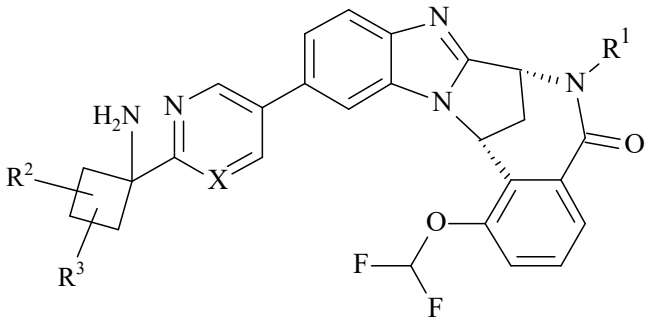
Claims:

1. A process for preparing a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

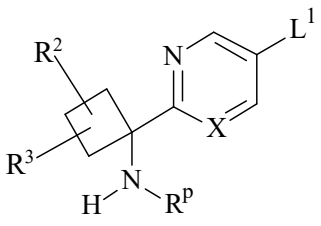
X represents N or C-F;

R^1 represents hydrogen or methyl;

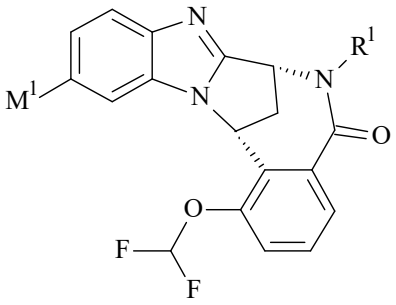
R^2 represents hydrogen, methyl or trifluoromethyl; and

R^3 represents hydrogen, cyano, hydroxy or hydroxymethyl,

comprising reacting a compound of formula (III) with a compound of formula (IV):



(III)



(IV)

wherein X, R^1, R^2 and R^3 are as defined above, L^1 represents a leaving group, M^1 represents a boronic acid moiety $-B(OH)_2$ or a cyclic ester thereof formed with an organic diol, and R^p represents an *N*-protecting group; in the presence of a transition metal catalyst; followed, as necessary, by removal of the *N*-protecting group R^p.

2. The process according to claim 1, wherein the leaving group L^1 is a halogen atom.

3. The process according to claim 1 or 2, wherein the leaving group L^1 is bromo.

4. The process according to any of claims 1 to 3, wherein the *N*-protecting group R^p represents *tert*-butoxycarbonyl or *tert*-butylsulfinyl.

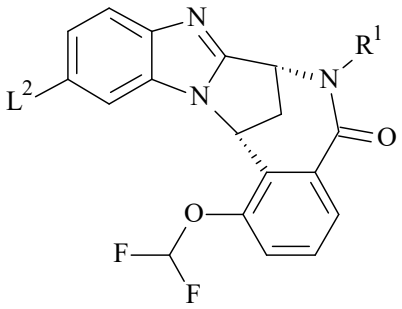
5. The process according to claim 4, wherein the *N*-protecting group R^p is removed by treatment with an acid.

6. The process according to any of claims 1 to 5, wherein the transition metal catalyst is tris(dibenzylideneacetone)dipalladium(0), or [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), or chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II).

7. The process according to claim 6, wherein the transition metal catalyst is utilised in conjunction with 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl or tricyclohexylphosphonium tetrafluoroborate.

8. The process according to any of claims 1 to 7, wherein the reaction between the compound of formula (III) and the compound of formula (IV) is performed in the presence of potassium phosphate or potassium carbonate.

