Compounds – 945

The present invention relates to morpholino pyrimidine compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy, for example in the treatment of proliferative disease such as cancer and particularly in disease mediated by an mTOR kinase and/or one or more PI3K enzyme.

It is now well understood that deregulation of oncogenes and tumour-suppressor genes contributes to the formation of malignant tumours, for example by way of increased cell proliferation or increased cell survival. It is also known that signalling pathways mediated by the PI3K/mTOR families have a central role in a number of cell processes including proliferation and survival, and deregulation of these pathways is a causative factor in a wide spectrum of human cancers and other diseases.

The mammalian target of the macrolide antibiotic Rapamycin (sirolimus) is the enzyme mTOR. This enzymes belongs to the phosphatidylinositol (PI) kinase-related kinase (PIKK) family of protein kinases, which also includes ATM, ATR, DNA-PK and hSMG-1. mTOR, like other PIKK family members, does not possess detectable lipid kinase activity, but instead functions as a serine/threonine kinase. Much of the knowledge of mTOR signalling is based upon the use of Rapamycin. Rapamycin first binds to the 12 kDa immunophilin FK506-binding protein (FKBP12) and this complex inhibits mTOR signalling (Tee and Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29-37). The mTOR protein consists of a catalytic kinase domain, an FKBP12-Rapamycin binding (FRB) domain, a putative repressor domain near the *C*-terminus and up to 20 tandemly-repeated HEAT motifs at the *N*-terminus, as well as FRAP-ATM-TRRAP (FAT) and FAT *C*-terminus domain (Huang and Houghton, Current Opinion in Pharmacology, 2003, 3, 371-377).

mTOR kinase is a key regulator of cell growth and has been shown to regulate a wide range of cellular functions including translation, transcription, mRNA turnover, protein stability, actin cytoskeleton reorganisation and autophagy (Jacinto and Hall, Nature Reviews Molecular and Cell Biology, 2005, 4, 117-126). mTOR kinase integrates signals from growth factors (such as insulin or insulin-like growth factor) and nutrients (such as amino acids and glucose) to regulate cell growth. mTOR kinase is activated by growth factors through the PI3K-Akt pathway. The most well characterised function of mTOR kinase in mammalian cells is regulation of translation through two pathways, namely activation of ribosomal S6K1 to

enhance translation of mRNAs that bear a 5'-terminal oligopyrimidine tract (TOP) and suppression of 4E-BP1 to allow CAP-dependent mRNA translation.

Generally, investigators have explored the physiological and pathological roles of mTOR using inhibition with Rapamycin and related Rapamycin analogues based on their specificity for mTOR as an intracellular target. However, recent data suggests that Rapamycin displays variable inhibitory actions on mTOR signalling functions and suggest that direct inhibition of the mTOR kinase domain may display substantially broader anti-cancer activities than that achieved by Rapamycin (Edinger *et al.*, Cancer Research, 2003, 63, 8451-8460). For this reason, potent and selective inhibitors of mTOR kinase activity would be useful to allow a more complete understanding of mTOR kinase function and to provide useful therapeutic agents.

There is now considerable evidence indicating that the pathways upstream of mTOR, such as the PI3K pathway, are frequently activated in cancer (Vivanco and Sawyers, Nature Reviews Cancer, 2002, 2, 489-501; Bjornsti and Houghton, Nature Reviews Cancer, 2004, 4, 335-348; Inoki *et al.*, Nature Genetics, 2005, 37, 19-24). For example, components of the PI3K pathway that are mutated in different human tumours include activating mutations of growth factor receptors and the amplification and/or overexpression of PI3K and Akt.

In addition there is evidence that endothelial cell proliferation may also be dependent upon mTOR signalling. Endothelial cell proliferation is stimulated by vascular endothelial cell growth factor (VEGF) activation of the PI3K-Akt-mTOR signalling pathway (Dancey, Expert Opinion on Investigational Drugs, 2005, 14, 313-328). Moreover, mTOR kinase signalling is believed to partially control VEGF synthesis through effects on the expression of hypoxia-inducible factor-1α (HIF-1α) (Hudson *et al.*, Molecular and Cellular Biology, 2002, 22, 7004-7014). Therefore, tumour angiogenesis may depend on mTOR kinase signalling in two ways, through hypoxia-induced synthesis of VEGF by tumour and stromal cells, and through VEGF stimulation of endothelial proliferation and survival through PI3K-Akt-mTOR signalling.

These findings suggest that pharmacological inhibitors of mTOR kinase should be of therapeutic value for treatment of the various forms of cancer comprising solid tumours such as carcinomas and sarcomas and the leukaemias and lymphoid malignancies. In particular, inhibitors of mTOR kinase should be of therapeutic value for treatment of, for example, cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate, and of cancer of the bile duct, bone, bladder, head

and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

In addition to tumourigenesis, there is evidence that mTOR kinase plays a role in an array of hamartoma syndromes. Recent studies have shown that the tumour suppressor proteins such as TSC1, TSC2, PTEN and LKB1 tightly control mTOR kinase signalling. Loss of these tumour suppressor proteins leads to a range of hamartoma conditions as a result of elevated mTOR kinase signalling (Tee and Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29-37). Syndromes with an established molecular link to dysregulation of mTOR kinase include Peutz-Jeghers syndrome (PJS), Cowden disease, Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome, Lhermitte-Duclos disease and Tuberous Sclerosis (TSC) (Inoki *et al.*, Nature Genetics, 2005, 37, 19-24). Patients with these syndromes characteristically develop benign hamartomatous tumours in multiple organs.

Recent studies have revealed a role for mTOR kinase in other diseases (Easton & Houghton, Expert Opinion on Therapeutic Targets, 2004, 8, 551-564). Rapamycin has been demonstrated to be a potent immunosuppressant by inhibiting antigen-induced proliferation of T cells, B cells and antibody production (Sehgal, Transplantation Proceedings, 2003, 35, 7S-14S) and thus mTOR kinase inhibitors may also be useful immunosuppressives. Inhibition of the kinase activity of mTOR may also be useful in the prevention of restenosis, that is the control of undesired proliferation of normal cells in the vasculature in response to the introduction of stents in the treatment of vasculature disease (Morice *et al.*, New England Journal of Medicine, 2002, 346, 1773-1780). Furthermore, the Rapamycin analogue, everolimus, can reduce the severity and incidence of cardiac allograft vasculopathy (Eisen *et al.*, New England Journal of Medicine, 2003, 349, 847-858). Elevated mTOR kinase activity has been associated with cardiac hypertrophy, which is of clinical importance as a major risk factor for heart failure and is a consequence of increased cellular size of cardiomyocytes (Tee & Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29-37). Thus mTOR kinase inhibitors are expected to be of value in the prevention and treatment of a wide variety of diseases in addition to cancer.

It is also believed that a number of these morpholino pyrimidine derivatives may have inhibitory activity against the phosphatidylinositol (PI) 3-kinases family of kinases.

Phosphatidylinositol (PI) 3-kinases (PI3Ks) are ubiquitous lipid kinases that function both as signal transducers downstream of cell-surface receptors and in constitutive intracellular membrane and protein trafficking pathways. All PI3Ks are dual-specificity enzymes with a lipid kinase activity that phosphorylates phosphoinositides at the 3-hydroxy position, and a less well characterised protein kinase activity. The lipid products of PI3K-catalysed reactions comprising phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P_3], phosphatidylinositol 3,4-bisphosphate [PI(3,4)P_2] and phosphatidylinositol 3-monophosphate [PI(3)P] constitute second messengers in a variety of signal transduction pathways, including those essential to cell proliferation, adhesion, survival, cytoskeletal rearrangement and vesicle trafficking. PI(3)P is constitutively present in all cells and its levels do not change dramatically following agonist stimulation. Conversely, PI(3,4)P_2 and PI(3,4,5)P_3 are nominally absent in most cells but they rapidly accumulate on agonist stimulation.

The downstream effects of PI3K-produced 3-phosphoinositide second messengers are mediated by target molecules containing 3-phosphoinositide binding domains such as the pleckstrin homology (PH) domain and the recently identified FYVE and phox domains. Well-characterised protein targets for PI3K include PDK1 and protein kinase B (PKB). In addition, tyrosine kinases like Btk and Itk are dependent on PI3K activity.

The PI3K family of lipid kinases can be classified into three groups according to their physiological substrate specificity (Vanhaesebroeck *et al.*, Trends in Biol. Sci., 1997, 22, 267). Class III PI3K enzymes phosphorylate PI alone. In contrast, Class II PI3K enzymes phosphorylate both PI and PI 4-phosphate [PI(4)P]. Class I PI3K enzymes phosphorylate PI, PI(4)P and PI 4,5-bisphosphate [PI(4,5)P_2], although only PI(4,5)P_2 is believed to be the physiological cellular substrate. Phosphorylation of PI(4,5)P_2 produces the lipid second messenger PI(3,4,5)P_3. More distantly related members of the lipid kinase superfamily are Class IV kinases such as mTOR (discussed above) and DNA-dependent kinase that phosphorylate serine/threonine residues within protein substrates. The most studied and understood of the PI3K lipid kinases are the Class I PI3K enzymes.

Class I PI3Ks are heterodimers consisting of a p110 catalytic subunit and a regulatory subunit. The family is further divided into Class Ia and Class Ib enzymes on the basis of regulatory partners and the mechanism of regulation. Class Ia enzymes consist of three distinct catalytic subunits (p110α, p110β and p110δ) that dimerise with five distinct regulatory subunits (p85α, p55α, p50α, p85β and p55γ), with all catalytic subunits being able to interact

with all regulatory subunits to form a variety of heterodimers. Class Ia PI3Ks are generally activated in response to growth factor-stimulation of receptor tyrosine kinases *via* interaction of their regulatory subunit SH2 domains with specific phospho-tyrosine residues of activated receptor or adaptor proteins such as IRS-1. Both p110α and p110β are constitutively expressed in all cell types, whereas p110δ expression is more restricted to leukocyte populations and some epithelial cells. In contrast, the single Class Ib enzyme consists of a p110γ catalytic subunit that interacts with a p101 regulatory subunit. Furthermore, the Class Ib enzyme is activated in response to G-protein coupled receptor systems (GPCRs) and its expression appears to be limited to leukocytes and cardiomyocytes.

There is now considerable evidence indicating that Class Ia PI3K enzymes contribute to tumourigenesis in a wide variety of human cancers, either directly or indirectly (Vivanco and Sawyers, Nature Reviews Cancer, 2002, 2, 489-501). For example, the p110α subunit is amplified in some tumours such as those of the ovary (Shayesteh *et al.*, Nature Genetics, 1999, 21, 99-102) and cervix (Ma *et al.*, Oncogene, 2000, 19, 2739-2744). More recently, activating mutations within the catalytic site of the p110α catalytic subunit have been associated with various other tumours such as those of the colorectal region and of the breast and lung (Samuels *et al.*, Science, 2004, 304, 554). Tumour-related mutations in the p85α regulatory subunit have also been identified in cancers such as those of the ovary and colon (Philp *et al.*, Cancer Research, 2001, 61, 7426-7429). In addition to direct effects, it is believed that activation of Class Ia PI3Ks contributes to tumourigenic events that occur upstream in signalling pathways, for example by way of ligand-dependent or ligand-independent activation of receptor tyrosine kinases, GPCR systems or integrins (Vara *et al.*, Cancer Treatment Reviews, 2004, 30, 193-204). Examples of such upstream signalling pathways include over-expression of the receptor tyrosine kinase erbB2 in a variety of tumours leading to activation of PI3K-mediated pathways (Harari *et al.*, Oncogene, 2000, 19, 6102-6114) and over-expression of the ras oncogene (Kauffmann-Zeh *et al.*, Nature, 1997, 385, 544-548). In addition, Class Ia PI3Ks may contribute indirectly to tumourigenesis caused by various downstream signalling events. For example, loss of the effect of the PTEN tumour-suppressor phosphatase that catalyses conversion of $PI(3,4,5)P_3$ back to $PI(4,5)P_2$ is associated with a very broad range of tumours *via* deregulation of PI3K-mediated production of $PI(3,4,5)P_3$ (Simpson and Parsons, Exp. Cell Res., 2001, 264, 29-41). Furthermore, augmentation of the effects of other PI3K-

mediated signalling events is believed to contribute to a variety of cancers, for example by activation of Akt (Nicholson and Anderson, Cellular Signalling, 2002, 14, 381-395).

In addition to a role in mediating proliferative and survival signalling in tumour cells, there is evidence that Class Ia PI3K enzymes contribute to tumourigenesis in tumour-associated stromal cells. For example, PI3K signalling is known to play an important role in mediating angiogenic events in endothelial cells in response to pro-angiogenic factors such as VEGF (Abid *et al.*, Arterioscler. Thromb. Vasc. Biol., 2004, 24, 294-300). As Class I PI3K enzymes are also involved in motility and migration (Sawyer, Expert Opinion Investig. Drugs, 2004, 13, 1-19), PI3K enzyme inhibitors should provide therapeutic benefit *via* inhibition of tumour cell invasion and metastasis. In addition, Class I PI3K enzymes play an important role in the regulation of immune cells contributing to pro-tumourigenic effects of inflammatory cells (Coussens and Werb, Nature, 2002, 420, 860-867).

These findings suggest that pharmacological inhibitors of Class I PI3K enzymes will be of therapeutic value for the treatment of various diseases including different forms of the disease of cancer comprising solid tumours such as carcinomas and sarcomas and the leukaemias and lymphoid malignancies. In particular, inhibitors of Class I PI3K enzymes should be of therapeutic value for treatment of, for example, cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate, and of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

PI3Kγ, the Class Ib PI3K, is activated by GPCRs, as was finally demonstrated in mice lacking the enzyme. Thus, neutrophils and macrophages derived from PI3Kγ-deficient animals failed to produce $PI(3,4,5)P_3$ in response to stimulation with various chemotactic substances (such as IL-8, C5a, fMLP and MIP-1a), whereas signalling through protein tyrosine kinase-coupled receptors to Class Ia PI3Ks was intact (Hirsch *et al.*, Science, 2000, 287(5455), 1049-1053; Li *et al.*, Science, 2002, 287(5455), 1046-1049; Sasaki *et al.*, Science 2002, 287(5455), 1040-1046). Furthermore, $PI(3,4,5)P_3$-mediated phosphorylation of PKB was not initiated by these GPCR ligands in PI3Kγ-null cells. Taken together, the results demonstrated that, at least in resting haematopoietic cells, PI3Kγ is the sole PI3K isoform that is activated by GPCRs *in vivo*. When murine bone marrow-derived neutrophils and peritoneal macrophages from wild-type and PI3K$\gamma^{-/-}$ mice were tested *in vitro*, a reduced, but not completely abrogated,

performance in chemotaxis and adherence assays was observed. However, this translated into a drastic impairment of IL-8 driven neutrophil infiltration into tissues (Hirsch *et al.*, Science, 2000, 287(5455), 1049-1053.). Recent data suggest that PI3Kγ is involved in the path finding process rather than in the generation of mechanical force for motility, as random migration was not impaired in cells that lacked PI3Kγ (Hannigan *et al.*, Proc. Nat. Acad. of Sciences of U.S.A., 2002, 99(6), 3603-8). Data linking PI3Kγ to respiratory disease pathology came with the demonstration that PI3Kγ has a central role in regulating endotoxin-induced lung infiltration and activation of neutrophils leading to acute lung injury (Yum *et al.*, J. Immunology, 2001, 167(11), 6601-8). The fact that although PI3Kγ is highly expressed in leucocytes, its loss seems not to interfere with haematopoiesis, and the fact that PI3Kγ-null mice are viable and fertile further implicates this PI3K isoform as a potential drug target. Work with knockout mice also established that PI3Kγ is an essential amplifier of mast cell activation (Laffargue *et al.*, Immunity, 2002, 16(3), 441-451).

Thus, in addition to tumourigenesis, there is evidence that Class I PI3K enzymes play a role in other diseases (Wymann *et al.*, Trends in Pharmacological Science, 2003, 24, 366-376). Both Class Ia PI3K enzymes and the single Class Ib enzyme have important roles in cells of the immune system (Koyasu, Nature Immunology, 2003, 4, 313-319) and thus they are therapeutic targets for inflammatory and allergic indications. Recent reports demonstrate that mice deficient in PI3Kγ and PI3Kδ are viable, but have attenuated inflammatory and allergic responses (Ali *et al.*, Nature, 2004, 431(7011), 1007-11). Inhibition of PI3K is also useful to treat cardiovascular disease *via* anti-inflammatory effects or directly by affecting cardiac myocytes (Prasad *et al.*, Trends in Cardiovascular Medicine, 2003, 13, 206-212). Thus, inhibitors of Class I PI3K enzymes are expected to be of value in the prevention and treatment of a wide variety of diseases in addition to cancer.

Several compounds that inhibit PI3Ks and phosphatidylinositol (PI) kinase-related kinase (PI3KKs) have been identified, including wortmannin and the quercetin derivative LY294002. These compounds are reasonably specific inhibitors of PI3Ks and PI3KKs over other kinases but they lack potency and display little selectivity within the PI3K families.

Accordingly, it would be desirable to provide further effective mTOR and/or PI3K inhibitors for use in the treatment of cancer, inflammatory or obstructive airways diseases, immune or cardiovascular diseases.

Morpholino pyrimidine derivatives and PI3K inhibitors are known in the art.

International Patent Application WO 2004/048365 discloses compounds that possess PI3K enzyme inhibitory activity and are useful in the treatment of cancer. These compounds are arylamino- and heteroarylamino-substituted pyrimidines which differ from the compounds of the present invention by virtue of their arylamino- and heteroarylamino substituents. WO 2004/048365 does not disclose compounds with the $-XR^1$ substituents of the present invention. Inhibitors of PI3K activity useful in the treatment of cancer are also disclosed in European Patent Application 1 277 738 which mentions 4-morpholino-substituted bicyclic heteroaryl compounds such as quinazoline and pyrido[3,2-*d*]pyrimidine derivatives and 4-morpholino-substituted tricyclic heteroaryl compounds but not monocyclic pyrimidine derivatives.

WO2007/080382, WO2008/023180 and WO2008/023159 disclose compounds that possess mTOR and/or PI3K enzyme inhibitory activity and are useful in the treatment of cancer. WO2007/080382, WO2008/023180 and WO2008/023159 do not disclose compounds comprising a cyclic moiety in the linker group X in the group $-XR^1$.

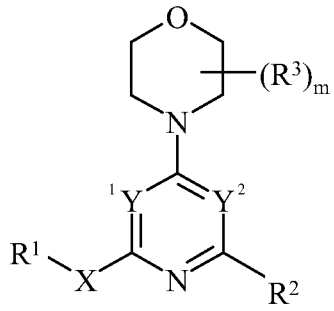
A number of compounds such as 4-morpholin-4-yl-6-(phenylsulfonylmethyl)-2-pyridin-4-yl-pyrimidine and 4-{6-[(phenylsulfonyl)methyl]-2-pyridin-2-ylpyrimidin-4-yl}morpholine have been registered in the Chemical Abstracts database but no utility has been indicated and there is no suggestion that these compounds have mTOR and/or PI3K inhibitory activity or useful therapeutic properties.

