxy and D¹;

(ii) aryl optionally substituted by one or more groups independently selected from oxy
30 and D²,

(iii) heteroaryl optionally substituted by one or more groups independently selected from
oxy and D³, or

(iv) heterocyclyl optionally substituted by one or more groups independently selected
from oxy and D⁴;

35

each of B¹ to B³ independently represents

(i) halo, -NO₂, -CN, -R^{3a}, -OR^{3b}, -S(O)_pR^{3c}, -S(O)_qN(R^{3d})(R^{3e}), -N(R^{3f})S(O)_rR^{3g},

-N(R^{3h})(R³ⁱ), -C(O)OR^{3j}, or -C(O)N(R^{3k})(R^{3l}),

(ii) aryl optionally substituted by one or more groups independently selected from oxy and E¹,

(iii) heteroaryl optionally substituted by one or more groups independently selected from oxy and E², or

(iv) heterocyclyl optionally substituted by one or more groups independently selected from oxy and E³;

each D¹ independently represents

(i) halo, -NO₂, -CN, -OR^{4b}, -S(O)_pR^{4c}, -S(O)_qN(R^{4d})(R^{4e}), -N(R^{4f})S(O)_rR^{4g}, -N(R^{4h})(R⁴ⁱ), -C(O)OR^{4j}, or -C(O)N(R^{4k})(R^{4l}),

(ii) aryl optionally substituted by one or more groups independently selected from oxy and E⁴,

(iii) heteroaryl optionally substituted by one or more groups independently selected from oxy and E⁵, or

(iv) heterocyclyl optionally substituted by one or more groups independently selected from oxy and E⁶;

each D² to D⁴ independently represents

(i) halo, -NO₂, -CN, -R^{4a}, -OR^{4b}, -S(O)_pR^{4c}, -S(O)_qN(R^{4d})(R^{4e}), -N(R^{4f})S(O)_rR^{4g}, -N(R^{4h})(R⁴ⁱ), -C(O)OR^{4j}, or -C(O)N(R^{4k})(R^{4l}),

(ii) aryl optionally substituted by one or more groups independently selected from oxy and E⁴,

(iii) heteroaryl optionally substituted by one or more groups independently selected from oxy and E⁵, or

(iv) heterocyclyl optionally substituted by one or more groups independently selected from oxy and E⁶;

each R^{3a} and R^{4a} independently represents C₁₋₃ alkyl optionally substituted with one or more fluoro;

each R^{3b} to R^{3l}, and R^{4b} to R^{4l} independently represents H or C₁₋₃ alkyl optionally substituted with one or more fluoro;

each E¹ to E⁶ independently represents halo, -NO₂, -CN, -R^{5a}, -OR^{5b}, -S(O)_pR^{5c}, -S(O)_qN(R^{5d})(R^{5e}), -N(R^{5f})S(O)_rR^{5g}, -N(R^{5h})(R⁵ⁱ), -C(O)OR^{5j}, or -C(O)N(R^{5k})(R^{5l});

each R^{5a} independently represents C₁₋₃ alkyl optionally substituted with one or more fluoro;

each R^{5b} to R^{5l} independently represents H or C₁₋₃ alkyl optionally substituted with one or
5 more fluoro; and

each p, q and r independently represents 0, 1 or 2.

2. A compound as claimed in Claim 1, wherein R¹ represents

- 10 (i) C₁₋₆ alkyl optionally substituted by one or more groups independently selected from oxy and A¹,
(ii) phenyl optionally substituted by one or more groups independently selected from A²,
or
(iii) -(CH₂)₂C(O)-G.

15 3. A compound as claimed in Claim 1 or 2, wherein R¹ represents:

- (i) C₁₋₆ alkyl optionally substituted by one or more groups independently selected from
oxy and A¹, or
(ii) -(CH₂)₂C(O)-G.

20 4. A compound as claimed in any one of Claims 1 to 3, wherein G represents -OH or a mono-glutamic acid group.

5. A compound as claimed in any one of Claims 1 to 4, wherein each A¹ independently
25 represents:

- (i) -R^{2a}, -N(R^{2f})S(O)_rR^{2g}, -C(O)OR^{2j} or -C(O)N(R^{2k})(R^{2l}),
(ii) phenyl optionally substituted by one or more groups independently selected from oxy
and B¹, or
(iii) heteroaryl optionally substituted by one or more groups independently selected from
30 oxy and B².