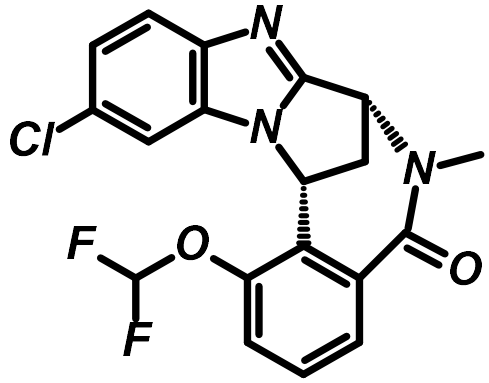
9. The process according to any of claims 1 to 8, wherein M^1 represents a cyclic ester of moiety $-B(OH)_2$ formed with pinacol and the compound of formula (IV) is prepared by reacting bis-(pinacolato)diboron with a compound of formula (V):



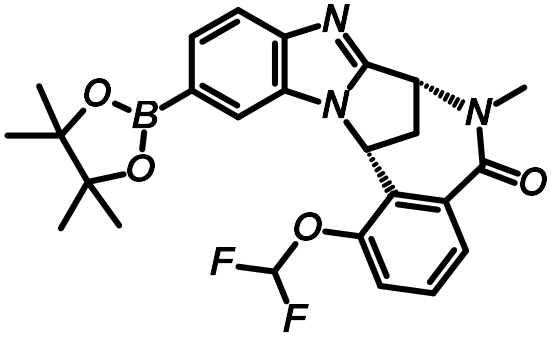
(V)

wherein L^2 represents a suitable leaving group; in the presence of a transition metal catalyst.

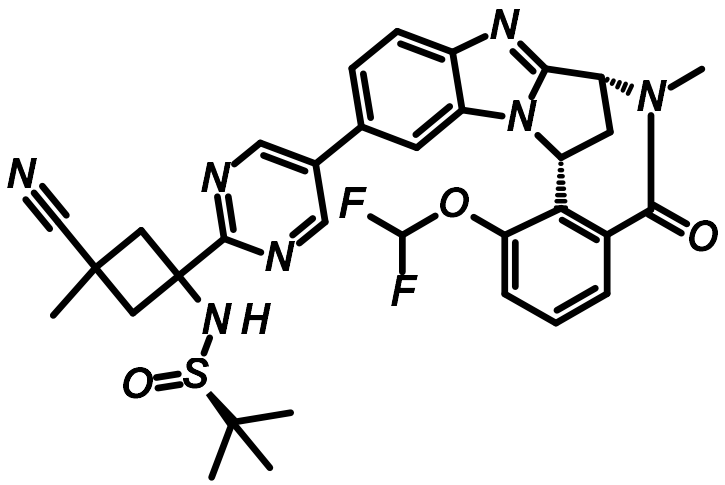
10. A compound which is selected from the following:



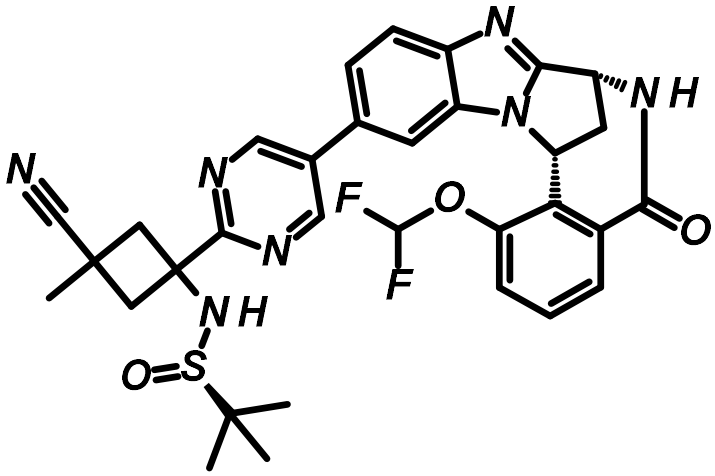
intermediate 3;



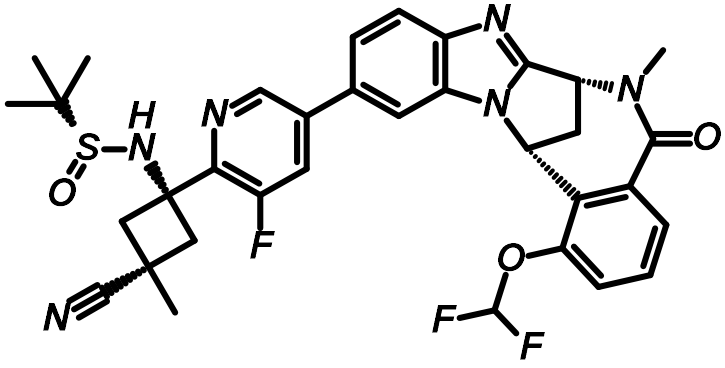
intermediate 4;