Surprisingly, we have found that certain morpholino pyrimidine derivatives possess useful therapeutic properties. Without wishing to be bound by theoretical constraints, it is believed that the therapeutic usefulness of the derivatives is derived from their inhibitory activity against mTOR kinase and/or one or more PI3K enzyme (such as the Class Ia enzyme and/or the Class Ib enzyme). Because signalling pathways mediated by the PI3K/mTOR families have a central role in a number of cell processes including proliferation and survival, and because deregulation of these pathways is a causative factor in a wide spectrum of human cancers and other diseases, it is expected that the derivatives will be therapeutically useful. In particular, it is expected that the derivatives will have anti-proliferative and/or apoptotic properties which means that they will be useful in the treatement of proliferative disease such as cancer. The compounds of the present invention may also be useful in inhibiting the uncontrolled cellular proliferation which arises from various non-malignant diseases such as

inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases.

Generally, the compounds of the present invention possess potent inhibitory activity against mTOR kinase but the compound may also possess potent inhibitory activity against one or more PI3K enzyme (such as the Class Ia enzyme and/or the Class Ib enzyme).

In accordance with an aspect of the present invention, there is provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}Y and **Y^2** are independently N or CR^8 provided that one of ^1Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, and $-S(O)_2NR^4CR^6R^7-$;

R^1 is a group selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $-NR^9SO_2R^{10}$;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, R^{11}, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ and $-NR^{13}SO_2R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}

$_{6}$alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, **R^{12}**, **R^{17}** and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, **R^{14}**, **R^{15}** and **R^{16}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

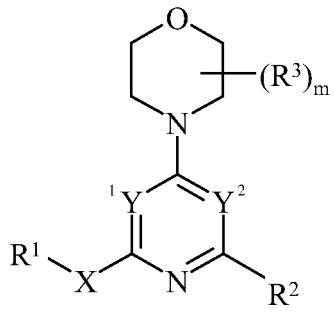
R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-}

$_6$alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

for use as a medicament in the treatment of proliferative disease.

In accordance with an aspect of the present invention, there is provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}Y and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, and $-S(O)_2NR^4CR^6R^7-$;

R^1 is a group selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $-NR^9SO_2R^{10}$;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ and $-NR^{13}SO_2R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}

$_{6}$alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

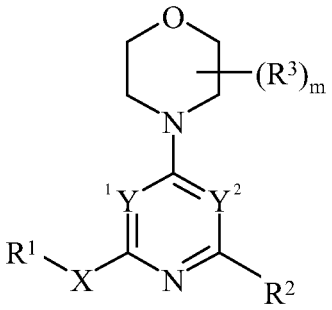
R^{11}, **R**^{12}, **R**^{17} and **R**^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, **R**^{14}, **R**^{15}, **R**^{16} and **R**^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R**^{18} and **R**^{19} together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

for use as a medicament in the treatment of proliferative disease.

In accordance with another aspect of the present invention, there is provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}Y and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$ and $-S(O)_2NR^4CR^6R^7-$;

R^1 is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $-NR^9SO_2R^{10}$;

or **X-R^1** is $-CR^6R^7OH$;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ and $-NR^{13}SO_2R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent

groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, **R^{12}**, **R^{17}** and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl,

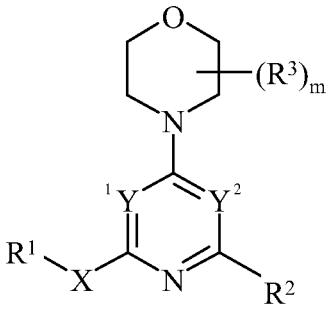
cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, **R^{14}**, **R^{15}**, **R^{16}** and **R^{19}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

for use as a medicament in the treatment of proliferative disease.

In accordance with another aspect of the present invention, there is provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

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^{1}**Y** and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from -CR^4=CR^{5}CR^{6}R^7-, -CR^{6}R^{7}CR^5=CR^4-, -C≡CCR^{6}R^7-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7- and -S(O)$_2$NR^{4}CR^{6}R^7-;

R^1 is a group selected from C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, carbocyclyl, carbocyclylC$_{1-6}$alkyl, heterocyclyl and heterocyclylC$_{1-6}$alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, -OR^9, -SR^9, -SOR^9, -SO$_2$R^9, -COR^9, -CO$_2$R^9, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} and –NR^{9}SO$_2$R^{10};

or **X-R^1** is -CR^{6}R^{7}OH;

R^2 is a group selected from C$_{1-6}$alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO$_2$R^{11}, -COR^{11}, -CO$_2$R^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12}, -NR^{11}COR^{12}, -NR^{11}COCONR^{12}R^{16}, -NR^{11}SO$_2$R^{12}, -NR^{17}CONR^{18}R^{19} and -NR^{17}CSNR^{18}R^{19};

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -SR^{13}, -SOR^{13}, -SO$_2$R^{13}, -COR^{13}, -CO$_2$R^{13}, -CONR^{13}R^{14}, -NR^{13}R^{14}, –NR^{13}COR^{14}, -NR^{13}CO$_2$R^{14} and –NR^{13}SO$_2$R^{14};

R^4 and **R^5** are independently hydrogen or C$_{1-6}$alkyl;

or **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, haloC$_{1-6}$alkyl, haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkylsulfonyl, C$_{1-6}$alkylsulfonylamino, C$_{1-6}$alkylsulfonyl(C$_{1-6}$alkyl)amino, sulfamoyl, C$_{1-6}$alkylsulfamoyl, bis(C$_{1-6}$alkyl)sulfamoyl, C$_{1-6}$alkanoylamino, C$_{1-6}$alkanoyl(C$_{1-6}$alkyl)amino, carbamoyl, C$_{1-6}$alkylcarbamoyl and bis(C$_{1-6}$alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from

halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, **R^{12}**, **R^{17}** and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

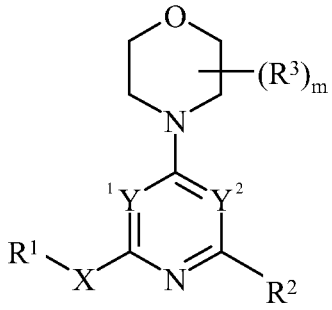
R^{13}, **R^{14}**, **R^{15}**, **R^{16}** and **R^{19}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino,

sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

for use as a medicament in the treatment of proliferative disease.

In accordance with another aspect of the present invention, there is provided the use of a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^1Y and **Y^2** are independently N or CR^8 provided that one of ^1Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$ and $-S(O)_2NR^4CR^6R^7-$;

R^1 is a group selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, $-R^9$, $-OR^9$, $-SR^9$,

-SOR^9, -SO_2R^9, -COR^9, -CO_2R^9, -$CONR^9R^{10}$, -NR^9R^{10}, –NR^9COR^{10}, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{15}$, -$NR^9COCONR^{10}R^{15}$ and –$NR^9SO_2R^{10}$;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, - SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, –$NR^{11}COR^{12}$, -$NR^{11}COCONR^{12}R^{16}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ and -$NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -SR^{13}, -SOR^{13}, -SO_2R^{13}, -COR^{13}, -CO_2R^{13}, -$CONR^{13}R^{14}$, -$NR^{13}R^{14}$, –$NR^{13}COR^{14}$, -$NR^{13}CO_2R^{14}$ and –$NR^{13}SO_2R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-}

$_{6}$alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

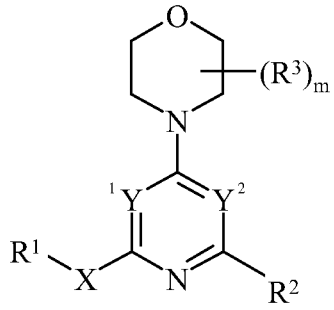
R^{13}, **R^{14}**, **R^{15}** and **R^{16}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R**^{18} and **R**^{19} together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

in the manufacture of a medicament for use in the treatment of proliferative disease.

In accordance with another aspect of the present invention, there is provided the use of a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}Y and **Y^{2}** are independently N or CR^{8} provided that one of ^{1}Y and Y^{2} is N and the other is CR^{8};

X is a linker group selected from -CR^{4}=CR^{5}CR^{6}R^{7}-, -CR^{6}R^{7}CR^{5}=CR^{4}-, -C≡CCR^{6}R^{7}-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^{7}-, -OCR^{6}R^{7}-, -SCR^{6}R^{7}-, -S(O)CR^{6}R^{7}-, -S(O)$_{2}$CR^{6}R^{7}-, -C(O)NR^{4}CR^{6}R^{7}-, -NR^{4}C(O)CR^{6}R^{7}-, -NR^{4}C(O)NR^{5}CR^{6}R^{7}-, -NR^{4}S(O)$_{2}$CR^{6}R^{7}- and -S(O)$_{2}$NR^{4}CR^{6}R^{7}-;

R^{1} is a group selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, -R^{9}, -OR^{9}, -SR^{9}, -SOR^{9}, -SO$_{2}$R^{9}, -COR^{9}, -CO$_{2}$R^{9}, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_{2}$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} and –NR^{9}SO$_{2}$R^{10};

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, - SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, –$NR^{11}COR^{12}$, -$NR^{11}COCONR^{12}R^{16}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ and -$NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -SR^{13}, -SOR^{13}, -SO_2R^{13}, -COR^{13}, -CO_2R^{13}, -$CONR^{13}R^{14}$, -$NR^{13}R^{14}$, –$NR^{13}COR^{14}$, -$NR^{13}CO_2R^{14}$ and –$NR^{13}SO_2R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}

$_{6}$alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

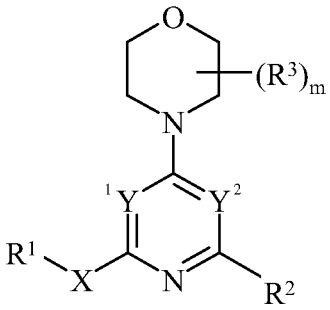
R^{11}, R^{12}, R^{17} and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, **R^{14}**, **R^{15}**, **R^{16}** and **R^{19}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

in the manufacture of a medicament for use in the treatment of proliferative disease.

In accordance with another aspect of the present invention, there is provided the use of a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}Y and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$ and $-S(O)_2NR^4CR^6R^7-$;

R^1 is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $-NR^9SO_2R^{10}$;

or **X-R^1** is $-CR^6R^7OH$;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ and $-NR^{13}SO_2R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or R^1 and R^4 together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro,

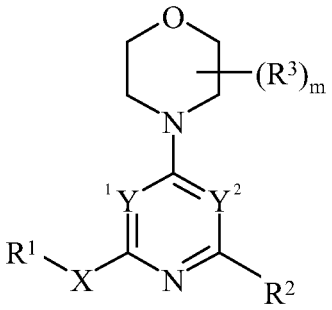
hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, **R**^{14}, **R**^{15}, **R**^{16} and **R**^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R**^{18} and **R**^{19} together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

in the manufacture of a medicament for use in the treatment of proliferative disease.

In accordance with another aspect of the present invention, there is provided the use of a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt; wherein

m is 0, 1, 2, 3 or 4;

^{1}Y and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ and $-S(O)_2NR^4CR^6R^7-$;

R^1 is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $-NR^9SO_2R^{10}$;

or **X-R^1** is $-CR^6R^7OH$

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, and $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-R^{13}CO_2R^{14}$ and $-NR^{13}SO_2R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl,

haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkylsulfonyl, C$_{1-6}$alkylsulfonylamino, C$_{1-6}$alkylsulfonyl(C$_{1-6}$alkyl)amino, sulfamoyl, C$_{1-6}$alkylsulfamoyl, bis(C$_{1-6}$alkyl)sulfamoyl, C$_{1-6}$alkanoylamino, C$_{1-6}$alkanoyl(C$_{1-6}$alkyl)amino, carbamoyl, C$_{1-6}$alkylcarbamoyl and bis(C$_{1-6}$alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, haloC$_{1-6}$alkyl, haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkylsulfonyl, C$_{1-6}$alkylsulfonylamino, C$_{1-6}$alkylsulfonyl(C$_{1-6}$alkyl)amino, sulfamoyl, C$_{1-6}$alkylsulfamoyl, bis(C$_{1-6}$alkyl)sulfamoyl, C$_{1-6}$alkanoylamino, C$_{1-6}$alkanoyl(C$_{1-6}$alkyl)amino, carbamoyl, C$_{1-6}$alkylcarbamoyl and bis(C$_{1-6}$alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C$_{1-6}$alkyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C$_{1-6}$alkyl, carbocyclyl, carbocyclylC$_{1-6}$alkyl, heterocyclyl and heterocyclylC$_{1-6}$alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, haloC$_{1-6}$alkyl, haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkylsulfonyl, C$_{1-6}$alkylsulfonylamino, C$_{1-6}$alkylsulfonyl(C$_{1-6}$alkyl)amino, sulfamoyl, C$_{1-6}$alkylsulfamoyl, bis(C$_{1-6}$alkyl)sulfamoyl, C$_{1-6}$alkanoylamino, C$_{1-6}$alkanoyl(C$_{1-6}$alkyl)amino, carbamoyl, C$_{1-6}$alkylcarbamoyl and bis(C$_{1-6}$alkyl)carbamoyl;

R^{11}, **R^{12}**, **R^{17}** and **R^{18}** are independently hydrogen or a group selected from C$_{1-6}$alkyl, carbocyclyl, carbocyclylC$_{1-6}$alkyl, heterocyclyl and heterocyclylC$_{1-6}$alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, haloC$_{1-6}$alkyl, haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl,

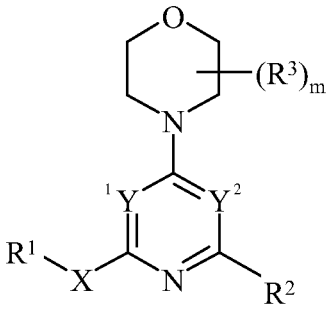
cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, **R^{14}**, **R^{15}**, **R^{16}** and **R^{19}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

in the manufacture of a medicament for use in the treatment of proliferative disease.

In accordance with a further aspect of the present invention, there is also provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}**Y** and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from -CR^4=CR^{5}CR^{6}R^7-, -CR^{6}R^{7}CR^5=CR^4-, -C≡CCR^{6}R^7-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7-, -NR^{4}S(O)$_2$CR^{6}R^7- and -S(O)$_2$NR^{4}CR^{6}R^7-;

R^1 is a group selected from hydrogen, C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, carbocyclyl, carbocyclylC$_{1-6}$alkyl, heterocyclyl and heterocyclylC$_{1-6}$alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, -R^9, -OR^9, -SR^9, -SOR^9, -O$_2$R^9, -COR^9, -CO$_2$R^9, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} and NR^{9}SO$_2$R^{10};

R^2 is a group selected from C$_{1-6}$alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO$_2$R^{11}, -COR^{11}, -CO$_2$R^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12}, -NR^{11}COR^{12}, -NR^{11}COCONR^{12}R^{16}, -NR^{11}SO$_2$R^{12}, -NR^{17}CONR^{18}R^{19} and -NR^{17}CSNR^{18}R^{19};

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -R^{13}, -SOR^{13}, -SO$_2$R^{13}, -COR^{13}, -CO$_2$R^{13}, -CONR^{13}R^{14}, -NR^{13}R^{14}, –NR^{13}COR^{14}, -NR^{13}CO2R^{14} and –NR^{13}SO$_2$R^{14};

R^4 and **R^5** are independently hydrogen or C$_{1-6}$alkyl;

or **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, haloC$_{1-6}$alkyl, haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkylsulfonyl, C$_{1-6}$alkylsulfonylamino, C$_{1-6}$alkylsulfonyl(C$_{1-6}$alkyl)amino, sulfamoyl, C$_{1-6}$alkylsulfamoyl, bis(C$_{1-6}$alkyl)sulfamoyl, C$_{1-6}$alkanoylamino, C$_{1-6}$alkanoyl(C$_{1-6}$alkyl)amino, carbamoyl, C$_{1-6}$alkylcarbamoyl and bis(C$_{1-6}$alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from

halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

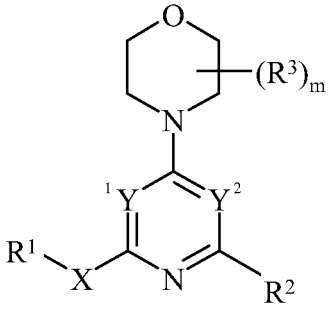
$\mathbf{R^{13}}$, $\mathbf{R^{14}}$, $\mathbf{R^{15}}$ and $\mathbf{R^{16}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino,

sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In accordance with a further aspect of the present invention, there is also provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}**Y** and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from -CR^4=CR^{5}CR^{6}R^7-, -CR^{6}R^{7}CR^5=CR^4-, -C≡CCR^{6}R^7-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7-, -NR^{4}S(O)$_2$CR^{6}R^7- and -S(O)$_2$NR^{4}CR^{6}R^7-;

R^1 is a group selected from hydrogen, C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, carbocyclyl, carbocyclylC$_{1-6}$alkyl, heterocyclyl and heterocyclylC$_{1-6}$alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, -R^9, -OR^9, -SR^9, -SOR^9, -O$_2$R^9, -COR^9, -CO$_2$R^9, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} and NR^{9}SO$_2$R^{10};

R^2 is a group selected from C$_{1-6}$alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO$_2$R^{11}, -COR^{11}, -CO$_2$R^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12}, -NR^{11}COR^{12}, -NR^{11}COCONR^{12}R^{16}, -NR^{11}SO$_2$R^{12}, -NR^{17}CONR^{18}R^{19} and -NR^{17}CSNR^{18}R^{19};

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -R^{13}, -SOR^{13}, -SO$_2$R^{13}, -COR^{13}, -CO$_2$R^{13}, -CONR^{13}R^{14}, -NR^{13}R^{14}, –NR^{13}COR^{14}, -NR^{13}CO2R^{14} and –NR^{13}SO$_2$R^{14};

R^4 and **R^5** are independently hydrogen or C$_{1-6}$alkyl;

or **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, haloC$_{1-6}$alkyl, haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkylsulfonyl, C$_{1-6}$alkylsulfonylamino, C$_{1-6}$alkylsulfonyl(C$_{1-6}$alkyl)amino, sulfamoyl, C$_{1-6}$alkylsulfamoyl, bis(C$_{1-6}$alkyl)sulfamoyl, C$_{1-6}$alkanoylamino, C$_{1-6}$alkanoyl(C$_{1-6}$alkyl)amino, carbamoyl, C$_{1-6}$alkylcarbamoyl and bis(C$_{1-6}$alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from

halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

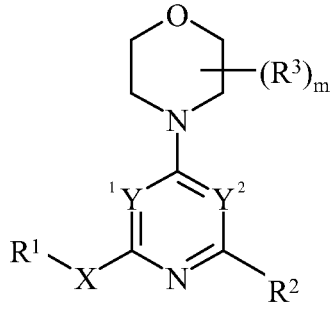
R^{11}, **R^{12}**, **R^{17}** and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, **R^{14}**, **R^{15}**, **R^{16}** and **R^{19}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino,

sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In accordance with a further aspect of the present invention, there is also provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^1Y and **Y^2** are independently N or CR^8 provided that one of ^1Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$ and $-S(O)_2NR^4CR^6R^7-$;

R^1 is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, $-R^9$, $-OR^9$, $-SR^9$,

-SOR^9, -O_2R^9, -COR^9, -CO_2R^9, -$CONR^9R^{10}$, -NR^9R^{10}, –NR^9COR^{10}, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{15}$, -$NR^9COCONR^{10}R^{15}$ and $NR^9SO_2R^{10}$;

or **X-R^1** is -CR^6R^7OH;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, -$NR^{11}COR^{12}$, -$NR^{11}COCONR^{12}R^{16}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ and -$NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -R^{13}, -SOR^{13}, -SO_2R^{13}, -COR^{13}, -CO_2R^{13}, -$CONR^{13}R^{14}$, -$NR^{13}R^{14}$, –$NR^{13}COR^{14}$, -$NR^{13}CO_2R^{14}$ and –$NR^{13}SO_2R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

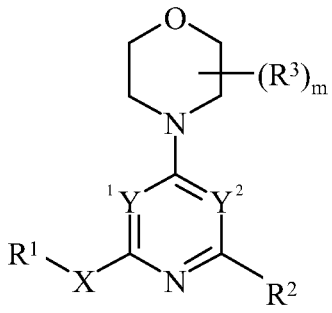
R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, R^{14}, R^{15}, R^{16} and R^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl,

cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl..

