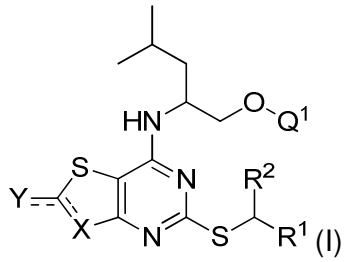
Claims

1. A compound of formula I,



(I)

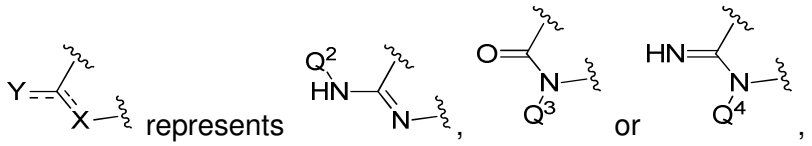
wherein

R^1 represents aryl or pyridyl, both of which are optionally substituted by one or more groups selected from halo, -CN, $-C(O)NR^3R^4$, $-S(O)_2R^5$, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein the latter three groups are optionally substituted by one or more F;

R^2 represents H or C_{1-6} alkyl optionally substituted by one or more F;

R^3 and R^4 each independently represent H or C_{1-6} alkyl optionally substituted by one of more F;

R^5 represents C_{1-6} alkyl optionally substituted by one or more F;



represents

,

or

,

wherein "〰" indicates a point of attachment to the rest of the molecule;

Q^1 and Q^2 each independently represent H or $-PO(OR^6)(OR^7)$;

Q^3 represents H or $-CH_2OPO(OR^6)(OR^7)$; and

Q^4 represents $-CH_2OPO(OR^6)(OR^7)$;

wherein R^6 and R^7 each independently represent H, C_{1-4} alkyl or C_{2-4} alkenyl;

wherein at least one of Q^1, and Q^2, Q^3 or Q^4 represents $-PO(OR^6)(OR^7)$ or $-CH_2OPO(OR^6)(OR^7)$;

or a pharmaceutically-acceptable salt thereof.

2. A compound as claimed in Claim 1, wherein R^1 represents phenyl or pyridyl, both of which are optionally substituted by one or more fluoro, chloro, bromo, -CN, $-C(O)NR^3R^4$ or $-S(O)_2Me$ group

optionally

wherein R^1 represents phenyl or pyridyl, both of which are optionally substituted by one or more fluoro, chloro or bromo group;

such as

wherein R^1 represents phenyl or 5-chloropyridin-2-yl.

3. A compound as claimed in of Claims 1 or Claim 2, wherein R^2 represents C_{1-6} alkyl optionally substituted by one or more F;

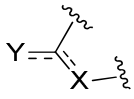
optionally

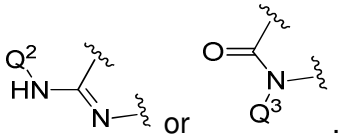
wherein R^2 represents C_{1-3} alkyl;

such as

wherein R^2 represents methyl.

4. A compound as claimed in any one of Claims 1 to 3, wherein one of Q^1 and Q^2, Q^3 or Q^4 represents $-PO(OR^6)(OR^7)$ or $-CH_2OPO(OR^6)(OR^7)$, and the remainder of Q^1, and (if present) Q^2 or Q^3 represent H.

5. A compound as claimed in any one of Claims 1 to 4, wherein  represents

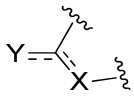
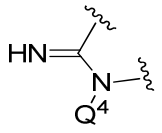


.

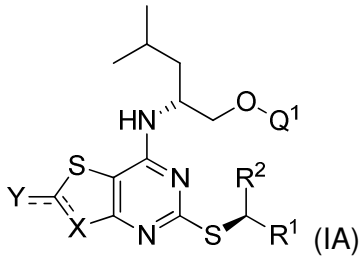
6. A compound as claimed in Claim 5, wherein Q^1 represents $-PO(OR^6)(OR^7)$; or

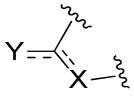
wherein Q^2 represents $-PO(OR^6)(OR^7)$; or

wherein Q^3 represents $-CH_2OPO(OR^6)(OR^7)$.

7. A compound as claimed in any one of Claims 1 to 4, wherein  represents .

8. A compound as claimed in any one of Claims 1 to 7, wherein the compound is a compound of formula IA,


(IA)

wherein R^1, R^2, Q^1, Q^2 and  are as defined in any one of the preceding claims, or a pharmaceutically-acceptable salt thereof.