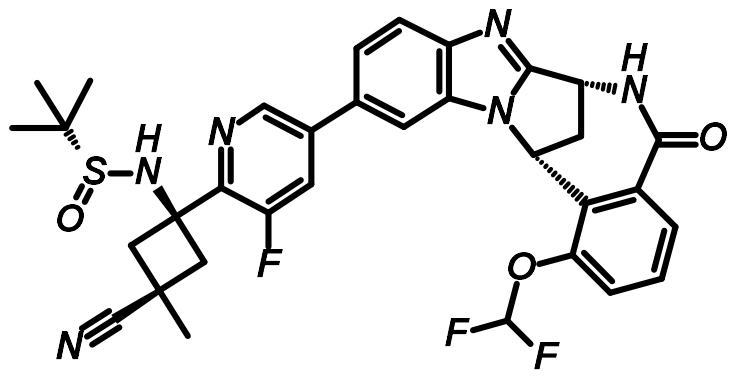
intermediate 5;



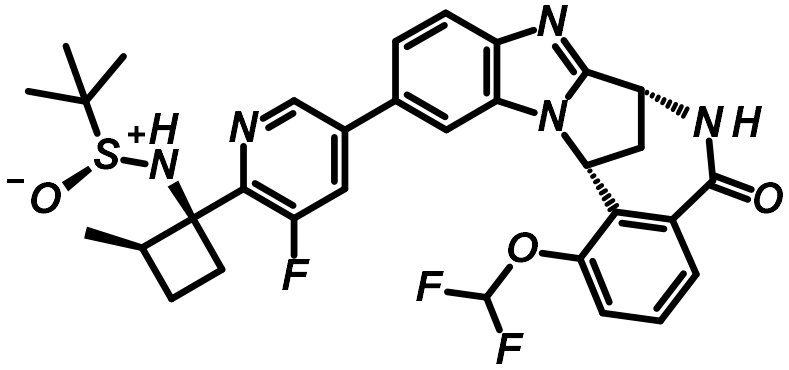
intermediate 6;

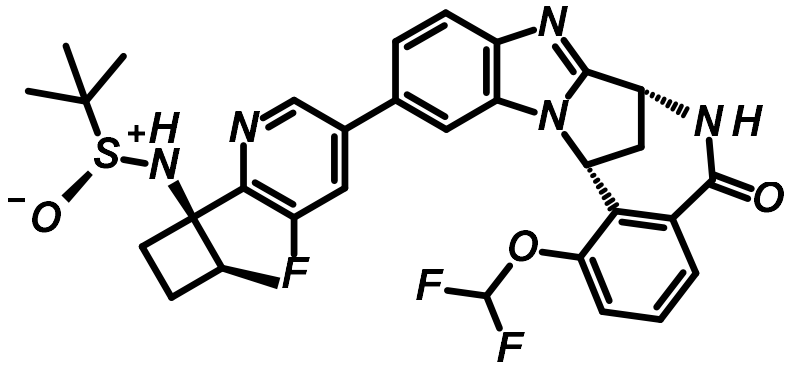


intermediate 8;

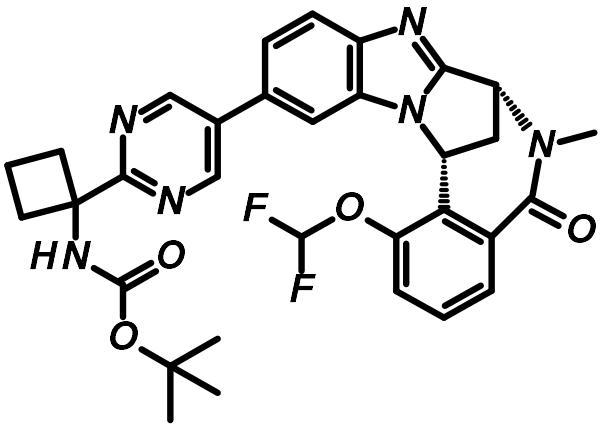


intermediate 9;