In accordance with a further aspect of the present invention, there is also provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}Y and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ and $-S(O)_2NR^4CR^6R^7-$;

R^1 is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-O_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $NR^9SO_2R^{10}$;

or **X-R^1** is $-CR^6R^7OH$;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, and $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -R^{13}, -SOR^{13}, -SO_2R^{13}, -COR^{13}, -CO_2R^{13}, -$CONR^{13}R^{14}$, -$NR^{13}R^{14}$, –$NR^{13}COR^{14}$, -$NR^{13}CO_2R^{14}$ and –$NR^{13}SO_2R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}

$_{6}$alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, **R^{14}**, **R^{15}**, **R^{16}** and **R^{19}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention. Solvates and mixtures thereof also form

an aspect of the present invention. For example, a suitable solvate of a compound of formula (I) is, for example, a hydrate such as a hemi-hydrate, a mono-hydrate, a di-hydrate or a tri-hydrate or an alternative quantity thereof.

The present invention relates to the compounds of formula (I) as herein defined as well as to salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (I) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of compounds of formula (I) as herein defined which are sufficiently basic to form such salts. Such acid addition salts include but are not limited to furmarate, methanesulfonate, hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulfuric acid. In addition where compounds of formula (I) are sufficiently acidic, salts are base salts and examples include but are not limited to, an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine, ethanolamine, diethanolamine, triethanolamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, dibenzylamine or amino acids such as lysine.

The compounds of formula (I) may also be provided as *in vivo* hydrolysable esters. An *in vivo* hydrolysable ester of a compound of formula (I) containing carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl, 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl, and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl; and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give

the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include C_{1-10}alkanoyl, for example formyl, acetyl, benzoyl, phenylacetyl, substituted benzoyl and phenylacetyl; C_{1-10}alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-C_{1-4}alkylcarbamoyl and *N*-(di-C_{1-4}alkylaminoethyl)-*N*-C_{1-4}alkylcarbamoyl (to give carbamates); di-C_{1-4}alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, C_{1-4}alkylaminomethyl and di-(C_{1-4}alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting *in vivo* hydrolysable esters include, for example, $R^AC(O)OC_{1-6}$alkyl-CO-, wherein R^A is for example, benzyloxy-C_{1-4}alkyl, or phenyl. Suitable substituents on a phenyl group in such esters include, for example, 4-C_{1-4}piperazino-C_{1-4}alkyl, piperazino-C_{1-4}alkyl and morpholino-C_{1-4}alkyl.

The compounds of the formula (I) may be also be administered in the form of a prodrug which is broken down in the human or animal body to give a compound of the formula (I). Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

In this specification the generic term "C_{p-q}alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only (i.e. *n*-propyl and isopropyl) and references to individual branched-chain alkyl groups such as "*tert*-butyl" are specific for the branched chain version only.

The prefix C_{p-q} in C_{p-q}alkyl and other terms (where p and q are integers) indicates the range of carbon atoms that are present in the group, for example C_{1-4}alkyl includes C_1alkyl

(methyl), C_2alkyl (ethyl), C_3alkyl (propyl as *n*-propyl and isopropyl) and C_4alkyl (n-butyl, sec-butyl, isobutyl and *tert*-butyl).

The term C_{p-q}alkoxy comprises –O-C_{p-q}alkyl groups.

The term C_{p-q}alkanoyl comprises –C(O)alkyl groups.

The term halo includes fluoro, chloro, bromo and iodo.

"Carbocyclyl" is a saturated, unsaturated or partially saturated monocyclic, bicyclic or tricyclic ring system containing from 3 to 14 ring atoms, wherein a ring CH_2 group may be replaced with a C=O group. "Carbocyclyl" includes "aryl", "C_{p-q}cycloalkyl" and "C_{p-q}cycloalkenyl".

"aryl" is an aromatic monocyclic, bicyclic or tricyclic carbcyclyl ring system.

"C_{p-q}cycloalkenyl" is an unsaturated or partially saturated monocyclic, bicyclic or tricyclic carbocyclyl ring system containing at least 1 C=C bond and wherein a ring CH_2 group may be replaced with a C=O group.

"C_{p-q}cycloalkyl" is a saturated monocyclic, bicyclic or tricyclic carbocyclyl ring system and wherein a ring CH_2 group may be replaced with a C=O group.

"Heterocyclyl" is a saturated, unsaturated or partially saturated monocyclic, bicyclic or tricyclic ring system containing from 3 to 14 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulfur or oxygen, which ring may be carbon or nitrogen linked and wherein a ring nitrogen or sulfur atom may be oxidised and wherein a ring CH_2 group may be replaced with a C=O group. "Heterocyclyl" includes "heteroaryl", "cycloheteroalkyl" and "cycloheteroalkenyl".

"Heteroaryl" is an aromatic monocyclic, bicyclic or tricyclic heterocyclyl, particularly having 5 to 10 ring atoms, of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulfur or oxygen where a ring nitrogen or sulfur may be oxidised.

"Cycloheteroalkenyl" is an unsaturated or partially saturated monocyclic, bicyclic or tricyclic heterocyclyl ring system, particularly having 5 to 10 ring atoms, of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulfur or oxygen, which ring may be carbon or nitrogen linked and wherein a ring nitrogen or sulfur atom may be oxidised and wherein a ring CH_2 group may be replaced with a C=O group.

"Cycloheteroalkyl" is a saturated monocyclic, bicyclic or tricyclic heterocyclic ring system, particularly having 5 to 10 ring atoms, of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulfur or oxygen, which ring may be carbon or nitrogen linked and wherein a ring

nitrogen or sulfur atom may be oxidised and wherein a ring CH_2 group may be replaced with a C=O group.

This specification may make use of composite terms to describe groups comprising more than one functionality. Unless otherwise described herein, such terms are to be interpreted as is understood in the art. For example carbocyclylC_{p-q}alkyl comprises C_{p-q}alkyl substituted by carbocyclyl, heterocyclylC_{p-q}alkyl comprises C_{p-q}alkyl substituted by heterocyclyl, and bis(C_{p-q}alkyl)amino comprises amino substituted by 2 C_{p-q}alkyl groups which may be the same or different.

HaloC_{p-q}alkyl is a C_{p-q}alkyl group that is substituted by 1 or more halo substituents and particuarly 1, 2 or 3 halo substituents. Similarly, other generic terms containing halo such as haloC_{p-q}alkoxy may contain 1 or more halo substituents and particluarly 1, 2 or 3 halo substituents.

HydroxyC_{p-q}alkyl is a C_{p-q}alkyl group that is substituted by 1 or more hydroxyl substituents and particularly by 1, 2 or 3 hydroxy substituents. Similarly other generic terms containing hydroxy such as hydroxyC_{p-q}alkoxy may contain 1 or more and particularly 1, 2 or 3 hydroxy substituents.

C_{p-q}alkoxyC_{p-q}alkyl is a C_{p-q}alkyl group that is substituted by 1 or more C_{p-q}alkoxy substituents and particularly 1, 2 or 3 C_{p-q}alkoxy substituents. Similarly other generic terms containing C_{p-q}alkoxy such as C_{p-q}alkoxyC_{p-q}alkoxy may contain 1 or more C_{p-q}alkoxy substituents and particularly 1, 2 or 3 C_{p-q}alkoxy substituents.

Where optional substituents are chosen from "1 or 2", from "1, 2, or 3" or from "1, 2, 3 or 4" groups or substituents it is to be understood that this definition includes all substituents being chosen from one of the specified groups i.e. all substitutents being the same or the substituents being chosen from two or more of the specified groups i.e. the substitutents not being the same.

Compounds of the present invention have been named with the aid of computer software (ACD/Name version 8.0).

"Proliferative disease(s)" includes malignant disease(s) such as cancer as well as non-malignant disease(s) such as inflammatory diseases, obstracutive airways diseases, immune diseases or cardiovascular diseases.

Suitable values for any R group or any part or substitutent for such groups include:

for C_{1-4}alkyl: methyl, ethyl, propyl, butyl, 2-methylpropyl and *tert*-butyl;

for C_{1-6}alkyl:	C_{1-4}alkyl, pentyl, 2,2-dimethylpropyl, 3-methylbutyl and hexyl;
for C_{3-6}cycloalkyl:	cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;
for C_{3-6}cycloalkylC_{1-4}alkyl:	cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl;
for aryl:	phenyl and naphthyl;
for arylC_{1-4}alkyl:	benzyl, phenethyl, naphthylmethyl and naphthylethyl;
for carbocylyl:	aryl, cyclohexenyl and C_{3-6}cycloalkyl;
for halo:	fluoro, chloro, bromo and iodo;
for C_{1-4}alkoxy:	methoxy, ethoxy, propoxy and isopropoxy;
for C_{1-6}alkoxy:	C_{1-4}alkoxy, pentyloxy, 1-ethylpropoxy and hexyloxy;
for C_{1-6}alkanoyl:	acetyl, propanoyl and 2-methylpropanoyl;
for heteroaryl:	pyridinyl, imidazolyl, quinolinyl, cinnolyl, pyrimidinyl, thienyl, pyrrolyl, pyrazolyl, thiazolyl, thiazolyl, triazolyl, oxazolyl, isoxazolyl, furanyl, pyridazinyl, pyrazinyl, indolyl, benzofuranyl, dibenzofuranyl and benzothienyl;
for heteroarylC_{1-4}alkyl:	pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thienylmethyl, theinylethyl, pyridinylmethyl, pyridinylethyl, pyrazinylmethyl, pyrazinylethyl, pyrimidinylmethyl, pyrimidinylethyl, pyrimidinylpropyl, pyrimidinylbutyl, imidazolylpropyl, imidazolylbutyl, quinolinylpropyl, 1,3,4-triazolylpropyl and oxazolylmethyl;
for heterocyclyl:	heteroaryl, pyrrolidinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoxazolyl, piperidinyl, piperazinyl, azetidinyl, morpholinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolinyl, dihydro-*2H*-pyranyl and tetrahydrofuranyl.

It should be noted that examples given for terms used in the description are not limiting.

Particular values of m, X, ^{1}Y and Y^2, X, R^1, X-R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{17}, R^{18} and R^{19}are as follows. Such values may be used idividually or in

combination where appropriate, in connection with any aspect of the invention, or part thereof, and with any of the definitions, claims or embodiments defined herein.

m

In one aspect of the invention m is 0, 1, 2 or 3.

In another aspect m is 0, 1 or 2.

In a further aspect m is 0 or 1.

In yet another aspect m is 0 so that R^3 is absent.

In yet another aspect m is 1 and R^3 is methyl.

In yet another aspect m is 1 and R^3 is hydroxymethyl.

In yet another aspect m is 1 and R^3 is ethyl.

In yet another aspect m is 1 and R^3 is dimethylcarbamoyl.

In yet another aspect m is 1 and R^3 is carbamoyl.

In yet another aspect m is 2 and each R^3 is methyl.

^1Y and Y^2

In one aspect of the invention ^1Y is N and Y^2 is CR^8.

In another aspect ^1Y is N and Y^2 is CH.

In yet another aspect ^1Y is CR^8 and Y^2 is N.

In a further aspect ^1Y is CH or CF and Y^2 is N.

In yet a further aspect ^1Y is CH and Y^2 is N.

X

In one aspect of the invention X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ and $-S(O)_2NR^4CR^6R^7-$.

In another aspect **X** is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ and $-S(O)_2NR^4CR^6R^7$.

In a further aspect X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$ and $-S(O)_2CR^6R^7-$.

In a further aspect X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$ and $-S(O)_2CR^6R^7-$.

In yet another aspect X is a linker group selected from $-SCR^6R^7-$, $-S(O)CR^6R^7-$ and $-S(O)_2CR^6R^7-$.

In another aspect X is $-SCR^6R^7-$ or $-S(O)_2CR^6R^7-$.

In another aspect X is $-S(O)_2CR^6R^7-$.

R^1

In one aspect of the invention R^1 is a group selected from C_{1-4}alkyl, C_{3-10}cycloalkyl, aryl, C_{3-10}cycloalkylC_{1-4}alkyl, arylC_{1-4}alkyl, cycloheteroalkyl, heteroaryl, cycloheteroalkylC_{1-4}alkyl, heteroarylC_{1-4}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$.

In another aspect, R^1 is a group selected from adamantyl, methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenethyl, pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thiadiazolyl, thiazolyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thiadiazolylmethyl, thiadiazolylethyl, thiazolylmethyl, thiazolylethyl, thienylmethyl, thienylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrimidinylethyl, pyrazinylmethyl and pyrazinylethyl, which group is optionally substituted by 1, 2 or 3 substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$.

In another aspect, R^1 is a group selected from adamantyl, methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenethyl, pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thienylmethyl, thienylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrimidinylethyl, pyrazinylmethyl and pyrazinylethyl, which group is optionally substituted by 1, 2 or 3 substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$.

In a further aspect, R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, imidazolyl, pyrrolidinyl, thiadiazolyl, thiazolyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, $-NHCOCH_3$, $-CONH_2$ and $-CONHCH_3$.

In a further aspect, R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, $-NHCOCH_3$, $-CONH_2$ and $-CONHCH_3$.

In yet another aspect R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2CH_2NHMe$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-fluoro-4-methylaminophenyl, 4-fluoro-2-methylphenyl, 5-fluoro-2-methylphenyl, 3-fluoro-4-(2-hydroxyethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-carbamoyl-2-chlorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-4-methylaminophenyl, 3-chloro-4-ethylaminophenyl, 3-chloro-4-(2-fluoroethylamino)phenyl, 3-chloro-4-(2-hydroxyethylamino)phenyl, 2-chloro-4-cyanophenyl, 4-cyanophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-(trifluoromethyl)phenyl, 2-methylphenyl, 4-methylphenyl, 4-(2-hydroxyethylamino)phenyl, 1H-imidazol-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 1-(difluoromethyl)pyrazol-4-yl, 1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl, 1,3-dimethylpyrazol-4-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, 5-fluoropyridin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2,4-dimethylthiazol-5-yl, 5-methyl-1,3,4-thiadiazol-2-yl, terahydrofuran-3-yl and terahydropyran-4-yl.

In yet another aspect R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, phenyl, 4-fluorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3,5-difluorophenyl, 2-(trifluoromethyl)phenyl, 2-methoxyphenyl, 2-methylphenyl, 4-(2-hydroxyethylamino)phenyl, 1H-imidazol-2-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, 5-fluoropyridin-3-yl, 2-oxopyrolidin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl and 3-methyl-1,3,4-thiadiazol-2-yl.

In yet another aspect R^1 is a group selected from methyl, isopropyl, cyclopropyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2NHC(O)CH_3$, phenyl, 4-fluorophenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-methylphenyl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, 2-oxopyrolidin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, and 3-methyl-1,3,4-thiadiazol-2-yl.

In yet another aspect R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, phenyl, 4-fluorophenyl, 4-chlorophenyl, 3,5-difluorophenyl, 2-(trifluoromethyl)phenyl, 4-(2-hydroxyethylamino)phenyl, 1H-imidazol-2-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, 5-fluoropyridin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl and 5-methyl-1,3,4-thiadiazol-2-yl.

In yet another aspect R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2CH_2NHMe$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-fluoro-4-methylaminophenyl, 4-fluoro-2-methylphenyl, 5-fluoro-2-methylphenyl, 3-fluoro-4-(2-hydroxyethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-carbamoyl-2-chlorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-4-methylaminophenyl, 3-chloro-4-ethylaminophenyl, 3-chloro-4-(2-fluoroethylamino)phenyl, 3-chloro-4-(2-hydroxyethylamino)phenyl, 2-chloro-4-cyanophenyl, 4-cyanophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-methylphenyl, 4-methylphenyl, 1H-imidazol-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 1-(difluoromethyl)pyrazol-4-yl, 1,3-dimethylpyrazol-4-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2,4-dimethylthiazol-5-yl and 5-methyl-1,3,4-thiadiazol-2-yl.

In yet another aspect R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, phenyl, 4-fluorophenyl, 4-chlorophenyl, 3,5-difluorophenyl, 1H-imidazol-2-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 4-methylthiazol-2-yl and 5-methyl-1,3,4-thiadiazol-2-yl.

In yet another aspect R^1 is a group selected from methyl, ethyl, cyclopropyl, $-CH_2CH_2CH_2OH$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 5-fluoropyridin-2-yl, pyridin-2-yl, thiazol-2-yl and 4-methylthiazol-2-yl.In yet another aspect R^1 is a group selected from $-CH_2CH_2CH_2OH$, phenyl, 4-fluorophenyl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl and 4-methylthiazol-2-yl.

In yet another aspect R^1 is methyl.

In yet another aspect R^1 is ethyl.

In yet another aspect R^1 is cyclopropyl.

In yet another aspect R^1 is $-CH_2CH_2CH_2OH$.

In yet another aspect R^1 is phenyl.

In yet another aspect R^1 is 2-fluorophenyl.

In yet another aspect R^1 is 3-fluorophenyl.

In yet another aspect R^1 is 4-fluorophenyl.

In yet another aspect R^1 is 2-chlorophenyl.

In yet another aspect R^1 is 2-methylphenyl.

In yet another aspect R^1 is 5-fluoropyridin-2-yl

In yet another aspect R^1 is pyridin-2-yl.

In yet another aspect R^1 is thiazol-2-yl.

In yet another aspect R^1 is 4-methylthiazol-2-yl.

X-R^1

In one embodiment X-R^1 is $-CR^6R^7OH$.

R^2

In one aspect of the invention R^2 is a group selected from carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$.

In one aspect of the invention R^2 is selected from carbocyclyl or heterocyclyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ or $-NR^{17}CSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from carbocyclyl or heterocyclyl which group is substituted by $-NHCONR^{18}R^{19}$ or $-NHCSNR^{18}R^{19}$and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from carbocyclyl or heterocyclyl which group is substituted by $-NHCONHR^{19}$ or $-NHCSNHR^{19}$and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is a group selected from 5 or 6 membered carbocyclyl or heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$.

In one aspect of the invention R^2 is selected from 5 or 6 membered carbocyclyl or heterocyclyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ or $-NR^{17}CSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from 5 or 6 membered carbocyclyl or heterocyclyl which group is substituted by $-NHCONR^{18}R^{19}$ or $-NHCSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from 5 or 6 membered carbocyclyl or heterocyclyl which group is substituted by $-NHCONHR^{19}$ or $-NHCSNHR^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from a 6 membered aryl and 5 or 6 membered heteroaryl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$.