9. A compound as claimed in any one of Claims 1 to 8, wherein R^6 and R^7 each independently represent $C_{1\text{-}3}$ alkyl or H, optionally wherein

(a) R^6 and R^7 each represent methyl or each represent ethyl; or

(b) R^6 represents *iso*-propyl and R^7 represents H..

10. A compound as claimed in Claim 9, wherein R^6 and R^7 each represent H.

11. A compound as claimed in any one of Claims 1 to 8, wherein one of Q^1 and Q^2, Q^3 or Q^4 represents $-PO(OR^6)(OR^7)$ or $-CH_2OPO(OR^6)(OR^7)$, and the remainder of Q^1, and (if present) Q^2 or Q^3 represent H, and R^6 and R^7 represent H.

12. A compound as claimed in Claim 1, wherein the compound is selected from the group consisting of:

(2*R*)-2-[(2-Amino-5-{[(1*S*)-1-phenylethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate;

(2*R*)-2-[(2-Amino-5-{[1-(2-fluorophenyl)ethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate;

(2*R*)-2-[(2-Amino-5-{[1-(2-chlorophenyl)ethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate;
(2*R*)-2-[(2-Amino-5-{[1-(5-chloropyridin-2-yl)ethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate;
(2*R*)-2-[(2-Amino-5-{[1-(3-fluoropyridin-2-yl)ethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate;
(2*R*)-2-[(2-Amino-5-{[1-(3-cyanophenyl)ethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate;
(2*R*)-2-[(2-Amino-5-{[1-(3-carbamoylphenyl)ethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate;
(2*R*)-2-{[2-Amino-5-({1-[4-(methylsulfonyl)phenyl]ethyl}sulfanyl)[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl]amino}-4-methylpentyl dihydrogen phosphate;
(2*R*)-2-[(2-Amino-5-{[4-(methylsulfonyl)benzyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate;
(2*R*)-2-({2-Amino-5-[(1-pyridin-2-ylethyl)sulfanyl][1,3]thiazolo[4,5-*d*]pyrimidin-7-yl}amino)-4-methylpentyl dihydrogen phosphate;
(2*R*)-2-[(2-Amino-5-{[(1*S*)-1-phenylethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dimethyl phosphate;
(2*R*)-2-[(2-Amino-5-{[(1*S*)-1-phenylethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl diethyl phosphate;
(2*R*)-2-[(2-Amino-5-{[(1*S*)-1-phenylethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl bis(1-methylethyl) phosphate;
(2*R*)-2-[(2-Amino-5-{[(1*S*)-1-phenylethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl 1-methylethyl hydrogen phosphate;
(2*R*)-2-[(2-Amino-5-{[1-(2-fluorophenyl)ethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl diethyl phosphate;
(2*R*)-2-[(2-Amino-5-{[1-(2-chlorophenyl)ethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl diethyl phosphate;
(2*R*)-2-[(2-Amino-5-{[1-(5-chloropyridin-2-yl)ethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl diethyl phosphate;
(2*R*)-2-[(2-Amino-5-{[1-(3-fluoropyridin-2-yl)ethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl diethyl phosphate;
(2*R*)-2-[(2-Amino-5-{[1-(3-cyanophenyl)ethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl diethyl phosphate;
[7-{[(1*R*)-1-(Hydroxymethyl)-3-methylbutyl]amino}-2-imino-5-{[(1*S*)-1-phenylethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-3(2*H*)-yl]methyl dihydrogen phosphate;
[5-{[1-(2-Fluorophenyl)ethyl]sulfanyl}-7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}-2-imino[1,3]thiazolo[4,5-*d*]pyrimidin-3(2*H*)-yl]methyl dihydrogen phosphate;
[5-{[1-(2-Chlorophenyl)ethyl]sulfanyl}-7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}-2-imino[1,3]thiazolo[4,5-*d*]pyrimidin-3(2*H*)-yl]methyl dihydrogen phosphate;
[5-{[1-(5-Chloropyridin-2-yl)ethyl]sulfanyl}-7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}-2-imino[1,3]thiazolo[4,5-*d*]pyrimidin-3(2*H*)-yl]methyl dihydrogen phosphate;
[7-{[(1*R*)-1-(Hydroxymethyl)-3-methylbutyl]amino}-2-imino-5-[(1-pyridin-2-ylethyl)sulfanyl][1,3]thiazolo[4,5-*d*]pyrimidin-3(2*H*)-yl]methyl dihydrogen phosphate;
[5-{[1-(3-Fluoropyridin-2-yl)ethyl]sulfanyl}-7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}-2-imino[1,3]thiazolo[4,5-*d*]pyrimidin-3(2*H*)-yl]methyl dihydrogen phosphate;