6. A compound as claimed in any one of Claims 1 to 5, wherein

R^{2a} represents aryl optionally substituted by one or more groups independently selected
from oxy and D²;

35 R^{2f} represents H;

R^{2g} represents aryl optionally substituted by one or more groups independently selected
from oxy and D²;

R^{2j} represents C₁₋₆ alkyl or H;

R^{2k} represents H; and

R^{2l} represents C₁₋₆ alkyl optionally substituted by one or more groups independently selected from oxy and D¹.

5

7. A compound as claimed in any one of Claims 1 to 6, wherein each R² independently represents, halo, -R^{1a} or -OR^{1b}.

8. A compound as claimed in any one of Claims 1 to 7, wherein

10 each R^{1a} independently represents C₁₋₆ alkyl or C₂₋₆ alkenyl each optionally substituted by one or more groups independently selected from oxy and fluoro; and each R^{1b} represents C₁₋₆ alkyl or phenyl.

9. A compound as claimed in any one of Claims 1 to 8, wherein n represents 0 or 1.

15

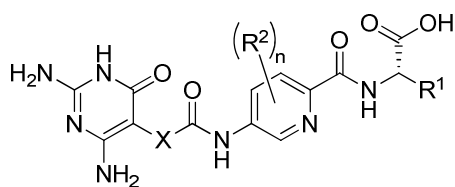
10. A compound as claimed in any one of Claims 1 to 9, wherein each R⁴ represents H.

11. A compound as claimed in any one of Claims 1 to 10, wherein R³ represents H.

20

12. A compound as claimed in any one of Claims 1 to 10, wherein X is -C(R⁴)₂-.

13. A compound as claimed in any one of Claims 1 to 12, wherein the compound of formula I is a compound of formula Ia



Ia

25

wherein R¹, R², X and n are as defined in any one of Claims 1 to 12.

14. A compound as claimed in Claim 1, selected from

(2S)-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino}pyridin-2-yl)formamido]pentanedioic acid,

30

(2S)-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino}pyridin-2-yl)formamido]-3-phenylpropanoic acid,

(2S)-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino}pyridin-2-yl)formamido]-3-methylbutanoic acid,

- (2S)-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)pyridin-2-yl)formamido]-4-(1H-1,2,3,4-tetrazol-5-yl)butanoic acid,
- (2S)-2-[(3-chloro-5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)pyridin-2-yl)formamido]pentanedioic acid,
- 5 (2S)-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)-3-fluoropyridin-2-yl)formamido]pentanedioic acid,
- (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]pyridin-2-yl)formamido]pentanedioic acid,
- (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]pyridin-2-yl)formamido]-3-phenylpropanoic acid,
- 10 (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]pyridin-2-yl)formamido]-4-(1H-1,2,3,4-tetrazol-5-yl)butanoic acid,
- (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]-3-fluoropyridin-2-yl)formamido]pentanedioic acid,
- 15 (2S)-3-cyclopentyl-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)pyridin-2-yl)formamido]propanoic acid,
- (2S)-2-cyclohexyl-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)pyridin-2-yl)formamido]acetic acid,
- (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]pyridin-2-yl)formamido]-3-methylbutanoic acid,
- 20 (2S)-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)pyridin-2-yl)formamido]-4-phenylbutanoic acid,
- (2S)-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)pyridin-2-yl)formamido]-2-phenylacetic acid,
- 25 (2S)-4-[(benzenesulfonyl)carbamoyl]-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)pyridin-2-yl)formamido]butanoic acid,
- (2S)-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)pyridin-2-yl)formamido]hexanedioic acid,
- (2S)-2-[(6-cyclopropoxy-5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)pyridin-2-yl)formamido]pentanedioic acid,
- 30 (2S)-2-[(3-chloro-5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]pyridin-2-yl)formamido]pentanedioic acid,
- (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]-3-methylpyridin-2-yl)formamido]pentanedioic acid,
- 35 (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]-6-ethenylpyridin-2-yl)formamido]pentanedioic acid,