In one aspect of the invention R^2 is selected from a 6 membered aryl and 5 or 6 membered heteroaryl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ or $-NR^{17}CSNR^{18}R^{19}$ and

optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and –$NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from a 6 membered aryl and 5 or 6 membered heteroaryl which group is substituted by –$NHCONR^{18}R^{19}$ or -$NHCSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and –$NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from a 6 membered aryl and 5 or 6 membered heteroaryl which group is substituted by –$NHCONHR^{19}$ or -$NHCSNHR^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and –$NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, -$NR^{11}COR^{12}$, -$NR^{11}COCONR^{12}R^{16}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ and -$NR^{17}CSNR^{18}R^{19}$.

In another aspect R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl, , which group is substituted by –$NR^{17}CONR^{18}R^{19}$ or -$NR^{17}CSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and –$NR^{11}COR^{12}$.

In another aspect R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is substituted by –$NHCONR^{18}R^{19}$ or -$NHCSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and –$NR^{11}COR^{12}$.

In another aspect R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is substituted by –$NHCONHR^{19}$ or -$NHCSNHR^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and –$NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is

optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$, -$NR^{11}COR^{12}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ and -$NR^{17}CSNR^{18}R^{19}$.

In another aspect R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is substituted by –$NR^{17}CONR^{18}R^{19}$ or -$NR^{17}CSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$.

In another aspect R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is substituted by –$NHCONR^{18}R^{19}$ or -$NHCSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$.

In another aspect R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is substituted by –$NHCONHR^{19}$ or -$NHCSNHR^{19}$and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$.

In one aspect of the invention R^2 is selected from phenyl, pyridinyl or pyrimidinyl which group is optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, -$CONHCH_3$ and -$CON(CH_3)_2$, -$NR^{11}COR^{12}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ and -$NR^{17}CSNR^{18}R^{19}$.

In one aspect of the invention R^2 is selected from phenyl or pyridinyl which group is optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$, -$NR^{11}COR^{12}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ and -$NR^{17}CSNR^{18}R^{19}$.

In another aspect R^2 is phenyl, pyridinyl or pyrimidinyl substituted by –$NR^{17}CONR^{18}R^{19}$ or -$NR^{17}CSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$.

In another aspect R^2 is phenyl or pyridinyl substituted by –$NR^{17}CONR^{18}R^{19}$ or -$NR^{17}CSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently

selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$.

In another aspect R^2 is phenyl or pyridinyl substituted by –$NHCONR^{18}R^{19}$ or -$NHCSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, -$CONHCH_3$ and -$CON(CH_3)_2$.

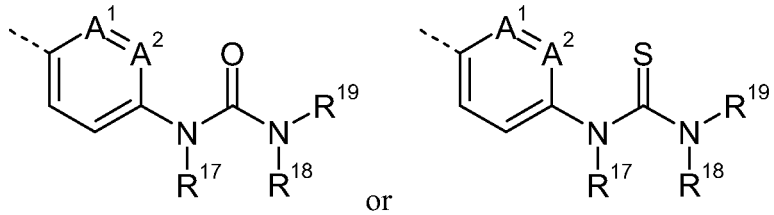
In another aspect R^2 is phenyl or pyridinyl substituted by –$NHCONHR^{19}$ or -$NHCSNHR^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, -$CONHCH_3$ and -$CON(CH_3)_2$.

In another aspect R^2 is phenyl or pyridinyl optionally substituted by -$NR^{17}CONR^{18}R^{19}$ or -$NR^{17}CSNR^{18}R^{19}$.

In another aspect R^2 is phenyl or pyridinyl optionally substituted by -$NHCONR^{18}R^{19}$ or -$NHCSNR^{18}R^{19}$.

In another aspect R^2 is phenyl or pyridinyl optionally substituted by –$NHCONHR^{19}$ or -$NHCSNHR^{19}$.

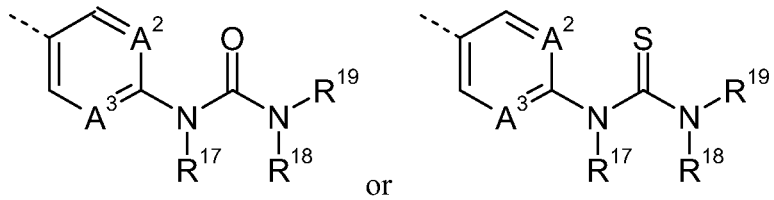
In another aspect R^2 is



or

wherein A^1 and A^2 are selected from CH or N provided that at least one of A^1 or A^2 is CH.

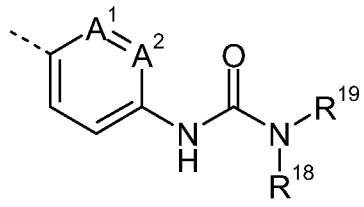
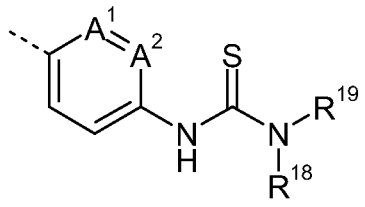
In another aspect R^2 is



or

wherein A^2 and A^3 are selected from CH or N.

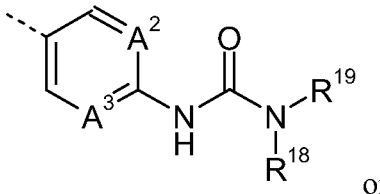
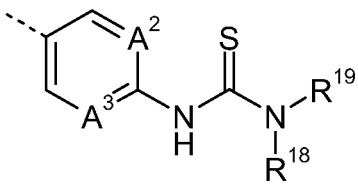
In another aspect R^2 is

or

wherein A^1 and A^2 are selected from CH or N provided that at least one of A^1 or A^2 is CH.

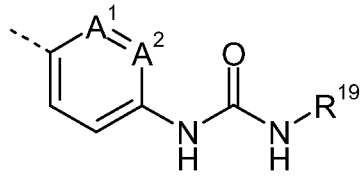
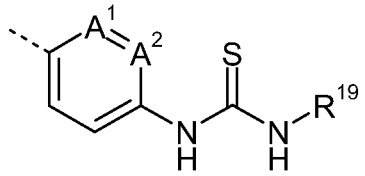
In another aspect R^2 is

or

wherein A^2 and A^3 are selected from CH or N.

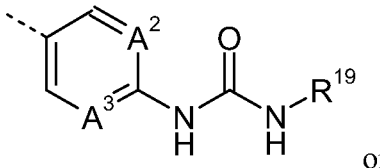
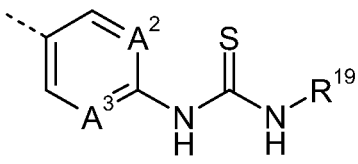
In another aspect R^2 is

or

wherein A^1 and A^2 are selected from CH or N provided that at least one of A^1 or A^2 is CH.

In another aspect R^2 is

or

wherein A^2 and A^3 are selected from CH or N.

In yet another aspect R^2 is 3-(hydroxymethyl)phenyl, 4-(hydroxymethyl)phenyl, 4-(cyanomethyl)phenyl, 3,4-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-phenoxyphenyl, 3-pyrrolidin-1ylphenyl, 3-(aminocarbonyl)phenyl, 4-(dimethylaminocarbonyl)phenyl, furan-3-yl, thien-3-yl, 5-(hydroxymethyl)thien-2-yl, pyridin-2-yl, pyridin-4-yl, 2-methoxypyridin-5-yl, 2-methoxypyrimidin-5-yl, 2-methoxynaphth-6-yl, 5,7-diazabicyclo[4.3.0]nona-2,4,8,10-tetraenyl, azaindolyl, indol-5-yl, 1-methylindol-5-yl, quinolin-6-yl, benzimidazolyl, benzofuran-2-yl, dibenzofuran-1-yl and benzothien-3-yl.

In yet a further aspect R^2 is pyridin-2-yl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-hydroxymethylphenyl, 4-hydroxymethylphenyl or indol-5-yl.

In yet a further aspect R^2 is azaindolyl, indol-5-yl, benzimidazolyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-hydroxymethylphenyl or 4-hydroxymethylphenyl

In another aspect R^2 is pyridin-2-yl.

In a further aspect R^2 is 3-hydroxyphenyl or 4-hydroxyphenyl.

In yet another aspect R^2 is 3-hydroxymethylphenyl or 4-hydroxymethylphenyl.

In yet a further aspect R^2 is indol-5-yl.

In one aspect R^2 is morpholinyl.

In another aspect R^2 is morpholino.

R^3

Each R^3 is independently selected from cyano, R^{13}, and $-CONR^{13}R^{14}$, wherein R^{13} and R^{14} are independently hydrogen or a C_{1-3}alkyl which is optionally substituted by one or more substituent groups selected from halo, cyano, hydroxy and C_{1-3}alkoxy.

Each R^3 is independently selected from hydrogen, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, and $-CONR^{13}R^{14}$, wherein R^{13} and R^{14} are independently hydrogen or a C_{1-3}alkyl.

Each R^3 is independently selected from hydrogen, methyl, ethyl, hydroxymethyl, carbamoyl and dimethylcarbamoyl.

R^4

In one aspect of the invention R^4 is hydrogen or methyl.

In another aspect R^4 is hydrogen.

R^4 and **R^1**

In another aspect of the invention, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ or $-NR^4S(O)_2CR^6R^7-$, **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-}

$_{6}$alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention, when **X** is -$NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$-, -$NR^4C(O)NR^5CR^6R^7$- or -$NR^4S(O)_2CR^6R^7$-, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 5-, 6- or 7-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention, when **X** is -$NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$-, -$NR^4C(O)NR^5CR^6R^7$- or -$NR^4S(O)_2CR^6R^7$-, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention, when **X** is -$NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$-, -$NR^4C(O)NR^5CR^6R^7$- or -$NR^4S(O)_2CR^6R^7$-, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a morpholine or piperazine ring which ring is optionally substituted by one or more methyl groups.

In another aspect of the invention, when **X** is -$NR^4C(O)CR^6R^7$-, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a morpholine or piperazine ring which ring is optionally substituted by one or more methyl groups.

$\underline{\mathbf{R^5}}$

In one aspect of the invention R^5 is hydrogen or methyl.

In another aspect R^5 is hydrogen.

In another aspect R^5 is methyl.

R^6 and R^7

In one aspect of the invention **R^6** and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention **R^6** and **R^7** together with the carbon atom to which they are attached form a 3- to 6-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect **R^6** and **R^7** together with the carbon atom to which they are attached form a 3- to 6-membered carbocyclic ring.

In another aspect **R^6** and **R^7** together with the carbon atom to which they are attached form a 3- to 5-membered carbocyclic ring.

In another aspect **R^6** and **R^7** together with the carbon atom to which they are attached form a 3- to 4-membered carbocyclic ring.

In another aspect **R^6** and **R^7** together with the carbon atom to which they are attached form a 3-membered carbocyclic ring.

In another aspect **R**^{6} and **R**^{7} together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring.

R^8

In one aspect of the invention R^8 is hydrogen or halo.

In another aspect R^8 is hydrogen or fluoro.

In a further aspect R^8 is hydrogen.

R^9

In one aspect of the invention R^9 is hydrogen or C_{1-4}alkyl optionally substituted by 1, 2 or 3 substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-4}alkoxy, amino, C_{1-4}alkylamino and bis(C_{1-4}alkyl)amino.

In another aspect R^9 is hydrogen or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halo substituents.

In a further aspect R^9 is hydrogen, methyl or trifluoromethyl.

R^{10}

In one aspect of the invention R^{10} is hydrogen.

R^{11}

In one aspect of the invention R^{11} is hydrogen or a group selected from C_{1-4}alkyl, aryl and cycloheteroalkyl which group is optionally substituted by 1, 2 or 3 groups selected from halo, hydroxy and cyano.

In another aspect R^{11} is hydrogen, methyl optionally substituted with hydroxy or cyano, phenyl or pyrrolidinyl.

In another aspect R^{11} is hydrogen or methyl.

R^{12}

In one aspect of the invention R^{12} is hydrogen or methyl.

R^{17}

In one aspect of the invention R^{17} is hydrogen or a group selected from C_{1-4}alkyl, aryl and cycloheteroalkyl which group is optionally substituted by 1, 2 or 3 groups selected from halo, hydroxy and cyano.

In another aspect R^{17} is hydrogen, methyl optionally substituted with hydroxy or cyano, phenyl or pyrrolidinyl.

In another aspect R^{17} is hydrogen or methyl.

In another aspect R^{17} is hydrogen.

R^{18}

In one aspect of the invention R^{18} is hydrogen or methyl.

In one aspect of the invention R^{18} is hydrogen

R^{19}

In one aspect of the invention R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, phenyl, naphthyl, pyrrolyl, imidazolyl, isoxazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, azaindolyl, indolyl, quinolinyl, benzimidazolyl, benzofuranyl, dibenzofuranyl, benzothienyl, pyrrolidinyl, pyrazinyl, oxetanyl, dioxothiolanyl, thiazolyl, thiadiazolyl, phenylC_{1-6}alkyl, naphthylC_{1-6}alkyl, pyrrolylC_{1-6}alkyl, imidazolylC_{1-6}alkyl, isoxazolylC_{1-6}alkyl, pyrazolylC_{1-6}alkyl, furanylC_{1-6}alkyl, thienylC_{1-6}alkyl, pyridinylC_{1-6}alkyl, pyrimidinylC_{1-6}alkyl, pyridazinylC_{1-6}alkyl, azaindolylC_{1-6}alkyl, indolylC_{1-6}alkyl, quinolinylC_{1-6}alkyl, benzimidazolylC_{1-6}alkyl, benzofuranylC_{1-6}alkyl, dibenzofuranylC_{1-6}alkyl, benzothienylC_{1-6}alkyl, pyrrolidinylC_{1-6}alkyl, pyrazinylC_{1-6}alkyl, oxetanylC_{1-6}alkyl, dioxothiolanylC_{1-6}alkyl, thiazolylC_{1-6}alkyl and thiadiazolylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, phenyl, naphthyl, pyrrolyl, imidazolyl, isoxazolyl, pyrazolyl, furanyl, thienyl,

pyridinyl, pyrimidinyl, pyridazinyl, azaindolyl, indolyl, quinolinyl, benzimidazolyl, benzofuranyl, dibenzofuranyl, benzothienyl, phenylC_{1-6}alkyl, naphthylC_{1-6}alkyl, pyrrolylC_{1-6}alkyl, imidazolylC_{1-6}alkyl, isoxazolylC_{1-6}alkyl, pyrazolylC_{1-6}alkyl, furanylC_{1-6}alkyl, thienylC_{1-6}alkyl, pyridinylC_{1-6}alkyl, pyrimidinylC_{1-6}alkyl, pyridazinylC_{1-6}alkyl, azaindolylC_{1-6}alkyl, indolylC_{1-6}alkyl, quinolinylC_{1-6}alkyl, benzimidazolylC_{1-6}alkyl, benzofuranylC_{1-6}alkyl, dibenzofuranylC_{1-6}alkyl, benzothienylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention R^{19} is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, dioxothiolanyl, imidazoylmethyl, isoxazolyl, oxazolyl, oxetanyl, pyrazinyl, pyrazolyl, pyrazolylmethyl, pyridinyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, thiazolyl and triazolyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, imidazoylmethyl, isoxazolyl, pyrazolyl, pyrazolylmethyl, pyridinyl and pyrimidinyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

$_6$alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention R^{19} is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -$CH_2C(CH_3)_2OH$, -$CH_2C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CH_2Cl, -$CH_2CH_2SO_2Me$, -$CH_2CH(OH)CF_3$, -CH_2CH_2CN, -CH_2CN, -CH_2CONMe_2, -CH_2CO_2H, 1-(methyl)cyclopropyl, -CH_2(1-hydroxycyclopropyl), 1-(hydroxymethyl)cyclopropyl, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, -CH_2CH_2(pyrrolidin-1-yl),-CH_2(imidazol-2-yl), -CH_2(imidazol-3-yl), 1-methylimidazol-4-yl, oxazolyl-2-yl, isoxazolyl-3-yl, 6-oxo-1H-pryrdin-2-yl, oxetan-3-yl, 1,1-dioxothiolan-3-yl, 5-methylisoxazol-3-yl, -CH_2(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, -CH_2(1-methylpyrazol-4-yl), 5-methylpyrazin-2-yl, -CH_2(2H-1,2,4-triazol-3-yl), 6-methoxypryridin-3-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, pyrimidin-2-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1-methylpyrazol-3-yl and 1H-pyrazol-3-yl.

In one aspect of the invention R^{19} is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, i-butyl, t-butyl, cyclopropyl, cyclobutyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -$CH_2C(CH_3)_2OH$, -$CH_2C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CH_2Cl, -$CH_2CH_2SO_2Me$, -$CH_2CH(OH)CF_3$, -CH_2CH_2CN, -CH_2CN, -CH_2CONMe_2, -CH_2CO_2H, 1-(methyl)cyclopropyl, -CH_2(1-hydroxycyclopropyl), 1-(hydroxymethyl)cyclopropyl, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, -CH_2CH_2(pyrrolidin-1-yl),-CH_2(imidazol-2-yl), 1-methylimidazol-4-yl, oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 1,1-dioxothiolan-3-yl, 5-methylisoxazol-3-yl, -CH_2(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, -CH_2(1-methylpyrazol-4-yl), 5-methylpyrazin-2-yl, -CH_2(2H-1,2,4-triazol-3-yl), 6-methoxypryridin-3-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl and 1-methylpyrazol-3-yl.

In one aspect of the invention R^{19} is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -$CH_2C(CH_3)_2OH$, -$CH_2C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CHF_2, -$CH_2CH_2SO_2Me$, -$CH_2CH(OH)CF_3$, -CH_2CH_2CN, -CH_2CN, -CH_2CONMe_2, 1-(methyl)cyclopropyl, 1-(hydroxymethyl)cyclopropyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, -CH_2CH_2(pyrrolidin-1-yl),-CH_2(imidazol-2-yl), -CH_2(imidazol-3-yl), oxazolyl-2-yl, isoxazolyl-3-yl, 6-oxo-1H-pryrdin-2-yl, oxetan-3-yl, 1,1-dioxothiolan-3-yl, 5-methylisoxazol-3-yl, -CH_2(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, -CH_2(1-methylpyrazol-4-yl), 5-methylpyrazin-2-yl, -CH_2(2H-1,2,4-triazol-3-yl), 6-methoxypryridin-3-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, pyrimidin-2-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1-methylpyrazol-3-yl and 1H-pyrazol-3-yl.

In one aspect of the invention R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, cyclopropyl, cyclobutyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CH_2Cl, -CH_2CH_2CN, -CH_2(1-hydroxycyclopropyl), 1-(hydroxymethyl)cyclopropyl, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, -CH_2CH_2(pyrrolidin-1-yl),-CH_2(imidazol-2-yl), 1-methylimidazol-4-yl, oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, 6-methoxypryridin-3-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl and 1-methylpyrazol-3-yl.

In one aspect of the invention R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, 4-methylphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, -CH_2(imidazol-2-yl), -CH_2(imidazol-3-yl), isoxazolyl-3-yl, 6-oxo-1H-pryrdin-2-yl, 5-methylisoxazol-3-yl, -CH_2(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, -CH_2(1-methylpyrazol-4-yl), 6-methoxypryridin-3-yl, 5-fluoropyridin-2-yl, pyrimidin-2-yl, and 1H-pyrazol-3-yl.