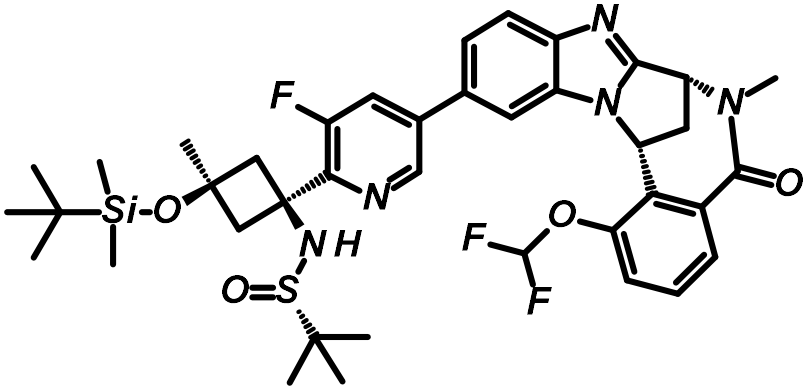




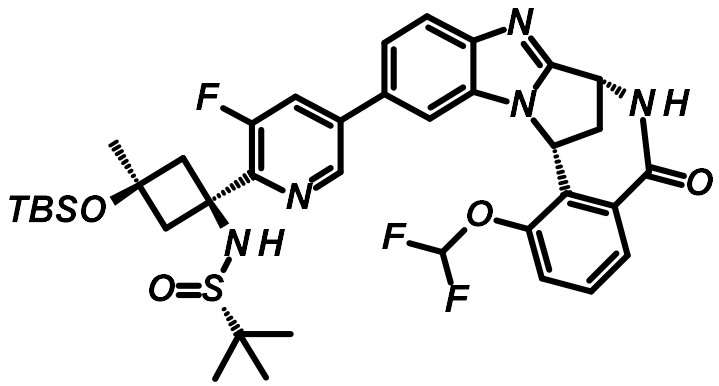
intermediates 12;



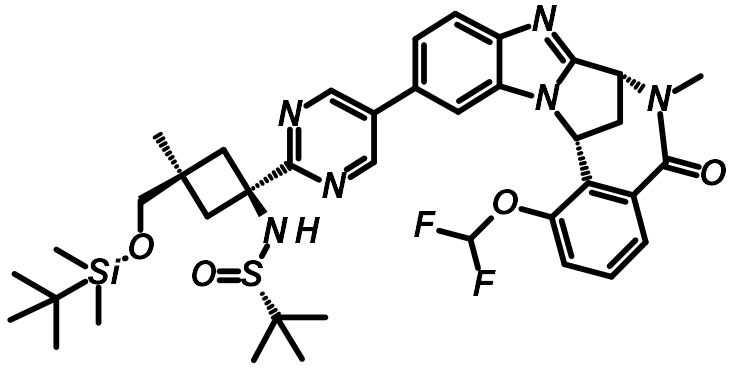
intermediate 17;



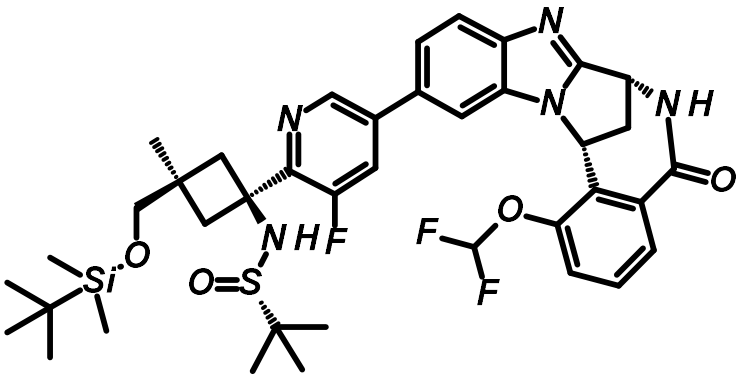
intermediate 24;