[5-{[1-(3-Cyanophenyl)ethyl]sulfanyl}-7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}-2-imino[1,3]thiazolo[4,5-*d*]pyrimidin-3(2*H*)-yl]methyl dihydrogen phosphate;
[5-{[(1*S*)-1-(5-Chloropyridin-2-yl)ethyl]sulfanyl}-7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}-2-oxo[1,3]thiazolo[4,5-*d*]pyrimidin-3(2*H*)-yl]methyl dihydrogen phosphate;
(2*R*)-2-[(5-{[(1*S*)-1-(5-chloropyridin-2-yl)ethyl]sulfanyl}-2-oxo-2,3-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate;
(2*R*)-4-Methyl-2-({2-oxo-5-[(1-pyridin-2-ylethyl)sulfanyl]-2,3-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl}amino)pentyl dihydrogen phosphate;
(2*R*)-4-Methyl-2-{[5-({1-[4-(methylsulfonyl)phenyl]ethyl}sulfanyl)-2-oxo-2,3-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl]amino}pentyl dihydrogen phosphate;
(2*R*)-2-[(5-{[1-(3-Carbamoylphenyl)ethyl]sulfanyl}-2-oxo-2,3-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate;
(2*R*)-2-[(5-{[1-(2-Chlorophenyl)ethyl]sulfanyl}-2-oxo-2,3-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate;
(2*R*)-2-[(5-{[1-(3-Cyanophenyl)ethyl]sulfanyl}-2-oxo-2,3-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate;
(2*R*)-2-[(5-{[(1*S*)-1-(5-Chloropyridin-2-yl)ethyl]sulfanyl}-2-oxo-2,3-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dimethyl phosphate;
(2*R*)-2-[(5-{[(1*S*)-1-(5-Chloropyridin-2-yl)ethyl]sulfanyl}-2-oxo-2,3-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl diethyl phosphate;
(7-{[(1*R*)-1-(Hydroxymethyl)-3-methylbutyl]amino}-5-{[(1*S*)-1-phenylethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-2-yl)phosphoramidic acid;
(5-{[1-(2-Chlorophenyl)ethyl]sulfanyl}-7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}[1,3]thiazolo[4,5-*d*]pyrimidin-2-yl)phosphoramidic acid;
(7-{[(1*R*)-1-(Hydroxymethyl)-3-methylbutyl]amino}-5-[(1-pyridin-2-ylethyl)sulfanyl][1,3]thiazolo[4,5-*d*]pyrimidin-2-yl)phosphoramidic acid;
(5-{[1-(3-Cyanophenyl)ethyl]sulfanyl}-7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}[1,3]thiazolo[4,5-*d*]pyrimidin-2-yl)phosphoramidic acid;
(5-{[1-(3-Fluoropyridin-2-yl)ethyl]sulfanyl}-7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}[1,3]thiazolo[4,5-*d*]pyrimidin-2-yl)phosphoramidic acid;
Diethyl(7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}-5-{[(1*S*)-1-phenylethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-2-yl)amidophosphate;
Dimethyl(7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}-5-{[(1*S*)-1-phenylethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-2-yl)amidophosphate;
Diethyl (5-{[1-(2-chlorophenyl)ethyl]sulfanyl}-7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}[1,3]thiazolo[4,5-*d*]pyrimidin-2-yl)amidophosphate;
Diethyl(7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}-5-[(1-pyridin-2-ylethyl)sulfanyl][1,3]thiazolo[4,5-*d*]pyrimidin-2-yl)amidophosphate;
Diethyl(5-{[1-(3-cyanophenyl)ethyl]sulfanyl}-7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}[1,3]thiazolo[4,5-*d*]pyrimidin-2-yl)amidophosphate; and
Diethyl(5-{[1-(3-fluoropyridin-2-yl)ethyl]sulfanyl}-7-{[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]amino}[1,3]thiazolo[4,5-*d*]pyrimidin-2-yl)amidophosphate,
or a pharmaceutically acceptable salt thereof.