In one aspect of the invention R^{19} is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, i-butyl, t-butyl, cyclopropyl, cyclobutyl, -CH_2(cyclopropyl),

$-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, 1-(methyl)cyclopropyl, 1-(hydroxymethyl)cyclopropyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, $-CH_2CH_2$(pyrrolidin-1-yl),$-CH_2$(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 1,1-dioxothiolan-3-yl, 5-methylisoxazol-3-yl, $-CH_2$(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, $-CH_2$(2H-1,2,4-triazol-3-yl), 6-methoxypryridin-3-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl, and 1-methylpyrazol-3-yl.

In one aspect of the invention R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, cyclopropyl, cyclobutyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2CN$, 1-(hydroxymethyl)cyclopropyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, $-CH_2CH_2$(pyrrolidin-1-yl), $-CH_2$(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, 6-methoxypryridin-3-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl, and 1-methylpyrazol-3-yl.

In one aspect of the invention R^{19} is a group selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, $-CH_2$(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, thiazol-2-yl and 1,2,4-thiadiazol-5-yl.

In one aspect of the invention R^{19} is a group selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2CN$, $-CH_2$(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, thiazol-2-yl and 1,2,4-thiadiazol-5-yl.

In one aspect of the invention R^{19} is hydrogen or a group selected from methyl, ethyl, cyclopropyl, 1-methylpyrazol-4-yl, and $-CH_2$(1-methylpyrazol-4-yl).

In one aspect of the invention R^{19} is methyl.

In one aspect of the invention R^{19} is ethyl.

In one aspect of the invention R^{19} is cyclopropyl.

In one aspect of the invention R^{19} is cyclobutyl.

In one aspect of the invention R^{19} is $-CH(CH_3)CH_2OH$.

In one aspect of the invention R^{19} is $-CH_2CH_2OH$.

In one aspect of the invention R^{19} is $-CH_2CH_2CH_2OH$.

In one aspect of the invention R^{19} is $-CH_2CHF_2$.

In one aspect of the invention R^{19} is $-CH_2CH_2F$.

In one aspect of the invention R^{19} is $-CH_2CH_2CN$.

In one aspect of the invention R^{19} is (1R)-2-hydroxy-1-methylethyl.

In one aspect of the invention R^{19} is (1S)-2-hydroxy-1-methylethyl.

In one aspect of the invention R^{19} is $-CH_2$(imidazol-2-yl).

In one aspect of the invention R^{19} is oxazolyl-2-yl.

In one aspect of the invention R^{19} is isoxazolyl-3-yl.

In one aspect of the invention R^{19} is 1-methylpyrazol-4-yl.

In one aspect of the invention R^{19} is 5-methylpyrazin-2-yl.

In one aspect of the invention R^{19} is thiazol-2-yl.

In one aspect of the invention R^{19} is 1,2,4-thiadiazol-5-yl.

R^{18} and R^{19}

In one aspect of the invention, R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention, R^{18} and R^{19} together with the nitrogen atom to which they are attached form a morpholine ring.

In one aspect of the invention, R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 3-hydroxypyrrolidin-1-yl group.

In one aspect of the invention there is provided a subset of compounds of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0, 1 or 2;

^{1}**Y** and **Y^{2}** are independently N or CR^{8} provided that one of ^{1}Y and Y^{2} is N and the other is CR^{8};

X is a linker group selected from -NR^{4}CR^{6}R^{7}-, -OCR^{6}R^{7}-, -SCR^{6}R^{7}-, -S(O)CR^{6}R^{7}-, -S(O)$_{2}$CR^{6}R^{7}-, -C(O)NR^{4}CR^{6}R^{7}-, -NR^{4}C(O)CR^{6}R^{7}-, -NR^{4}C(O)NR^{5}CR^{6}R^{7}- and -S(O)$_{2}$NR^{4}CR^{6}R^{7};

R^{1} is a group selected from C$_{1-6}$alkyl, carbocyclyl, carbocyclylC$_{1-6}$alkyl, heterocyclyl and heterocyclylC$_{1-6}$alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^{9}, -OR^{9}, -COR^{9}, -CONR^{9}R^{10}, -NR^{9}R^{10} and -NR^{9}COR^{10};
or **X-R^{1}** is –CR^{6}R^{7}OH;

R^{2} is a group selected from carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO$_{2}$R^{11}, -COR^{11}, -CO$_{2}$R^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12}, -NR^{11}COR^{12}, -NR^{11}COCONR^{12}R^{16}, -NR^{11}SO$_{2}$R^{12}, -NR^{17}CONR^{18}R^{19} and -NR^{17}CSNR^{18}R^{19};

each R^{3}, when present, is selected from cyano, R^{13}, and -CONR^{13}R^{14};

R^{4} and **R^{5}** are independently hydrogen or C$_{1-6}$alkyl;
or, when **X** is -NR^{4}CR^{6}R^{7}-, -NR^{4}C(O)CR^{6}R^{7}- or -NR^{4}C(O)NR^{5}CR^{6}R^{7}-, **R^{1}** and **R^{4}** together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, haloC$_{1-6}$alkyl, haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkylsulfonyl, C$_{1-6}$alkylsulfonylamino, C$_{1-6}$alkylsulfonyl(C$_{1-6}$alkyl)amino, sulfamoyl, C$_{1-6}$alkylsulfamoyl, bis(C$_{1-6}$alkyl)sulfamoyl, C$_{1-6}$alkanoylamino, C$_{1-6}$alkanoyl(C$_{1-6}$alkyl)amino, carbamoyl, C$_{1-6}$alkylcarbamoyl and bis(C$_{1-6}$alkyl)carbamoyl;

R^{6} and **R^{7}** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, haloC$_{1-6}$alkyl, haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkylsulfonyl, C$_{1-6}$alkylsulfonylamino, C$_{1-6}$alkylsulfonyl(C$_{1-6}$alkyl)amino,

sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, R^{12}, R^{17} and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{13} and **R^{14}** are independently hydrogen or a C_{1-3}alkyl which is optionally substituted by one or more substituent groups selected from halo, cyano, hydroxy and C_{1-3}alkoxy; and

R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino,

sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention there is provided a subset of compounds of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0, 1 or 2;

^{1}Y and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ and $-S(O)_2NR^4CR^6R^7-$;

R^1 is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$;

or **X-R^1** is $-CR^6R^7OH$;

R^2 is a group selected from carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is selected from C_{1-3}alkyl, hydroxyC_{1-3}alkyl, and $-CONR^{13}R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ or $-NR^4C(O)NR^5CR^6R^7-$, **R^1** and **R^4** together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N,

O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

$\mathbf{R^{13}}$ and $\mathbf{R^{14}}$ are independently hydrogen or a C_{1-3}alkyl; and

$\mathbf{R^{19}}$ is hydrogen, cyano or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl,

hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.In another aspect of the invention there is provided a subset of compounds of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0, 1 or 2;

^{1}Y and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ and $-S(O)_2NR^4CR^6R^7$;

R^1 is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$;

or **X-R^1** is $-CR^6R^7OH$;

R^2 is a group selected from carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is methyl or ethyl;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ or $-NR^4C(O)NR^5CR^6R^7-$, **R^1** and **R^4** together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}

$_{6}$alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{6} and **R**^{7} together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{8} is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^{9} and **R**^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, **R**^{12}, **R**^{17} and **R**^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention there is provided a subset of compounds of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0, 1 or 2;

$^{1}\mathbf{Y}$ and $\mathbf{Y^{2}}$ are independently N or CR^{8} provided that one of ^{1}Y and Y^{2} is N and the other is CR^{8};

X is a linker group selected from $-NR^{4}CR^{6}R^{7}-$, $-OCR^{6}R^{7}-$, $-SCR^{6}R^{7}-$, $-S(O)CR^{6}R^{7}-$, $-S(O)_{2}CR^{6}R^{7}-$, $-C(O)NR^{4}CR^{6}R^{7}-$, $-NR^{4}C(O)CR^{6}R^{7}-$, $-NR^{4}C(O)NR^{5}CR^{6}R^{7}-$ and $-S(O)_{2}NR^{4}CR^{6}R^{7}$;

$\mathbf{R^{1}}$ is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^{9}, $-OR^{9}$, $-COR^{9}$, $-CONR^{9}R^{10}$, $-NR^{9}R^{10}$ and $-NR^{9}COR^{10}$;

or $\mathbf{X\text{-}R^{1}}$ is $-CR^{6}R^{7}OH$;

$\mathbf{R^{2}}$ is a group selected from carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_{2}R^{11}$, $-COR^{11}$, $-CO_{2}R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_{2}R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each $\mathbf{R^{3}}$, when present, is methyl;

$\mathbf{R^{4}}$ and $\mathbf{R^{5}}$ are independently hydrogen or C_{1-6}alkyl;

or, when **X** is $-NR^{4}CR^{6}R^{7}-$, $-NR^{4}C(O)CR^{6}R^{7}-$ or $-NR^{4}C(O)NR^{5}CR^{6}R^{7}-$, $\mathbf{R^{1}}$ and $\mathbf{R^{4}}$ together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-}

$_{6}$alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{6} and **R^{7}** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{8} is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^{9} and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, R^{12}, R^{17} and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)

$_{6}$alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention there is provided a subset of compounds of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0, 1 or 2;

^{1}Y and **Y^{2}** are independently N or CR^{8} provided that one of ^{1}Y and Y^{2} is N and the other is CR^{8};

X is a linker group selected from -$NR^{4}CR^{6}R^{7}$-, -$OCR^{6}R^{7}$-, -$SCR^{6}R^{7}$-, -$S(O)CR^{6}R^{7}$-, -$S(O)_{2}CR^{6}R^{7}$-, -$C(O)NR^{4}CR^{6}R^{7}$-, -$NR^{4}C(O)CR^{6}R^{7}$-, -$NR^{4}C(O)NR^{5}CR^{6}R^{7}$- and -$S(O)_{2}NR^{4}CR^{6}R^{7}$;

R^{1} is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^{9}, -OR^{9}, -COR^{9}, -$CONR^{9}R^{10}$, -$NR^{9}R^{10}$ and -$NR^{9}COR^{10}$;

or **X-R^{1}** is –$CR^{6}R^{7}OH$;

R^{2} is a group selected from carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -$SO_{2}R^{11}$, -COR^{11}, -$CO_{2}R^{11}$, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, -$NR^{11}COR^{12}$, -$NR^{11}COCONR^{12}R^{16}$, -$NR^{11}SO_{2}R^{12}$, -$NR^{17}CONR^{18}R^{19}$ and -$NR^{17}CSNR^{18}R^{19}$;

each R^{3}, when present, is methyl;

R^{4} and **R^{5}** are independently hydrogen or C_{1-6}alkyl;

or, when **X** is -$NR^{4}CR^{6}R^{7}$-, -$NR^{4}C(O)CR^{6}R^{7}$- or -$NR^{4}C(O)NR^{5}CR^{6}R^{7}$-, **$R^{1}$** and **$R^{4}$** together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally

substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, R^{12}, R^{17} and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl,

(C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention there is provided a subset of compounds of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0, 1 or 2;

^1Y and **Y^2** are independently N or CR^8 provided that one of ^1Y and Y^2 is N and the other is CR^8;

X is a linker group selected from -$NR^4CR^6R^7$-, -OCR^6R^7-, -SCR^6R^7-, -$S(O)CR^6R^7$-, -$S(O)_2CR^6R^7$-, -$C(O)NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$-, -$NR^4C(O)NR^5CR^6R^7$- and -$S(O)_2NR^4CR^6R^7$;

R^1 is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} and -NR^9COR^{10};

or **X-R^1** is –CR^6R^7OH;

R^2 is a group selected from aryl and heteroaryl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, -$NR^{11}COR^{12}$, -$NR^{11}COCONR^{12}R^{16}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ and -$NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is methyl;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ or $-NR^4C(O)NR^5CR^6R^7-$, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

$\mathbf{R^{19}}$ is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more

substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention there is provided a subset of compounds of formula (I), or a pharmaceutically acceptable salt thereof;

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R^1 is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} and -NR^9COR^{10};

or **X-R^1** is –CR^6R^7OH;

R^2 is selected from aryl and heteroaryl which group is substituted by –$NR^{17}CONR^{18}R^{19}$ or –$NR^{17}CSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and –$NR^{11}COR^{12}$;

each R^3, when present, is methyl;

R^4 and R^5 are independently hydrogen or C_{1-6}alkyl;

or, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ or $-NR^4C(O)NR^5CR^6R^7-$, R^1 and R^4 together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention there is provided a subset of compounds of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0, 1 or 2;

^1Y and **Y^2** are independently N or CR^8 provided that one of ^1Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$ and $-S(O)_2CR^6R^7-$;

R^1 is a group selected from adamantyl, methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenethyl, pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thiadiazolyl, thiazolyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thiadiazolylmethyl, thiadiazolylethyl, thiazolylmethyl, thiazolylethyl, thienylmethyl, thienylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrimidinylethyl,

pyrazinylmethyl and pyrazinylethyl, which group is optionally substituted by 1, 2 or 3 substituent group selected from halo, cyano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} and –NR^9COR^{10};

or **X-R^1** is –$C(CH_3)_2OH$ or –CH_2OH;

R^2 is selected from 5 or 6 membered aryl and heteroaryl which group is substituted by -$NHCONR^{18}R^{19}$ or –$NHCSNR^{18}R^{19}$and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and –$NR^{11}COR^{12}$;

each R^3, when present, is methyl;

R^4 is hydrogen or C_{1-6}alkyl;

or, when **X** is -$NR^4CR^6R^7$-, **R^1** and **R^4** together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected

from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, **R^{12}** and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention there is provided a subset of compounds of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0, 1 or 2;

^1Y and **Y^2** are independently N or CR^8 provided that one of ^1Y and Y^2 is N and the other is CR^8;

X is a linker group selected from -$NR^4CR^6R^7$-, -OCR^6R^7-, -SCR^6R^7-, -$S(O)CR^6R^7$- and -$S(O)_2CR^6R^7$-;

$\mathbf{R^1}$ is a group selected from adamantyl, methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenethyl, pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thienylmethyl, thienylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrimidinylethyl, pyrazinylmethyl and pyrazinylethyl, which group is optionally substituted by 1, 2 or 3 substituent group selected from halo, cyano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} and –NR^9COR^{10};

or $\mathbf{X\text{-}R^1}$ is –$C(CH_3)_2OH$ or –CH_2OH;

$\mathbf{R^2}$ is selected from 5 or 6 membered aryl and heteroaryl which group is substituted by -$NHCONR^{18}R^{19}$ or –$NHCSNR^{18}R^{19}$and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and –$NR^{11}COR^{12}$;

each $\mathbf{R^3}$, when present, is methyl;

$\mathbf{R^4}$ is hydrogen or $C_{1\text{-}6}$alkyl;

or, when **X** is -$NR^4CR^6R^7$-, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkoxy, hydroxy$C_{1\text{-}6}$alkyl, hydroxy$C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$alkoxy$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy$C_{1\text{-}6}$alkoxy, amino, $C_{1\text{-}6}$alkylamino, bis($C_{1\text{-}6}$alkyl)amino, amino$C_{1\text{-}6}$alkyl, ($C_{1\text{-}6}$alkyl)amino$C_{1\text{-}6}$alkyl, bis($C_{1\text{-}6}$alkyl)amino$C_{1\text{-}6}$alkyl, cyano$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkylsulfonyl, $C_{1\text{-}6}$alkylsulfonylamino, $C_{1\text{-}6}$alkylsulfonyl($C_{1\text{-}6}$alkyl)amino, sulfamoyl, $C_{1\text{-}6}$alkylsulfamoyl, bis($C_{1\text{-}6}$alkyl)sulfamoyl, $C_{1\text{-}6}$alkanoylamino, $C_{1\text{-}6}$alkanoyl($C_{1\text{-}6}$alkyl)amino, carbamoyl, $C_{1\text{-}6}$alkylcarbamoyl and bis($C_{1\text{-}6}$alkyl)carbamoyl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkoxy, hydroxy$C_{1\text{-}6}$alkyl, hydroxy$C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$alkoxy$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy$C_{1\text{-}6}$alkoxy, amino, $C_{1\text{-}6}$alkylamino,

bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

$\mathbf{R^{19}}$ is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino,

sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0 or1;

^{1}Y is CH and **Y^2** is N;

X is a -$S(O)_2CR^6R^7$- linker group;

R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, imidazolyl, pyrrolidinyl, thiadiazolyl, thiazolyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -$NHCOCH_3$, -$CONH_2$ and -$CONHCH_3$;

or **–XR^1** is –$C(CH_3)_2OH$ or –CH_2OH;

R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is substituted by –$NHCONHR^{19}$ or -$NHCSNHR^{19}$and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and -$NR^{11}COR^{12}$;

R^3, when present, is methyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12} and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy,

hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0 or1;

^{1}Y is CH and **Y^2** is N;

X is a -$S(O)_2CR^6R^7$- linker group;

R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -$NHCOCH_3$, -$CONH_2$ and –$CONHCH_3$;

or **–XR^1** is –$C(CH_3)_2OH$ or –CH_2OH;

R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is substituted by –$NHCONHR^{19}$ or -$NHCSNHR^{19}$and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and -$NR^{11}COR^{12}$;

R^3, when present, is methyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-}

$_{6}$alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12} and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0, 1 or 2;

X is a -$S(O)_2CR^6R^7$- linker group selected;

^1Y is CH and **Y^2** is N.

R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, imidazolyl, pyrrolidinyl, thiadiazolyl, thiazolyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -$NHCOCH_3$, -$CONH_2$ and -$CONHCH_3$;

R^2 is phenyl or pyridinyl substituted by –NHCONHR^{19} or –NHCSNHR^{19}and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$;

R^3, when present, is methyl or ethyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl; and

R^{19} is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, dioxothiolanyl, imidazoylmethyl, isoxazolyl, oxazolyl, oxetanyl, pyrazinyl, pyrazolyl, pyrazolylmethyl, pyridinyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, thiazolyl and triazolyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

m is 1;

X is a -$S(O)_2CR^6R^7$- linker group selected;

^1Y is CH and **Y^2** is N.

R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, imidazolyl, pyrrolidinyl, thiadiazolyl, thiazolyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl,

thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -$NHCOCH_3$, -$CONH_2$ and -$CONHCH_3$;

R^2 is phenyl or pyridinyl substituted by –$NHCONHR^{19}$ or –$NHCSNHR^{19}$and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$;

R^3 is methyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl; and

R^{19} is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, dioxothiolanyl, imidazoylmethyl, isoxazolyl, oxazolyl, oxetanyl, pyrazinyl, pyrazolyl, pyrazolylmethyl, pyridinyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, thiazolyl and triazolyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

m is 1;

X is a -$S(O)_2CR^6R^7$- linker group selected;

^1Y is CH and **Y^2** is N.