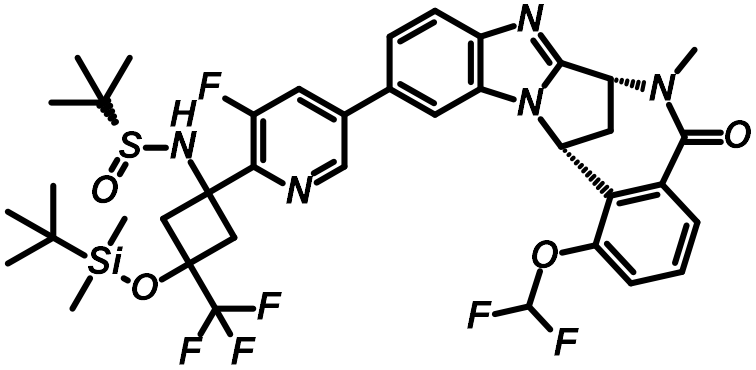
intermediate 25;



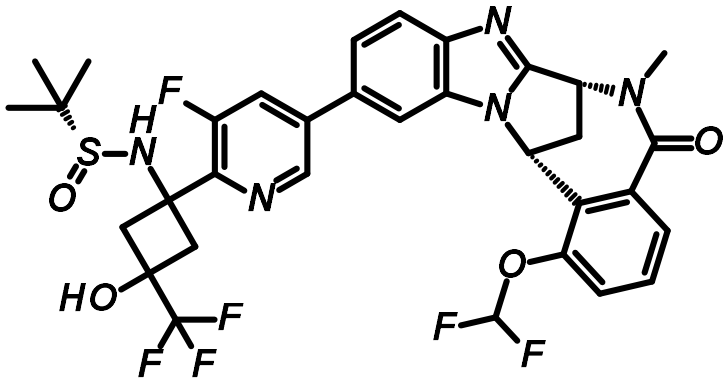
intermediate 33;



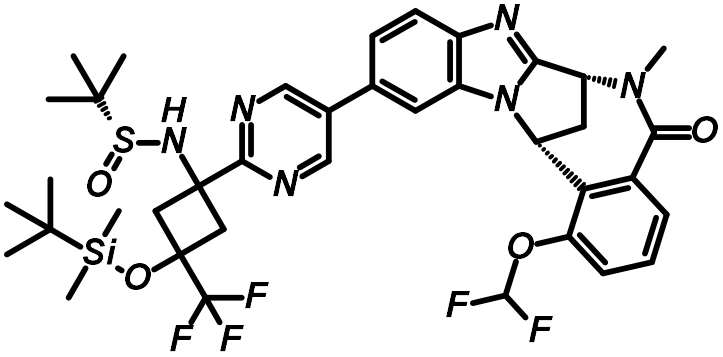
intermediate 35;



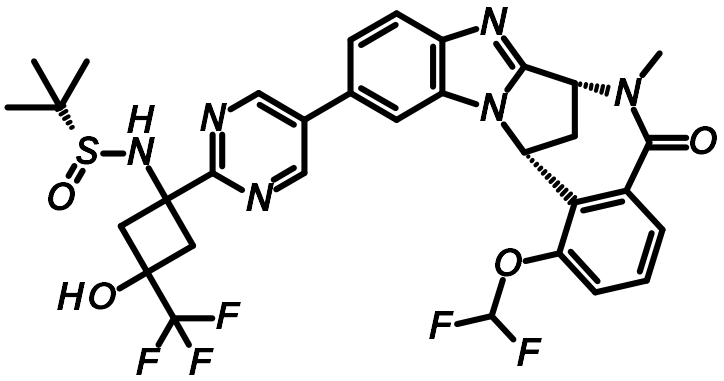
intermediate 42;