13. A compound as claimed in Claim 12, wherein the compound is (2*R*)-2-[(2-Amino-5-{[(1*S*)-1-phenylethyl]sulfanyl}[1,3]thiazolo[4,5-*d*]pyrimidin-7-yl)amino]-4-methylpentyl dihydrogen phosphate, or a pharmaceutically acceptable salt thereof.

14. A compound as claimed in any one of Claims 1 to 13, wherein the pharmaceutically-acceptable salt is a base addition salt;
optionally
wherein the pharmaceutically-acceptable salt is an ammonium salt or an alkali metal salt.

15. A pharmaceutical composition comprising a compound a defined in any one of Claims 1 to 14, including pharmaceutically-acceptable salts thereof, in admixture with one or more pharmaceutically-acceptable excipient;optionally

wherein the pharmaceutical composition further comprises water and less than 20% (w/w) of solubilising excipients, such as

(a) wherein the pharmaceutical composition is in the form of an aqueous solution, or

(b) wherein the composition is in the form of a powder.

16. A compound as defined in any one of Claims 1 to 14, including pharmaceutically-acceptable salts thereof, or a pharmaceutical composition as defined in any one of Claim 15, for use in medicine.

17. A compound as defined in any one of Claims 1 to 14, including pharmaceutically-acceptable salts thereof, or a pharmaceutical composition as defined in any one of Claim 15, for use in the treatment and/or prevention of a disease or disorder associated with elevated levels of CX3CR1 and/or CX3CL1, wherein

the disease or disorder associated with elevated levels of CX3CR1 and/or CX3CL1 is selected from acute and/or chronic inflammation, macular degeneration, pulmonary arterial hypertension, asthma, pulmonary fibrosis, atopic dermatitis, pruritus, osteoarthritis, osteoporosis, aplastic anaemia, ankylosing spondylitis, multiple sclerosis, systemic sclerosis, rheumatoid arthritis, arteriosclerosis, atherosclerosis, unstable angina, myocardial infarction, carotid artery diseases, chronic heart failure, inflammatory cardiomyopathy, peripheral artery disease, diabetes, Alzheimer's disease, traumatic brain injury, pain, chronic pain, fibromyalgia, neuropathic pain, chemotherapy-induced pain,

intervertebral disc herniation, cancer, liver cirrhosis, IgA nephropathy, renal inflammation, lupus, ischemia reperfusion injury, ischemic acute renal failure, contrast-induced kidney injury, colitis, Crohn's disease, inflammatory bowel disease, pancreatitis, human immunodeficiency virus, human immunodeficiency virus-1 human immunodeficiency virus-associated dementia, stroke, Parkinson's disease, depression, anxiety, schizophrenia and autism spectrum disorders; wherein cancer is optionally selected from ovarian cancer, lung cancer, prostate cancer, liver cancer, pancreatic cancer, B-cell lymphomas and breast cancer; or

the disease or disorder associated with elevated levels of CX3CR1 and/or CX3CL1 is selected from myocardial infarction, arteriosclerosis, multiple sclerosis, rheumatoid arthritis, Crohn's disease, pancreatitis, neuropathic pain chemotherapy-induced pain and cancer; or

the disease or disorder associated with elevated levels of CX3CR1 and/or CX3CL1 is selected from atopic dermatitis, multiple sclerosis, rheumatoid arthritis, atherosclerosis, myocardial infarction, chronic heart failure, inflammatory cardiomyopathy, fibromyalgia, neuropathic pain, chemotherapy-induced pain, B-cell lymphomas, breast cancer, IgA nephropathy, lupus, ischemic acute renal failure and pancreatitis.

18. A combination product comprising:

(I) a compound as defined in any one of Claims 1 to 14, or a pharmaceutically acceptable salt thereof; and

(II) one or more other therapeutic agent that is useful in the treatment or prevention of a disease or disorder as defined in Claim 17,

wherein each of components (I) and (II) is formulated in admixture, optionally with a pharmaceutically-acceptable excipient, such as a pharmaceutically-acceptable adjuvant diluent or carrier.