R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, $-NHCOCH_3$, $-CONH_2$ and $-CONHCH_3$;

R^2 is phenyl or pyridinyl substituted by $-NHCONHR^{19}$ or $-NHCSNHR^{19}$and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, $-CONH_2$, $-CONHCH_3$ and $-CON(CH_3)_2$;

R^3 is methyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl; and

R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, imidazoylmethyl, isoxazolyl, pyrazolyl, pyrazolylmethyl, pyridinyl and pyrimidinyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

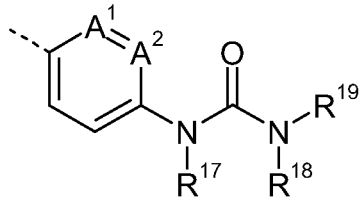
m is 1;

X is a $-S(O)_2CR^6R^7-$ linker group;

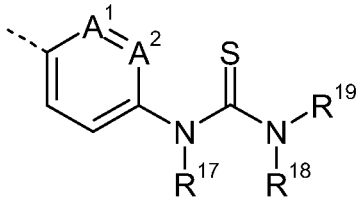
^{1}**Y** is CH and **Y**^{2} is N.

R^{1} is a group selected from methyl, isopropyl, cyclopropyl, cyclohexyl, -CH_2CH_2OH, -$CH_2CH_2NHC(O)CH_3$, phenyl, 4-fluorophenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-methylphenyl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, 2-oxopyrolidin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, and 3-methyl-1,3,4-thiadiazol-2-yl;

R^{2} is



or



wherein **A**^{1} and **A**^{2} are selected from CH or N provided that at least one of A^1 or A^2 is CH;

R^{17} is hydrogen;

R^{18} is hydrogen;

R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, 4-methylphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-flurophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, -CH_2(imidazol-2-yl), -CH_2(imidazol-3-yl), isoxazolyl-3-yl, 6-oxo-1H-pryrdin-2-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, -CH_2(1-methylpyrazol-4-yl), -CH_2(1-methylpyrazol-4-yl), 6-methoxypryridin-3-yl, 5-fluoropyridin-2-yl, pyrimidin-2-yl, and 1H-pyrazol-3-yl;

R^{3} is methyl; and

R^{6} and **R**^{7} together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl,

cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

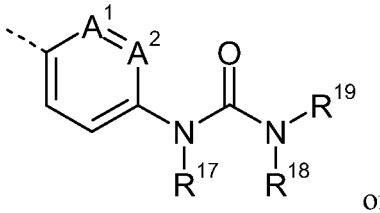
m is 0, 1 or 2;

X is a $-S(O)_2CR^6R^7-$ linker group;

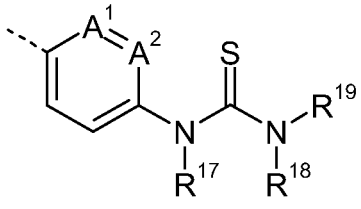
^{1}**Y** is CH and $\mathbf{Y^2}$ is N.

$\mathbf{R^1}$ is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2CH_2NHMe$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-fluoro-4-methylaminophenyl, 4-fluoro-2-methylphenyl, 5-fluoro-2-methylphenyl, 3-fluoro-4-(2-hydroxyethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-carbamoyl-2-chlorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-4-methylaminophenyl, 3-chloro-4-ethylaminophenyl, 3-chloro-4-(2-fluoroethylamino)phenyl, 3-chloro-4-(2-hydroxyethylamino)phenyl, 2-chloro-4-cyanophenyl, 4-cyanophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-(trifluoromethyl)phenyl, 2-methylphenyl, 4-methylphenyl, 4-(2-hydroxyethylamino)phenyl, 1H-imidazol-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 1-(difluoromethyl)pyrazol-4-yl, 1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl, 1,3-dimethylpyrazol-4-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, 5-fluoropyridin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2,4-dimethylthiazol-5-yl, 5-methyl-1,3,4-thiadiazol-2-yl, terahydrofuran-3-yl and terahydropyran-4-yl;

$\mathbf{R^2}$ is



or



wherein $\mathbf{A^1}$ and $\mathbf{A^2}$ are selected from CH or N provided that at least one of A^1 or A^2 is CH;

$\mathbf{R^{17}}$ is hydrogen;

R^{18} is hydrogen;

R^{19} is is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, i-butyl, t-butyl, cyclopropyl, cyclobutyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, $-CH_2CO_2H$, 1-(methyl)cyclopropyl, $-CH_2$(1-hydroxycyclopropyl), 1-(hydroxymethyl)cyclopropyl, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, $-CH_2CH_2$(pyrrolidin-1-yl),$-CH_2$(imidazol-2-yl), 1-methylimidazol-4-yl, oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 1,1-dioxothiolan-3-yl, 5-methylisoxazol-3-yl, $-CH_2$(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, $-CH_2$(1-methylpyrazol-4-yl), 5-methylpyrazin-2-yl, $-CH_2$(2H-1,2,4-triazol-3-yl), 6-methoxypryridin-3-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl and 1-methylpyrazol-3-yl;

R^3, when present, is methyl or ethyl; and

R^6 and R^7 together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

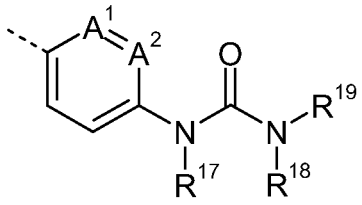
m is 1;

X is a $-S(O)_2CR^6R^7-$ linker group;

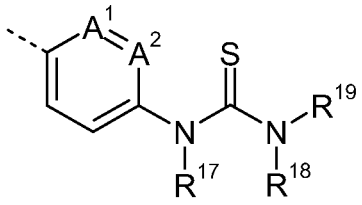
^{1}**Y** is CH and **Y**^{2} is N.

R^{1} is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2OCH_3$, -$CH_2CH_2NHC(O)CH_3$, -$CH_2C(O)NH_2$, -$CH_2C(O)NHMe$, phenyl, 4-fluorophenyl, 4-chlorophenyl, 3,5-difluorophenyl, 2-(trifluoromethyl)phenyl, 4-(2-hydroxyethylamino)phenyl, 1H-imidazol-2-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, 5-fluoropyridin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl and 5-methyl-1,3,4-thiadiazol-2-yl;

R^{2} is



or



wherein **A**^{1} and **A**^{2} are selected from CH or N provided that at least one of A^1 or A^2 is CH;

R^{17} is hydrogen;

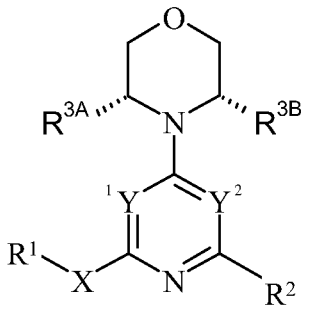
R^{18} is hydrogen;

R^{19} is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, i-butyl, t-butyl, cyclopropyl, cyclobutyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -$CH_2C(CH_3)_2OH$, -$CH_2C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CHF_2, -$CH_2CH_2SO_2Me$, -$CH_2CH(OH)CF_3$, -CH_2CH_2CN, -CH_2CN, -CH_2CONMe_2, 1-(methyl)cyclopropyl, 1-(hydroxymethyl)cyclopropyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, -CH_2CH_2(pyrrolidin-1-yl),-CH_2(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 1,1-dioxothiolan-3-yl, 5-methylisoxazol-3-yl, -CH_2(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, -CH_2(2H-1,2,4-triazol-3-yl), 6-methoxypryridin-3-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl, and 1-methylpyrazol-3-yl;

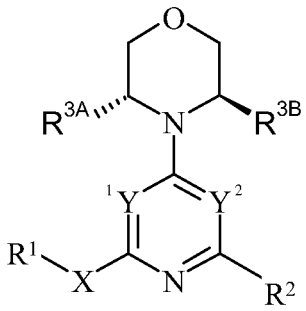
R^{3} is methyl; and

R^6 and **R**^{7} together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

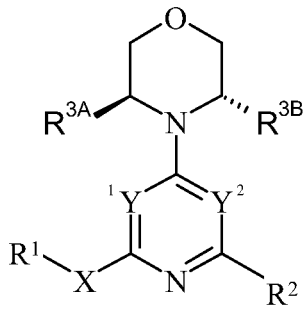
In one aspect of the invention there is provided a subset of compounds of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

or a pharmaceutically acceptable salt thereof;

^{1}Y and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7- and -S(O)$_2$NR^{4}CR^{6}R^7;

R^1 is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, -OR^9, -COR^9, -CONR^{9}R^{10}, -NR^{9}R^{10} and -NR^{9}COR^{10};

or **X-R^1** is –C(CH$_3$)$_2$OH or –CH$_2$OH;

R^2 is selected from aryl and heteroaryl which group is substituted by –NR^{17}CONR^{18}R^{19} or -NR^{17}CSNR^{18}R^{19}and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12} and –NR^{11}COR^{12};

$\mathbf{R^4}$ and $\mathbf{R^5}$ are independently hydrogen or C_{1-6}alkyl

or, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ or $-NR^4C(O)NR^5CR^6R^7-$, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

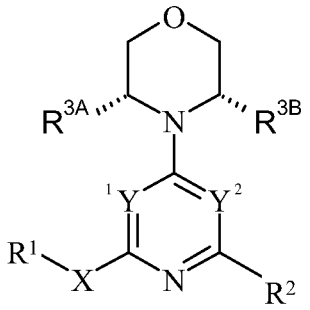
$\mathbf{R^{19}}$ is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl; and

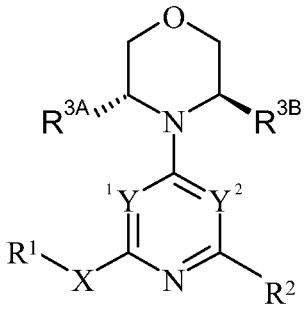
when $\mathbf{R^{3A}}$ is hydrogen, $\mathbf{R^{3B}}$ is hydrogen, methyl, ethyl, hydroxymethyl, dimethylcarbamoyl or carbamoyl; or

when $\mathbf{R^{3A}}$ is methyl, $\mathbf{R^{3B}}$ is methyl..

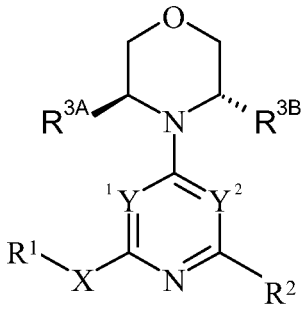
In one aspect of the invention there is provided a subset of compounds of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

or a pharmaceutically acceptable salt thereof;

^{1}**Y** and **Y^{2}** are independently N or CR^{8} provided that one of ^{1}Y and Y^{2} is N and the other is CR^{8};

X is a linker group selected from -NR^{4}CR^{6}R^{7}-, -OCR^{6}R^{7}-, -SCR^{6}R^{7}-, -S(O)CR^{6}R^{7}-, -S(O)$_{2}$CR^{6}R^{7}-, -C(O)NR^{4}CR^{6}R^{7}-, -NR^{4}C(O)CR^{6}R^{7}-, -NR^{4}C(O)NR^{5}CR^{6}R^{7}- and -S(O)$_{2}$NR^{4}CR^{6}R^{7};

R^{1} is a group selected from C$_{1-6}$alkyl, carbocyclyl, carbocyclylC$_{1-6}$alkyl, heterocyclyl and heterocyclylC$_{1-6}$alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^{9}, -OR^{9}, -COR^{9}, -CONR^{9}R^{10}, -NR^{9}R^{10} and -NR^{9}COR^{10};

or **X-R^{1}** is –C(CH$_{3}$)$_{2}$OH or –CH$_{2}$OH;

R^{2} is selected from aryl and heteroaryl which group is substituted by –NR^{17}CONR^{18}R^{19} or -NR^{17}CSNR^{18}R^{19}and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12} and –NR^{11}COR^{12};

R^{3A} and **R^{3B}** independently is hydrogen, methyl or ethyl;

R^{4} and **R^{5}** are independently hydrogen or C$_{1-6}$alkyl

or, when **X** is -NR^{4}CR^{6}R^{7}-, -NR^{4}C(O)CR^{6}R^{7}- or -NR^{4}C(O)NR^{5}CR^{6}R^{7}-, **R^{1}** and **R^{4}** together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, haloC$_{1-6}$alkyl, haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkylsulfonyl, C$_{1-6}$alkylsulfonylamino, C$_{1-6}$alkylsulfonyl(C$_{1-6}$alkyl)amino, sulfamoyl, C$_{1-6}$alkylsulfamoyl, bis(C$_{1-6}$alkyl)sulfamoyl, C$_{1-6}$alkanoylamino, C$_{1-6}$alkanoyl(C$_{1-6}$alkyl)amino, carbamoyl, C$_{1-6}$alkylcarbamoyl and bis(C$_{1-6}$alkyl)carbamoyl;

R^{6} and **R^{7}** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, haloC$_{1-6}$alkyl, haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkylsulfonyl, C$_{1-6}$alkylsulfonylamino, C$_{1-6}$alkylsulfonyl(C$_{1-6}$alkyl)amino,

sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

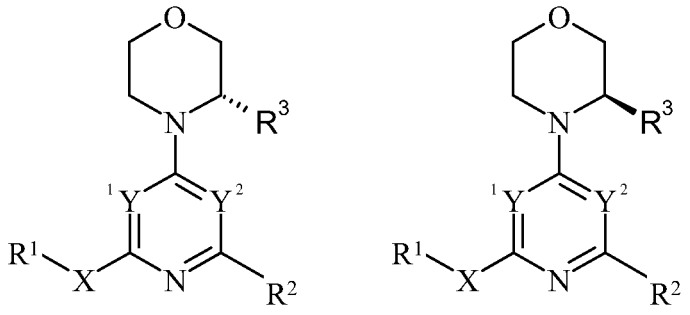
$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

$\mathbf{R^{19}}$ is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention there is provided a subset of compounds of formula (Ia) or (Ib)



(Ia) (Ib)

or a pharmaceutically acceptable salt thereof;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7- and -S(O)$_2$NR^{4}CR^{6}R^7;

R^1 is a group selected from C$_{1-6}$alkyl, carbocyclyl, carbocyclylC$_{1-6}$alkyl, heterocyclyl and heterocyclylC$_{1-6}$alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, -OR^9, -COR^9, -CONR^{9}R^{10}, -NR^{9}R^{10} and -NR^{9}COR^{10};

or **X-R^1** is –C(CH$_3$)$_2$OH or –CH$_2$OH;

R^2 is selected from aryl and heteroaryl which group is substituted by –NR^{17}CONR^{18}R^{19} or -NR^{17}CSNR^{18}R^{19}and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12} and –NR^{11}COR^{12};

R^3 is hydrogen, methyl or ethyl;

R^4 and **R^5** are independently hydrogen or C$_{1-6}$alkyl

or, when **X** is -NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7- or -NR^{4}C(O)NR^{5}CR^{6}R^7-, **R^1** and **R^4** together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, haloC$_{1-6}$alkyl, haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-}$

$_{6}$alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{6} and **R**^{7} together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{8} is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

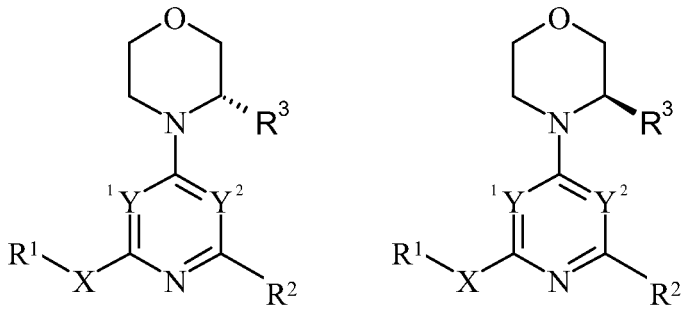
R^{9} and **R**^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, **R**^{12}, **R**^{17} and **R**^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention there is provided a subset of compounds of formula (Ia) or (Ib)



(Ia) (Ib)

or a pharmaceutically acceptable salt thereof;

$\mathbf{^1Y}$ and $\mathbf{Y^2}$ are independently N or CR^8 provided that one of ^1Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ and $-S(O)_2NR^4CR^6R^7$;

$\mathbf{R^1}$ is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$;

or $\mathbf{X\text{-}R^1}$ is $-C(CH_3)_2OH$ or $-CH_2OH$;

$\mathbf{R^2}$ is selected from aryl and heteroaryl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ or $-NR^{17}CSNR^{18}R^{19}$and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$;

$\mathbf{R^3}$ is methyl;

$\mathbf{R^4}$ and $\mathbf{R^5}$ are independently hydrogen or C_{1-6}alkyl

or, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ or $-NR^4C(O)NR^5CR^6R^7-$, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

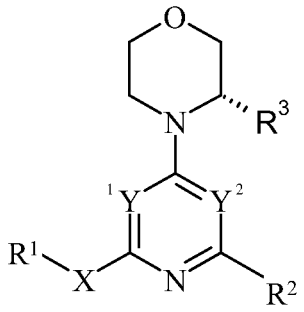
$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

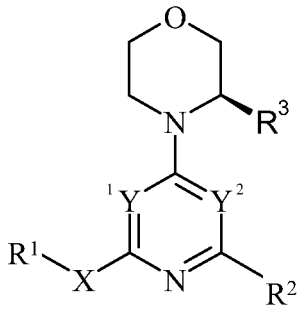
R[19] is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R**[18] and **R**[19] together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention there is provided a subset of compounds of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

^{1}Y and **Y**[2] are independently N or CR[8] provided that one of ^{1}Y and Y[2] is N and the other is CR[8];

X is a linker group selected from -NR[4]CR[6]R[7]-, -OCR[6]R[7]-, -SCR[6]R[7]-, -S(O)CR[6]R[7]- and -S(O)$_2$CR[6]R[7]-;

R[1] is a group selected from adamantyl, methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenethyl, pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thiadiazolyl, thiazolyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thiadiazolylmethyl, thiadiazolylethyl, thiazolylmethyl, thiazolylethyl, thienylmethyl, thienylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrimidinylethyl, pyrazinylmethyl and pyrazinylethyl, which group is optionally substituted by 1, 2 or 3 substituent group selected from halo, cyano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} and –NR^9COR^{10};

or **X-R**[1] is –$C(CH_3)_2OH$ or –CH_2OH;

R[2] is selected from 5 or 6 membered aryl and heteroaryl which group is substituted by -$NHCONR^{18}R^{19}$ or -$NHCSNR^{18}R^{19}$and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and –$NR^{11}COR^{12}$;

R[3] is methyl;

R[4] is hydrogen or C_{1-6}alkyl;

or, when **X** is -$NR^4CR^6R^7$-, **R**[1] and **R**[4] together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R[6] and **R**[7] together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino,

bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

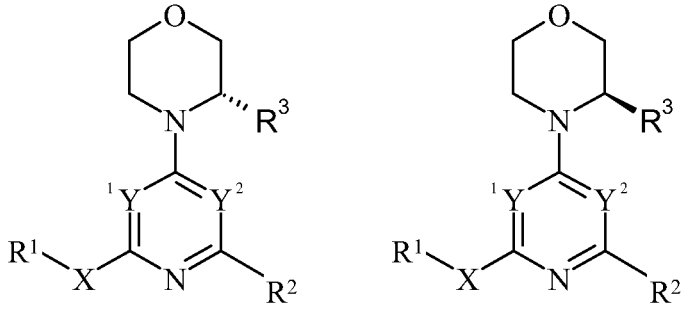
R^{11}, R^{12} and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino,

sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention there is provided a subset of compounds of formula (Ia) or (Ib)



(Ia) (Ib)

or a pharmaceutically acceptable salt thereof;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$ and $-S(O)_2CR^6R^7-$;