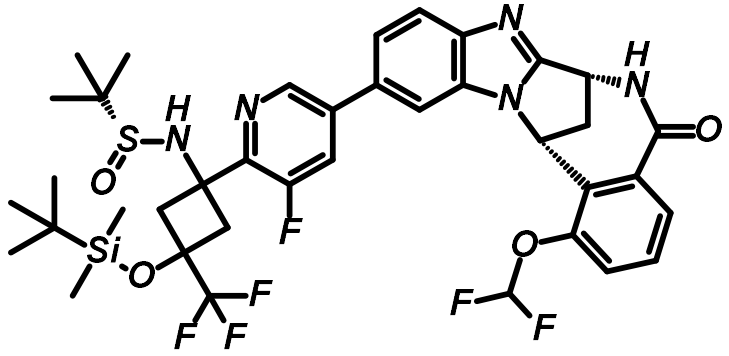
intermediate 43;



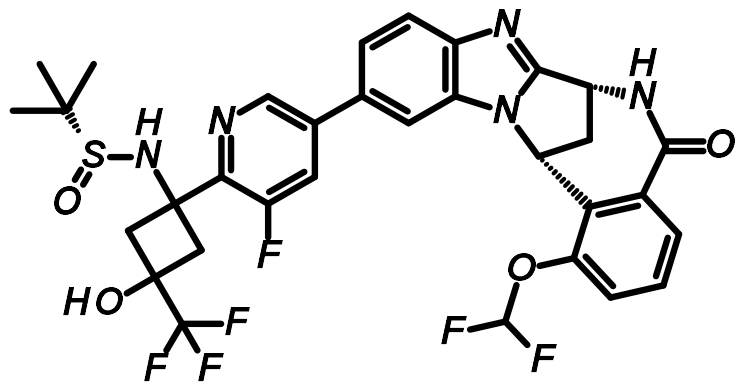
intermediate 45;



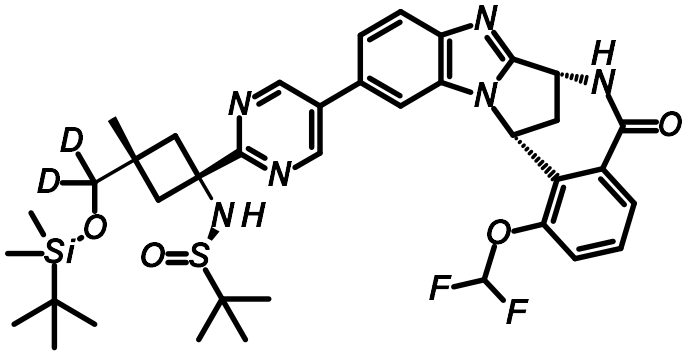
intermediate 46;



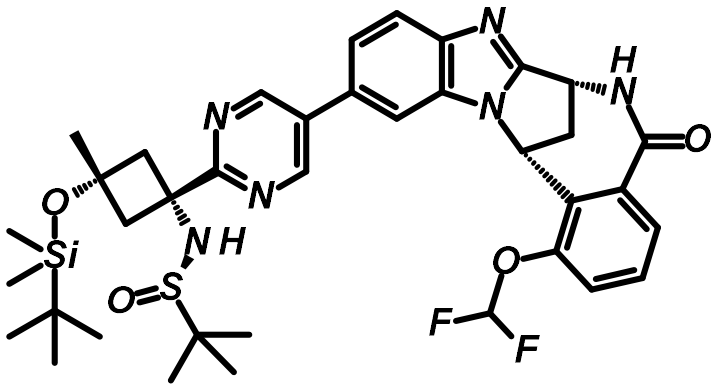
intermediate 47;