19. A kit-of-parts comprising:

(a) a pharmaceutical composition as defined in Claims 15; and

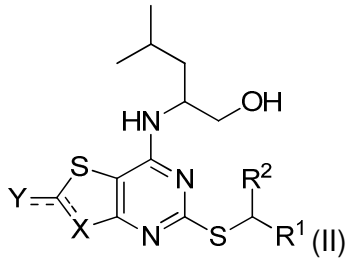
(b) a pharmaceutical composition comprising one or more other therapeutic agent that is useful in the treatment or prevention of a disease or disorder as defined in Claim 17, formulated in admixture with a pharmaceutically-acceptable excipient,

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

20. A process for the preparation of a compound as defined in any one of Claims 1 to 14, which process comprises:

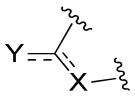
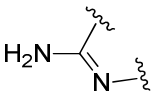
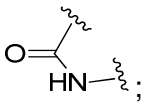
(a) for compounds wherein Q^1represents -$PO(OR^6)(OR^7)$, wherein R^6 and R^7 are as defined in any one of the preceding claims

(i) reacting a compound of formula II



(II)

wherein R^1 and R^2 are as defined in any one of the preceding claims; and

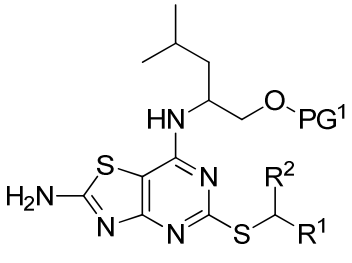
 represents  or ;

with phosphorus oxychloride in the presence of a suitable solvent and a suitable base; then

(ii) adding water or R^6OH/R^7OH to the reaction mixture;

(b) for compounds wherein Q^2 represents -$PO(OR^6)(OR^7)$,

reacting a compound of formula III



(III)

wherein:

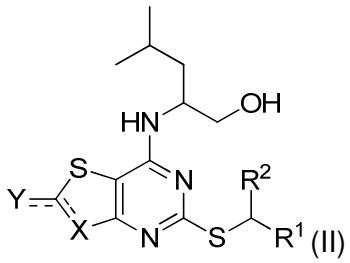
R^1 and R^2 are as defined in any one of the preceding claims; and

PG^1 represents a suitable oxygen protecting group;

in the presence of phosphorus pentachloride, a suitable solvent and, optionally, a suitable base;

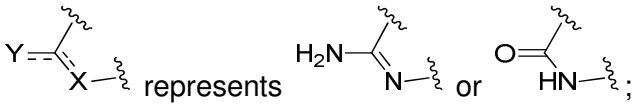
(c) for compounds wherein Q^3 or Q^4 represents $-CH_2OPO(OR^6)(OR^7)$ and at least one of R^6 and R^7 represents C_{1-4} alkyl or C_{2-4} alkenyl,

reacting a compound of formula II



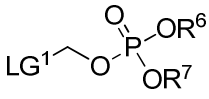
(II)

wherein R^1 and R^2 are as defined herein; and



;

with a compound of formula IV

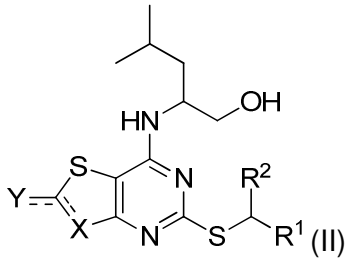


(IV)

wherein R^6 and R^7 are as defined in any one of the preceding claims with the proviso that at least one of R^6 and R^7 represents C_{1-4} alkyl or C_{2-4} alkenyl and LG^1 represents a suitable leaving group;
in the presence of a suitable base and a suitable solvent;

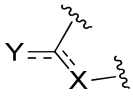
(d) for compounds wherein Q^3 or Q^4 represents $-CH_2OPO(OH)_2$,

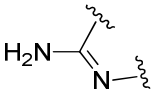
(i) reacting a compound of formula II

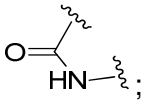


(II)

wherein R^1 and R^2 are as defined herein; and

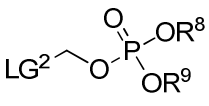


represents 

or 

;

with a compound of formula V



(V)

wherein R^8 and R^9 represent C_{1-6} alkyl and LG^2 represents a suitable leaving group; in the presence of a suitable base and a suitable solvent; and

(ii) reacting the product formed in the presence of a suitable acid and a suitable solvent.