R^1 is a group selected from adamantyl, methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenethyl, pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thienylmethyl, thienylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrimidinylethyl, pyrazinylmethyl and pyrazinylethyl, which group is optionally substituted by 1, 2 or 3 substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$;

or **X-R**^{1} is $-C(CH_3)_2OH$ or $-CH_2OH$;

R^2 is selected from 5 or 6 membered aryl and heteroaryl which group is substituted by $-NHCONR^{18}R^{19}$ or $-NHCSNR^{18}R^{19}$and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$;

R^3 is methyl;

R^4 is hydrogen or C_{1-6}alkyl;

or, when **X** is -$NR^4CR^6R^7$-, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

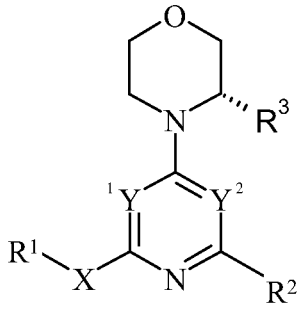
$\mathbf{R^{11}}$, $\mathbf{R^{12}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

$\mathbf{R^{19}}$ is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more

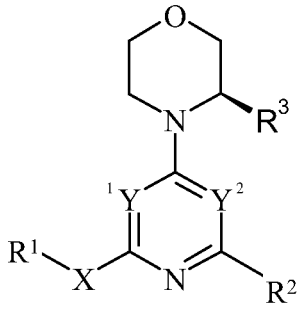
substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R**^{18} and **R**^{19} together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another particular class of compound of formula (Ia) or (Ib),



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

^{1}Y is CH and **Y^2** is N;

X is a -S(O)$_2$CR^{6}R^7- linker group;

R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, imidazolyl, pyrrolidinyl, thiadiazolyl, thiazolyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2

substituent group selected from amino, halo, cyano, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -$NHCOCH_3$, -$CONH_2$ and -$CONHCH_3$;

or $-XR^1$ is $-C(CH_3)_2OH$ or $-CH_2OH$;

R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is substituted by $-NHCONHR^{19}$ or $-NR^{17}CSNR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$;

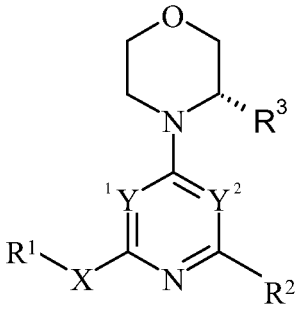
R^3 is methyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

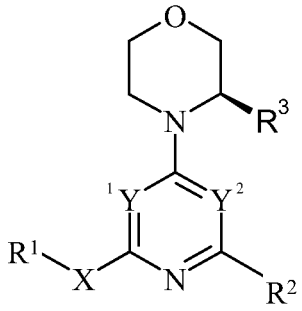
R^{11}, R^{12} and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another particular class of compound of formula (Ia) or (Ib),



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

^{1}**Y** is CH and **Y**^{2} is N;

X is a -S(O)$_2$CR^{6}R^7- linker group;

R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -NHCOCH$_3$, -CONH$_2$ and –CONHCH$_3$;

or –XR^1 is –C(CH$_3$)$_2$OH or –CH$_2$OH;

R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is substituted by –NHCONHR^{19} or -NR^{17}CSNR^{18}R^{19} and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12} and –NR^{11}COR^{12};

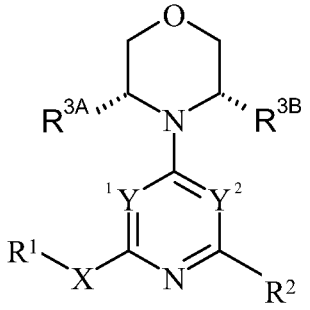
R^3 is methyl;

R^6 and **R**^{7} together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, haloC$_{1-6}$alkyl, haloC$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkoxy, amino, C$_{1-6}$alkylamino, bis(C$_{1-6}$alkyl)amino, aminoC$_{1-6}$alkyl, (C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, bis(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkylsulfonyl, C$_{1-6}$alkylsulfonylamino, C$_{1-6}$alkylsulfonyl(C$_{1-6}$alkyl)amino, sulfamoyl, C$_{1-6}$alkylsulfamoyl, bis(C$_{1-6}$alkyl)sulfamoyl, C$_{1-6}$alkanoylamino, C$_{1-6}$alkanoyl(C$_{1-6}$alkyl)amino, carbamoyl, C$_{1-6}$alkylcarbamoyl and bis(C$_{1-6}$alkyl)carbamoyl;

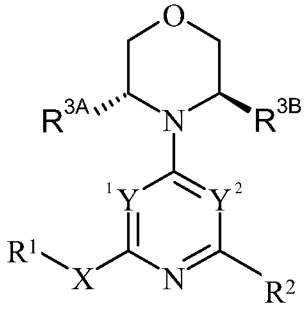
R^{11}, R^{12} and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

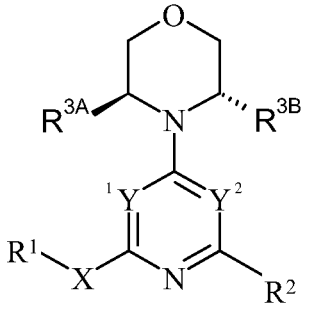
In a further particular class of compound of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

or a pharmaceutically acceptable salt thereof;

X is a $-S(O)_2CR^6R^7-$ linker group;

^1Y is CH and **Y^2** is N.

R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, imidazolyl, pyrrolidinyl, thiadiazolyl, thiazolyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, $-NHCOCH_3$, $-CONH_2$ and $-CONHCH_3$;

$\mathbf{R^2}$ is phenyl or pyridinyl substituted by –NHCONHR^{19} or -NHCSNHR^{19} and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$;

$\mathbf{R^{3A}}$ and $\mathbf{R^{3B}}$ each independently is hydrogen, methyl or ethyl;

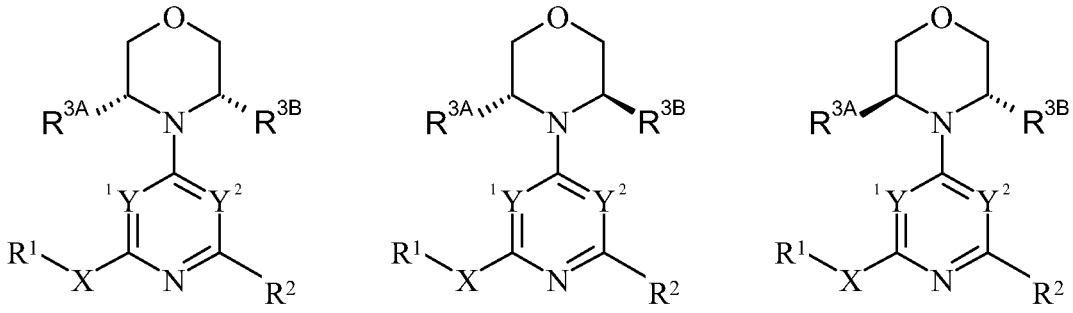
$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^{19}}$ is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, dioxothiolanyl, imidazoylmethyl, isoxazolyl, oxazolyl, oxetanyl, pyrazinyl, pyrazolyl, pyrazolylmethyl, pyridinyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, thiazolyl and triazolyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl; and

when $\mathbf{R^{3A}}$ is hydrogen, $\mathbf{R^{3B}}$ is hydrogen, methyl, ethyl, hydroxymethyl, dimethylcarbamoyl or carbamoyl; or

when $\mathbf{R^{3A}}$ is methyl, $\mathbf{R^{3B}}$ is methyl.

In a further particular class of compound of formula (Ia) or (Ib)



(IA) (IB) (IC)

or a pharmaceutically acceptable salt thereof;

X is a $-S(O)_2CR^6R^7-$ linker group;

^{1}**Y** is CH and **Y**^{2} is N.

R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, imidazolyl, pyrrolidinyl, thiadiazolyl, thiazolyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, $-NHCOCH_3$, $-CONH_2$ and $-CONHCH_3$;

R^2 is phenyl or pyridinyl substituted by $-NHCONHR^{19}$ or $-NHCSNHR^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, $-CONH_2$, $-CONHCH_3$ and $-CON(CH_3)_2$;

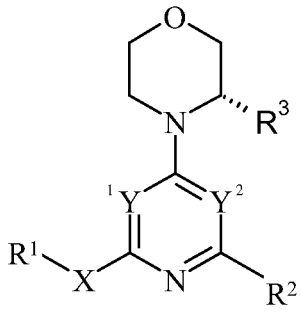
R^{3A} and **R**^{3B} each independently is hydrogen, methyl or ethyl;

R^6 and **R**^{7} together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl; and

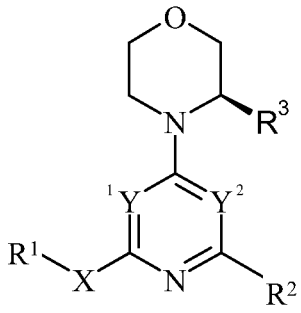
R^{19} is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, dioxothiolanyl, imidazoylmethyl, isoxazolyl, oxazolyl, oxetanyl, pyrazinyl, pyrazolyl,

pyrazolylmethyl, pyridinyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, thiazolyl and triazolyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

X is a $-S(O)_2CR^6R^7-$ linker group;

^{1}Y is CH and **Y^2** is N.

R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, imidazolyl, pyrrolidinyl, thiadiazolyl, thiazolyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, $-NHCOCH_3$, $-CONH_2$ and $-CONHCH_3$;

R^2 is phenyl or pyridinyl substituted by $-NHCONHR^{19}$ or $-NHCSNHR^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, $-CONH_2$, $-CONHCH_3$ and $-CON(CH_3)_2$;

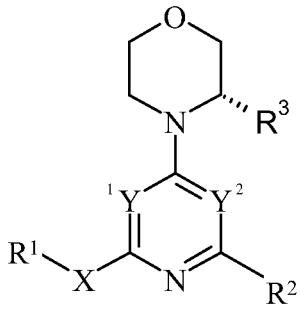
R^3 is methyl;

R^6 and **R^7** together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from

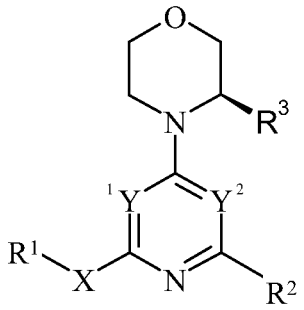
halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl; and

$\mathbf{R^{19}}$ is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, dioxothiolanyl, imidazoylmethyl, isoxazolyl, oxazolyl, oxetanyl, pyrazinyl, pyrazolyl, pyrazolylmethyl, pyridinyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, thiazolyl and triazolyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

X is a $-S(O)_2CR^6R^7-$ linker group;

^{1}**Y** is CH and $\mathbf{Y^2}$ is N.

$\mathbf{R^1}$ is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is

optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -$NHCOCH_3$, -$CONH_2$ and -$CONHCH_3$;

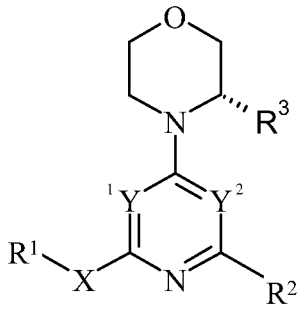
$\mathbf{R^2}$ is phenyl or pyridinyl substituted by –$NHCONHR^{19}$ or -$NHCSNHR^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$;

$\mathbf{R^3}$ is methyl;

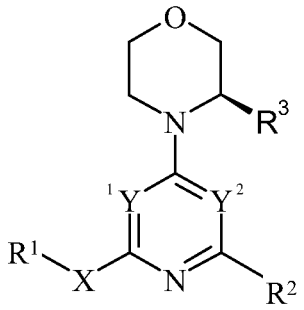
$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl; and

$\mathbf{R^{19}}$ is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, imidazoylmethyl, isoxazolyl, pyrazolyl, pyrazolylmethyl, pyridinyl and pyrimidinyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

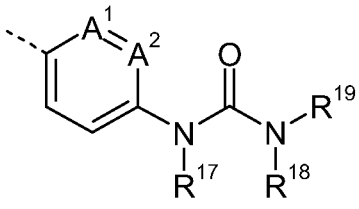
m is 1;

X is a $-S(O)_2CR^6R^7-$ linker group;

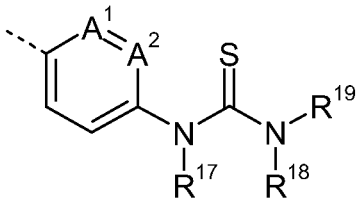
^{1}**Y** is CH and **Y^2** is N.

R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, phenyl, 4-fluorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3,5-difluorophenyl, 2-(trifluoromethyl)phenyl, 4-(2-hydroxyethylamino)phenyl, 2-methoxyphenyl, 2-methylphenyl, 1H-imidazol-2-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, 5-fluoropyridin-3-yl, 2-oxopyrolidin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl and 3-methyl-1,3,4-thiadiazol-2-yl;

R^2 is



or



wherein **A^1** and **A^2** are selected from CH or N provided that at least one of A^1 or A^2 is CH;

R^{17} is hydrogen;

R^{18} is hydrogen; and

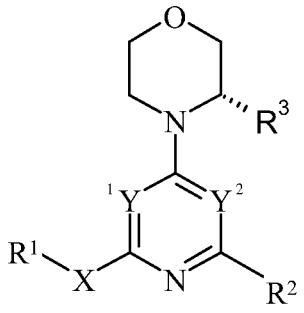
R^{19} is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$,

$-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, 1-(methyl)cyclopropyl, 1-(hydroxymethyl)cyclopropyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, $-CH_2CH_2$(pyrrolidin-1-yl),$-CH_2$(imidazol-2-yl), $-CH_2$(imidazol-3-yl), oxazolyl-2-yl, isoxazolyl-3-yl, 6-oxo-1H-pryrdin-2-yl, oxetan-3-yl, 1,1-dioxothiolan-3-yl, 5-methylisoxazol-3-yl, $-CH_2$(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, $-CH_2$(1-methylpyrazol-4-yl), 5-methylpyrazin-2-yl, $-CH_2$(2H-1,2,4-triazol-3-yl), 6-methoxypryridin-3-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, pyrimidin-2-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1-methylpyrazol-3-yl and 1H-pyrazol-3-yl;

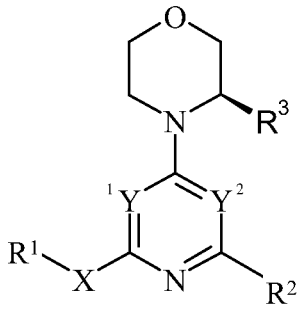
R^3 is methyl; and

R^6 and **R**^{7} together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

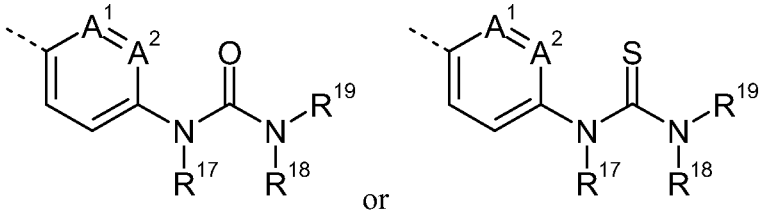
m is 1;

X is a -$S(O)_2CR^6R^7$- linker group;

^{1}**Y** is CH and **Y**^{2} is N.

R^1 is a group selected from methyl, isopropyl, cyclopropyl, cyclohexyl, -CH_2CH_2OH, -$CH_2CH_2NHC(O)CH_3$, phenyl, 4-fluorophenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-methylphenyl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, 2-oxopyrolidin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, and 3-methyl-1,3,4-thiadiazol-2-yl;

R^2 is



or

wherein **A**^{1} and **A**^{2} are selected from CH or N provided that at least one of A^1 or A^2 is CH;

R^{17} is hydrogen;

R^{18} is hydrogen; and

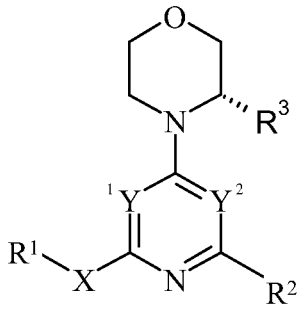
R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, 4-methylphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-flurophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, -CH_2(imidazol-2-yl), -CH_2(imidazol-3-yl), isoxazolyl-3-yl, 6-oxo-1H-pryrdin-2-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, -CH_2(1-methylpyrazol-4-yl), -CH_2(1-methylpyrazol-4-yl), 6-methoxypryridin-3-yl, 5-fluoropyridin-2-yl, pyrimidin-2-yl, and 1H-pyrazol-3-yl;

R^3 is methyl; and

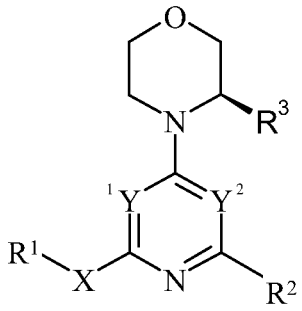
R^6 and **R**^{7} together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{-6}alkoxy, amino, C_{1-6}alkylamino,

bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

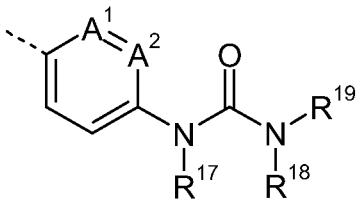
m is 1;

X is a $-S(O)_2CR^6R^7-$ linker group;

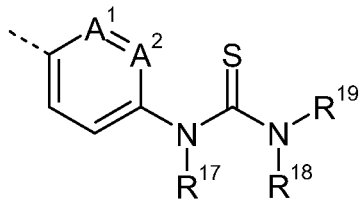
^{1}**Y** is CH and **Y^2** is N.

R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, phenyl, 4-fluorophenyl, 4-chlorophenyl, 3,5-difluorophenyl, 2-(trifluoromethyl)phenyl, 4-(2-hydroxyethylamino)phenyl, 1H-imidazol-2-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, 5-fluoropyridin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl and 5-methyl-1,3,4-thiadiazol-2-yl;

R^2 is



or



wherein **A^1** and **A^2** are selected from CH or N provided that at least one of A^1 or A^2 is CH;

R^{17} is hydrogen;

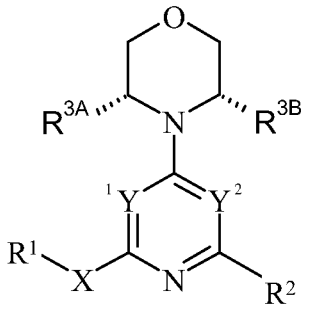
R^{18} is hydrogen; and

$\mathbf{R^{19}}$ is is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, i-butyl, t-butyl, cyclopropyl, cyclobutyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, 1-(methyl)cyclopropyl, 1-(hydroxymethyl)cyclopropyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, $-CH_2CH_2$(pyrrolidin-1-yl),$-CH_2$(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 1,1-dioxothiolan-3-yl, 5-methylisoxazol-3-yl, $-CH_2$(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, $-CH_2$(2H-1,2,4-triazol-3-yl), 6-methoxypryridin-3-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl, and 1-methylpyrazol-3-yl;

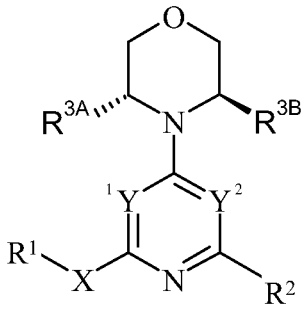
$\mathbf{R^3}$ is methyl; and

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring.