(2S)-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)pyridin-2-yl)formamido]butanedioic acid,
 (2S)-2-[(4S)-4-carboxy-4-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)pyridin-2-yl)formamido]butanamido]pentanedioic acid,
 5 (2S)-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)-3-fluoropyridin-2-yl)formamido]-4-(1H-1,2,3,4-tetrazol-5-yl)butanoic acid,
 (2R)-2-[(4S)-4-carboxy-4-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)pyridin-2-yl)formamido]butanamido]pentanedioic acid,
 (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]-6-phenoxy)pyridin-2-yl)formamido]pentanedioic acid,
 10 (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]-6-phenyl)pyridin-2-yl)formamido]pentanedioic acid,
 (2S)-2-[(4S)-4-carboxy-4-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]pyridin-2-yl)formamido]butanamido]pentanedioic acid,
 15 (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]-6-methoxy)pyridin-2-yl)formamido]pentanedioic acid,
 (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]-3-(trifluoromethyl)pyridin-2-yl)formamido]pentanedioic acid,
 (2S)-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)-3-fluoropyridin-2-yl)formamido]-3-methylbutanoic acid,
 20 (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]-3-fluoropyridin-2-yl)formamido]-4-(1H-1,2,3,4-tetrazol-5-yl)butanoic acid,
 (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]-3-fluoropyridin-2-yl)formamido]-3-phenylpropanoic acid,
 25 (2S)-2-[(5-[2-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)acetamido]-3-fluoropyridin-2-yl)formamido]-3-methylbutanoic acid, and
 (2S)-2-[(5-[(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl]amino)-3-fluoropyridin-2-yl)formamido]-3-phenylpropanoic acid,
 or a pharmaceutically acceptable salt thereof.

30

15. A compound as claimed in any one of Claims 1 to 14 for use as a pharmaceutical.

16. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 14, and optionally one or more pharmaceutically-acceptable excipient.

35

17. A compound as claimed in any one of Claims 1 to 14 for use in the treatment or prophylaxis of a disease or disorder where modulation of methylenetetrahydrofolate dehydrogenase/cyclohydrolase 2 (MTHFD2) activity exerts a therapeutic effect.
- 5 18. Use of a compound as defined in any one of Claims 1 to 14 for the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder where modulation of methylenetetrahydrofolate dehydrogenase/cyclohydrolase 2 (MTHFD2) activity exerts a therapeutic effect.
- 10 19. The compound for use, or the use as claimed in Claim 17 or 18, wherein the disease or disorder where modulation of methylenetetrahydrofolate dehydrogenase/cyclohydrolase 2 (MTHFD2) activity exerts a therapeutic effect is a cell proliferation disorder.
- 15 20. The compound for use, or the use as claimed in Claim 19, wherein the cell proliferation disorder is a selected from the group consisting of cancer; inflammation; autoimmune diseases; and host-versus-graft diseases.
- 20 21. The compound for use, or the use as claimed in Claim 20, wherein the inflammation or host-versus-graft disease is selected from the group consisting of:
asthma, COPD, rheumatoid arthritis, systemic lupus erythematosus, irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, multiple sclerosis, lymphoproliferative diseases, rejection after organ transplantation, Wegener's granulomatosis, psoriasis, Mb Bechterews, Behcets disease, Guillain Barre, dermatomyositis, myositis, polymyositis,
25 primary biliary cirrhosis, anti-phospholipid syndrome, autoimmune hepatitis, autoimmune cardiomyopathy, alopecia areata, atherosclerosis, type 1 diabetes, autoimmune uveitis, Goodpasteure's syndrome, Graves' disease, Hashimoto's disease, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, Sjögren's syndrome, giant cell arteritis, vasculitis, Churg-Strauss syndrome, postpolio syndrome,
30 idiopathic thrombocytopenic purpura, Peyronie disease and Dupuytren's contracture.

22. The compound for use, or the use as claimed in Claim 20, wherein the cancer is selected from the group consisting of leukemia; lymphomas; carcinomas, including adenocarcinomas; lymphoblastomas; glioblastomas; neuroblastomas; lymphomas; and sarcomas.

5

23. A combination product comprising:

(I) a compound as claimed in any one of Claims 1 to 14; and

(II) one or more other therapeutic agent that is useful in the treatment of a disease or disorder where modulation of methylenetetrahydrofolate dehydrogenase/cyclohydrolase

10 2 (MTHFD2) activity exerts a therapeutic effect,

wherein each of components (I) and (II) is formulated in admixture, optionally with one or more pharmaceutically-acceptable excipient.