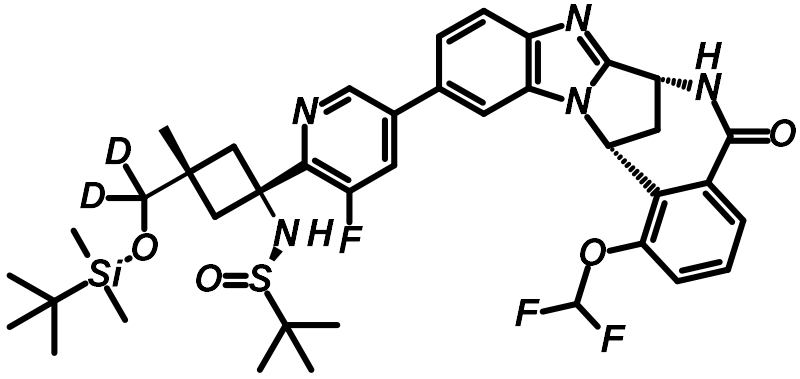
intermediate 48;



intermediate 56;

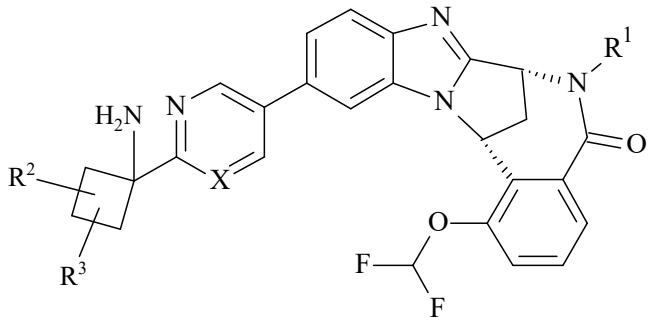


intermediate 57;



intermediate 59.

11. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

X represents N or C-F;

R^1 represents hydrogen or methyl;

R^2 represents hydrogen, methyl or trifluoromethyl; and

R^3 represents hydrogen, cyano, hydroxy or hydroxymethyl,

for use in the treatment and/or prevention of an inflammatory or autoimmune disorder selected from the group consisting of psoriasis, ankylosing spondylitis, psoriatic arthropathy, rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, hidradenitis suppurativa, inflammatory bowel disease, Behçet's disease, scleroderma, systemic sclerosis, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, fibrosing disorders, and diabetic nephropathy; a neurological or neurodegenerative disorder selected from the group consisting of Alzheimer's disease, Parkinson's disease, and spinal cord injury; a cardiovascular disorder selected from the group consisting of cardiac hypertrophy and myocardial infarction; a metabolic disorder selected from the group consisting of diabetes and metabolic syndrome; an ocular disorder which is retinopathy; or an oncological disorder selected from the group consisting of haematological malignancy and non-haematological malignancy (including solid tumour cancer, sarcoma, meningioma, glioblastoma multiforme, neuroblastoma, melanoma, gastric carcinoma and renal cell carcinoma).

12. A compound according to claim 11 for use in the treatment and/or prevention of an inflammatory bowel disease selected from Crohn's disease, ulcerative colitis, indeterminate colitis and pouchitis.

13. A compound according to claim 11 for use in the treatment and/or prevention of a fibrosing disorder selected from hepatic and pulmonary fibrosis.

14. A compound according to claim 11 for use in the treatment and/or prevention of insulin-dependent diabetes mellitus, juvenile diabetes, diabetic retinopathy, proliferative retinopathy, non-proliferative retinopathy and retinopathy of prematurity.

15. A compound according to claim 11 for use in the treatment and/or prevention of a haematological malignancy selected from leukaemia and lymphoma, or a non-haematological malignancy selected from solid tumour cancer, sarcoma, meningioma, glioblastoma multiforme, neuroblastoma, melanoma, gastric carcinoma and renal cell carcinoma.

16. A compound according to any one of claims 11 to 15, wherein the compound is selected from the following:
cis-3-amino-3-{5-[(7*R*,14*R*)-1-(difluoromethoxy)-6-methyl-5-oxo-5,6,7,14-tetrahydro-7,14-methanobenzimidazo[1,2-*b*][2,5]benzodiazocin-11-yl]pyrimidin-2-yl}-1-methyl-cyclobutanecarbonitrile;
cis-3-amino-3-{5-[(7*R*,14*R*)-1-(difluoromethoxy)-5-oxo-5,6,7,14-tetrahydro-7,14-methanobenzimidazo[1,2-*b*][2,5]benzodiazocin-11-yl]pyrimidin-2-yl}-1-methyl-cyclobutanecarbonitrile;
cis-3-amino-3-{5-[(7*R*,14*R*)-1-(difluoromethoxy)-6-methyl-5-oxo-5,6,7,14-tetrahydro-7,14-methanobenzimidazo[1,2-*b*][2,5]benzodiazocin-11-yl]-3-fluoropyridin-2-yl}-1-methylcyclobutanecarbonitrile;
cis-3-amino-3-{5-[(7*R*,14*R*)-1-(difluoromethoxy)-5-oxo-5,6,7,14-tetrahydro-7,14-methanobenzimidazo[1,2-*b*][2,5]benzodiazocin-11-yl]-3-fluoropyridin-2-yl}-1-methyl-cyclobutanecarbonitrile;

(7*R*,14*R*)-11-{6-[(1*S*,2*R*)-1-amino-2-methylcyclobutyl]-5-fluoropyridin-3-yl}-1-(difluoromethoxy)-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*][2,5]benzodiazocin-5(14*H*)-one;

(7*R*,14*R*)-11-{6-[(1*R*,2*S*)-1-amino-2-methylcyclobutyl]-5-fluoropyridin-3-yl}-1-(difluoromethoxy)-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-one;

(7*R*,14*R*)-11-[2-(1-aminocyclobutyl)pyrimidin-5-yl]-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*][2,5]benzodiazocin-5(14*H*)-one;

(7*R*,14*R*)-11-[6-(*cis*-1-amino-3-hydroxy-3-methylcyclobutyl)-5-fluoropyridin-3-yl]-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-one;

(7*R*,14*R*)-11-[6-(*cis*-1-amino-3-hydroxy-3-methylcyclobutyl)-5-fluoropyridin-3-yl]-1-(difluoromethoxy)-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*][2,5]benzodiazocin-5(14*H*)-one;

(7*R*,14*R*)-11-{2-[*cis*-1-amino-3-(hydroxymethyl)-3-methylcyclobutyl]pyrimidin-5-yl}-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-one;

(7*R*,14*R*)-11-{6-[*cis*-1-amino-3-(hydroxymethyl)-3-methylcyclobutyl]-5-fluoropyridin-3-yl}-1-(difluoromethoxy)-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-one;

(7*R*,14*R*)-11-{6-[*cis*-1-amino-3-hydroxy-3-(trifluoromethyl)cyclobutyl]-5-fluoropyridin-3-yl}-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-one;

(7*R*,14*R*)-11-{2-[*cis*-1-amino-3-hydroxy-3-(trifluoromethyl)cyclobutyl]pyrimidin-5-yl}-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-one;

(7*R*,14*R*)-11-{6-[*cis*-1-amino-3-hydroxy-3-(trifluoromethyl)cyclobutyl]-5-fluoropyridin-3-yl}-1-(difluoromethoxy)-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-one;

(7*R*,14*R*)-11-(2-{*cis*-1-amino-3-[hydroxy(dideutero)methyl]-3-methylcyclobutyl}-pyrimidin-5-yl)-1-(difluoromethoxy)-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-one;

(7*R*,14*R*)-11-{2-[*cis*-1-amino-3-(hydroxymethyl)-3-methylcyclobutyl]pyrimidin-5-yl}-1-(difluoromethoxy)-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*][2,5]benzodiazocin-5(14*H*)-one; and

(7*R*,14*R*)-11-(6-{*cis*-1-amino-3-[hydroxy(dideutero)methyl]-3-methylcyclobutyl}-5-fluoropyridin-3-yl)-1-(difluoromethoxy)-6,7-dihydro-7,14-methanobenzimidazo[1,2-*b*]-[2,5]benzodiazocin-5(14*H*)-one.