24. A kit-of-parts comprising:

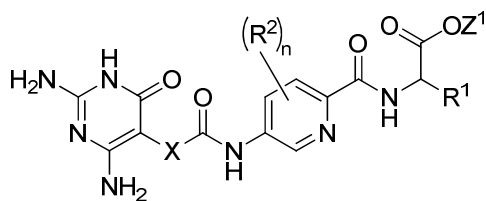
15 (a) a pharmaceutical formulation as claimed in Claim 16; and

(b) one or more other therapeutic agent that is useful in the treatment of a disease or disorder where modulation of methylenetetrahydrofolate dehydrogenase/cyclohydrolase 2 (MTHFD2) activity exerts a therapeutic effect, optionally in admixture with one or more pharmaceutically-acceptable excipient,

20 which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

25. A process for the preparation of a compound of formula I as defined in any one of Claims 1 to 13, comprising the steps of:

25 (i) hydrolysis of a corresponding ester of formula II



II

wherein R¹, R² and n are as defined in any one of Claims 1 to 13 and Z¹ represents

(a) C₁₋₆ alkyl optionally substituted with one or more phenyl, or

(b) phenyl,

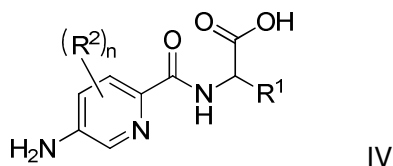
30 under conditions known to those skilled in the art, such as in the presence of aqueous hydroxide ions;

(ii) for compounds comprising one or more additional carboxylic acid moiety, hydrolysis of a compound of formula I, as defined in any one of Claims 1 to 13, or a compound of formula II wherein the one or more additional carboxylic acid moieties are instead present as a group of formula $-C(O)OZ^2$, wherein each Z^2 independently represents

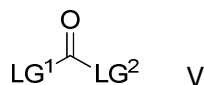
- 5 (a) C_{1-6} alkyl optionally substituted with one or more phenyl, or
 (b) phenyl,

under conditions known to those skilled in the art, such as in the presence of aqueous hydroxide ions;

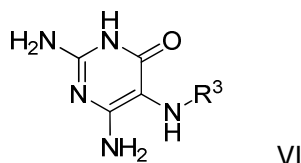
- 10 (iii) for compounds wherein X represents $-NH-$, reaction of a compound of formula IV



or a suitably protected derivative thereof, wherein R^1 , R^2 and n are as defined in any one of Claims 1 to 13, with a compound of formula V

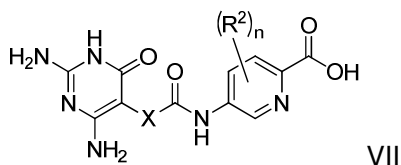


- 15 wherein LG^1 and LG^2 each represent suitable leaving groups, and a compound of formula VI

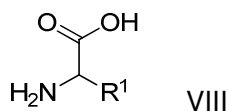


wherein R^3 is as defined in any one of Claims 1 to 13, or a suitable salt thereof under conditions known to those skilled in the art, such as in the presence of a suitable solvent
 20 and optionally a suitable base;

(iv) reaction of a compound of formula VII

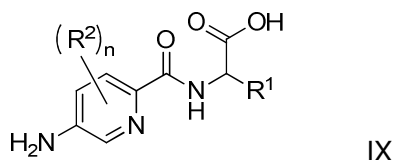


or a suitably protected derivative thereof, wherein R^2 and n are as defined in any one of
 25 Claims 1 to 13, with a compound of formula VIII

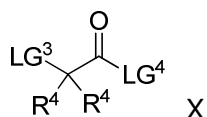


wherein R¹ is as defined for compounds of formula I in any one of Claims 1 to 13, under conditions known to those skilled in the art; or

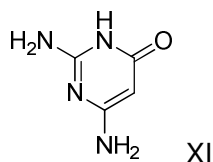
- 5 (v) for compounds wherein X represents -CH₂-, reaction of a compound of formula IX



or a suitably protected derivative thereof, wherein R¹, R² and n are as defined for compounds of formula I in any one of Claims 1 to 13, with a compound of formula X



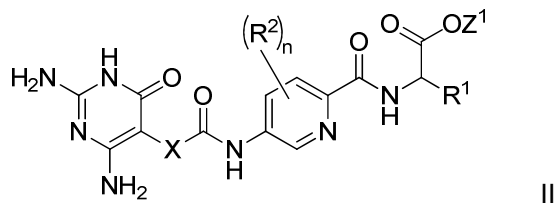
- 10 wherein each R⁴ is as defined in any one of Claims 1 to 13, and each of LG³ and LG⁴ independently represents a leaving group, and a compound of formula XI



or a suitably protected derivative thereof, under conditions known to those skilled in the art.

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26. A compound of formula II



or a salt thereof,

wherein R¹, R², n and X are as defined in any one of Claims 1 to 13, and

- 20 Z¹ represents

- (a) C₁₋₆ alkyl optionally substituted with one or more phenyl, or
- (b) phenyl.