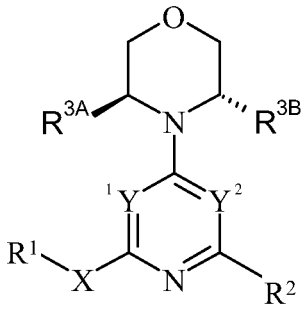
In a further particular class of compound of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

or a pharmaceutically acceptable salt thereof;

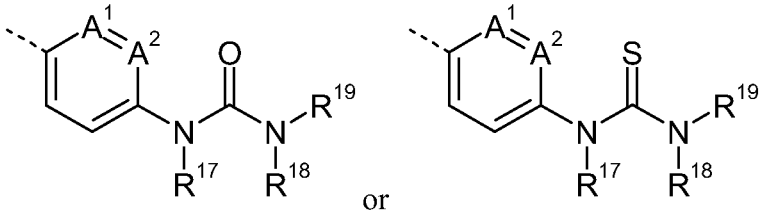
X is a $-S(O)_2CR^6R^7-$ linker group;

$^1\mathbf{Y}$ is CH and $\mathbf{Y^2}$ is N;

$\mathbf{R^1}$ is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2CH_2NHMe$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-fluoro-4-methylaminophenyl,

4-fluoro-2-methylphenyl, 5-fluoro-2-methylphenyl, 3-fluoro-4-(2-hydroxyethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-carbamoyl-2-chlorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-4-methylaminophenyl, 3-chloro-4-ethylaminophenyl, 3-chloro-4-(2-fluoroethylamino)phenyl, 3-chloro-4-(2-hydroxyethylamino)phenyl, 2-chloro-4-cyanophenyl, 4-cyanophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-(trifluoromethyl)phenyl, 2-methylphenyl, 4-methylphenyl, 4-(2-hydroxyethylamino)phenyl, 1H-imidazol-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 1-(difluoromethyl)pyrazol-4-yl, 1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl, 1,3-dimethylpyrazol-4-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, 5-fluoropyridin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2,4-dimethylthiazol-5-yl, 5-methyl-1,3,4-thiadiazol-2-yl, terahydrofuran-3-yl and terahydropyran-4-yl;

R² is



or

wherein **A¹** and **A²** are selected from CH or N provided that at least one of A^1 or A^2 is CH;

R¹⁷ is hydrogen;

R¹⁸ is hydrogen; and

R¹⁹ is is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, i-butyl, t-butyl, cyclopropyl, cyclobutyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, $-CH_2CO_2H$, 1-(methyl)cyclopropyl, $-CH_2$(1-hydroxycyclopropyl), 1-(hydroxymethyl)cyclopropyl, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, $-CH_2CH_2$(pyrrolidin-1-yl),$-CH_2$(imidazol-2-yl),

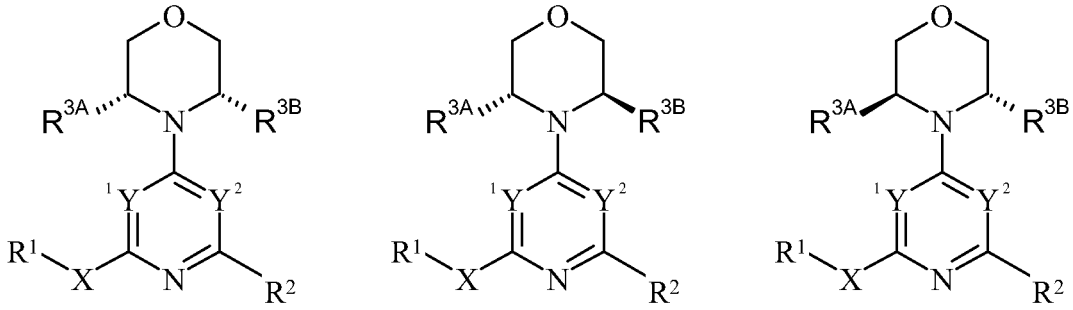
1-methylimidazol-4-yl, oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 1,1-dioxothiolan-3-yl, 5-methylisoxazol-3-yl, -CH_2(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, -CH_2(1-methylpyrazol-4-yl), 5-methylpyrazin-2-yl, -CH_2(2H-1,2,4-triazol-3-yl), 6-methoxypryridin-3-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl and 1-methylpyrazol-3-yl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

when $\mathbf{R^{3A}}$ is hydrogen, $\mathbf{R^{3B}}$ is hydrogen, methyl, ethyl, hydroxymethyl, dimethylcarbamoyl or carbamoyl; or

when $\mathbf{R^{3A}}$ is methyl, $\mathbf{R^{3B}}$ is methyl.

In a further particular class of compound of formula (IA), (IB) or (IC)



(IA) (IB) (IC)

or a pharmaceutically acceptable salt thereof;

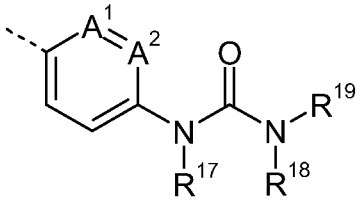
X is a -$S(O)_2CR^6R^7$- linker group;

^{1}**Y** is CH and $\mathbf{Y^2}$ is N;

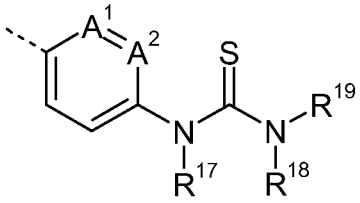
$\mathbf{R^1}$ is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2C(OH)(CH_3)_2$, -$CH_2CH_2CH_2OCHF_2$, -$CH_2CH_2OCH_3$, -$CH_2CH_2NHC(O)CH_3$, -CH_2CH_2NHMe, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-fluoro-4-methylaminophenyl, 4-fluoro-2-methylphenyl, 5-fluoro-2-methylphenyl, 3-fluoro-4-(2-hydroxyethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-carbamoyl-2-chlorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-4-methylaminophenyl, 3-chloro-4-ethylaminophenyl, 3-chloro-4-(2-fluoroethylamino)phenyl, 3-chloro-4-(2-hydroxyethylamino)phenyl, 2-chloro-4-cyanophenyl, 4-cyanophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-methylphenyl, 4-methylphenyl,

1H-imidazol-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 1-(difluoromethyl)pyrazol-4-yl, 1,3-dimethylpyrazol-4-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2,4-dimethylthiazol-5-yl and 5-methyl-1,3,4-thiadiazol-2-yl;

R^2 is



or



wherein **A^1** and **A^2** are selected from CH or N provided that at least one of A^1 or A^2 is CH;

R^{17} is hydrogen;

R^{18} is hydrogen; and

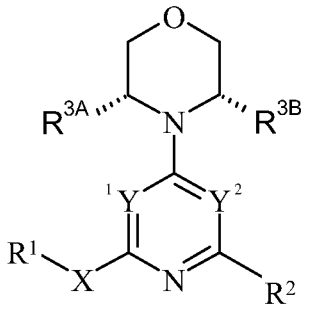
R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, cyclopropyl, cyclobutyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CH_2Cl, -CH_2CH_2CN, -CH_2(1-hydroxycyclopropyl), 1-(hydroxymethyl)cyclopropyl, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, -CH_2CH_2(pyrrolidin-1-yl),-CH_2(imidazol-2-yl), 1-methylimidazol-4-yl, oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, 6-methoxypryridin-3-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl and 1-methylpyrazol-3-yl;

R^6 and **R^7** together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

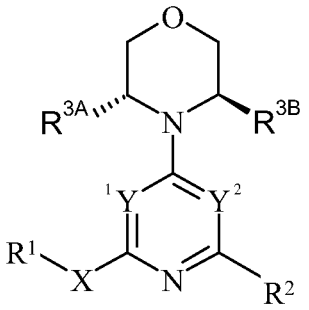
when **R^{3A}** is hydrogen, **R^{3B}** is hydrogen, methyl or ethyl; or

when **R^{3A}** is methyl, **R^{3B}** is methyl.

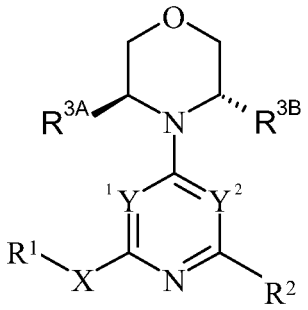
In a further particular class of compound of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

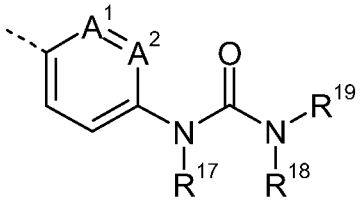
or a pharmaceutically acceptable salt thereof;

X is a $-S(O)_2CR^6R^7-$ linker group;

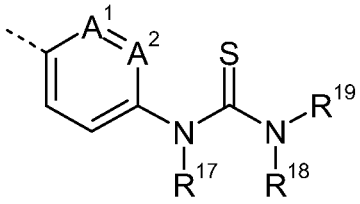
^{1}**Y** is CH and **Y^2** is N;

R^1 is a group selected from methyl, ethyl, cyclopropyl, $-CH_2CH_2CH_2OH$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 5-fluoropyridin-2-yl, pyridin-2-yl, thiazol-2-yl and 4-methylthiazol-2-yl;

R^2 is



or



wherein **A^1** and **A^2** are selected from CH or N provided that at least one of A^1 or A^2 is CH;

R^{17} is hydrogen;

R^{18} is hydrogen; and

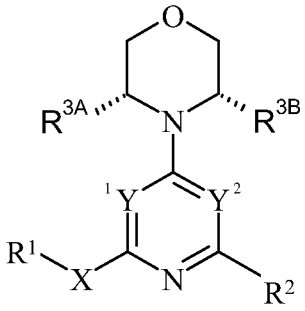
R^{19} is a group selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, $-CH_2$(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, thiazol-2-yl and 1,2,4-thiadiazol-5-yl;

R^6 and **R^7** together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

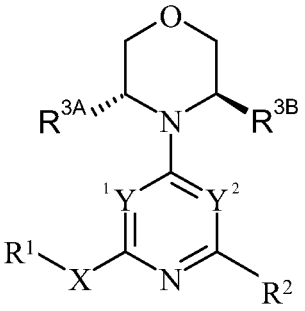
when **R^{3A}** is hydrogen, **R^{3B}** is hydrogen, methyl or ethyl; or

when **R^{3A}** is methyl, **R^{3B}** is methyl.

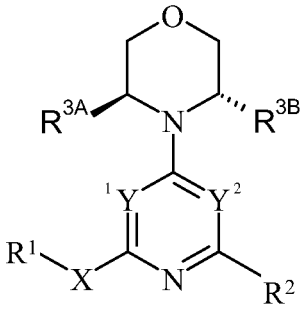
In a further particular class of compound of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

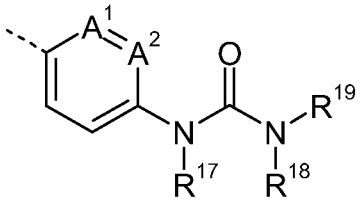
or a pharmaceutically acceptable salt thereof;

X is a $-S(O)_2CR^6R^7-$ linker group;

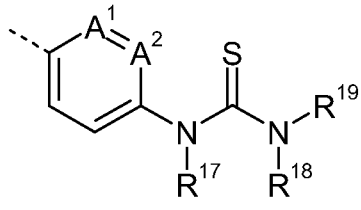
^{1}**Y** is CH and **Y^2** is N;

R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2CH_2NHMe$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-fluoro-4-methylaminophenyl, 4-fluoro-2-methylphenyl, 5-fluoro-2-methylphenyl, 3-fluoro-4-(2-hydroxyethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-carbamoyl-2-chlorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-4-methylaminophenyl, 3-chloro-4-ethylaminophenyl, 3-chloro-4-(2-fluoroethylamino)phenyl, 3-chloro-4-(2-hydroxyethylamino)phenyl, 2-chloro-4-cyanophenyl, 4-cyanophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-(trifluoromethyl)phenyl, 2-methylphenyl, 4-methylphenyl, 4-(2-hydroxyethylamino)phenyl, 1H-imidazol-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 1-(difluoromethyl)pyrazol-4-yl, 1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl, 1,3-dimethylpyrazol-4-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, 5-fluoropyridin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2,4-dimethylthiazol-5-yl, 5-methyl-1,3,4-thiadiazol-2-yl, terahydrofuran-3-yl and terahydropyran-4-yl;

R^2 is



or



wherein A^1 and A^2 are CH;

R^{17} is hydrogen;

R^{18} is hydrogen; and

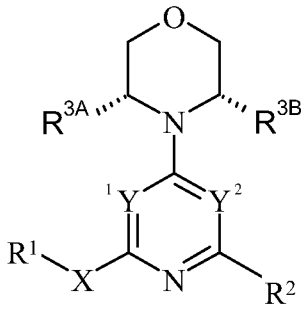
R^{19} is is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, i-butyl, t-butyl, cyclopropyl, cyclobutyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, $-CH_2CO_2H$, 1-(methyl)cyclopropyl, $-CH_2$(1-hydroxycyclopropyl), 1-(hydroxymethyl)cyclopropyl, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, $-CH_2CH_2$(pyrrolidin-1-yl),$-CH_2$(imidazol-2-yl), 1-methylimidazol-4-yl, oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 1,1-dioxothiolan-3-yl, 5-methylisoxazol-3-yl, $-CH_2$(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, $-CH_2$(1-methylpyrazol-4-yl), 5-methylpyrazin-2-yl, $-CH_2$(2H-1,2,4-triazol-3-yl), 6-methoxypryridin-3-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl and 1-methylpyrazol-3-yl;

R^6 and R^7 together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

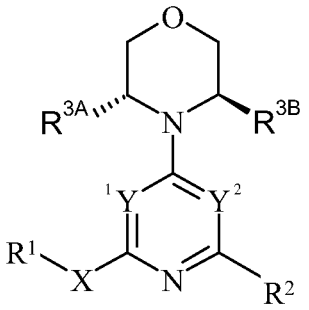
when R^{3A} is hydrogen, R^{3B} is hydrogen, methyl, ethyl, hydroxymethyl, dimethylcarbamoyl or carbamoyl; or

when $R^{3'}$ is methyl, R^3 is methyl.

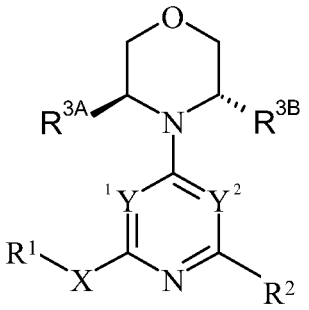
In a further particular class of compound of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

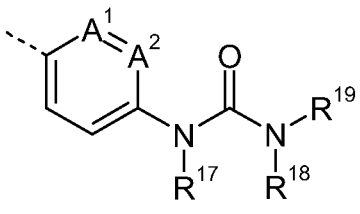
or a pharmaceutically acceptable salt thereof;

X is a $-S(O)_2CR^6R^7-$ linker group;

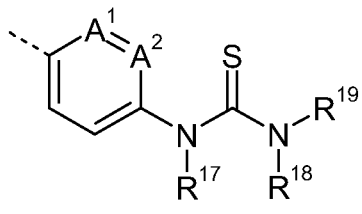
^{1}**Y** is CH and **Y**^{2} is N;

R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2CH_2NHMe$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-fluoro-4-methylaminophenyl, 4-fluoro-2-methylphenyl, 5-fluoro-2-methylphenyl, 3-fluoro-4-(2-hydroxyethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-carbamoyl-2-chlorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-4-methylaminophenyl, 3-chloro-4-ethylaminophenyl, 3-chloro-4-(2-fluoroethylamino)phenyl, 3-chloro-4-(2-hydroxyethylamino)phenyl, 2-chloro-4-cyanophenyl, 4-cyanophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-methylphenyl, 4-methylphenyl, 1H-imidazol-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 1-(difluoromethyl)pyrazol-4-yl, 1,3-dimethylpyrazol-4-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2,4-dimethylthiazol-5-yl and 5-methyl-1,3,4-thiadiazol-2-yl;

R^2 is



or



wherein **A**^{1} and **A**^{2} are CH;

R^{17} is hydrogen;

R^{18} is hydrogen; and

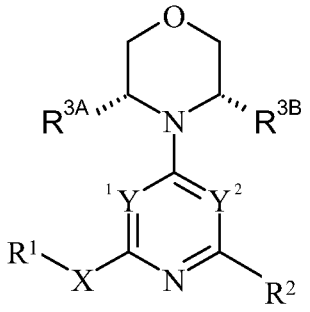
$\mathbf{R^{19}}$ is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, cyclopropyl, cyclobutyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CH_2Cl, -CH_2CH_2CN, -CH_2(1-hydroxycyclopropyl), 1-(hydroxymethyl)cyclopropyl, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, -CH_2CH_2(pyrrolidin-1-yl),-CH_2(imidazol-2-yl), 1-methylimidazol-4-yl, oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, 6-methoxypryridin-3-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl and 1-methylpyrazol-3-yl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

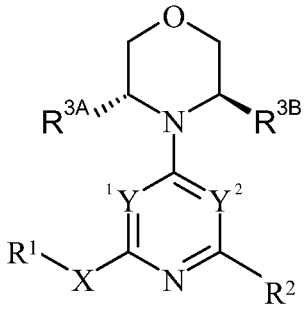
when $\mathbf{R^{3A}}$ is hydrogen, $\mathbf{R^{3B}}$ is hydrogen, methyl or ethyl; or

when $\mathbf{R^{3A}}$ is methyl, $\mathbf{R^{3B}}$ is methyl.

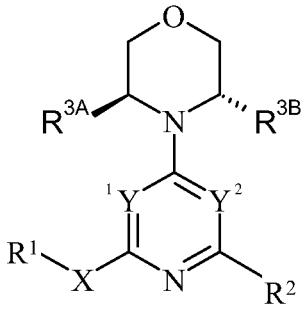
In a further particular class of compound of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

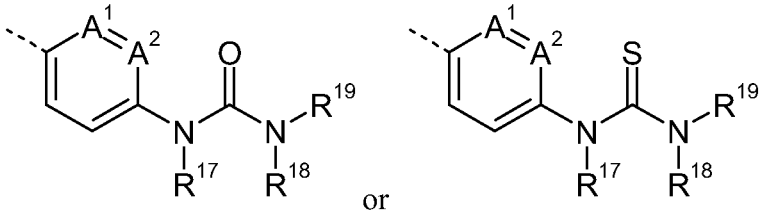
or a pharmaceutically acceptable salt thereof;

$\mathbf{X}$ is a -$S(O)_2CR^6R^7$- linker group;

$^1\mathbf{Y}$ is CH and $\mathbf{Y^2}$ is N;

$\mathbf{R^1}$ is a group selected from methyl, ethyl, cyclopropyl, -$CH_2CH_2CH_2OH$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 5-fluoropyridin-2-yl, pyridin-2-yl, thiazol-2-yl and 4-methylthiazol-2-yl;

$\mathbf{R^2}$ is



or

wherein $\mathbf{A^1}$ and $\mathbf{A^2}$ are CH;

$\mathbf{R^{17}}$ is hydrogen;

$\mathbf{R^{18}}$ is hydrogen; and

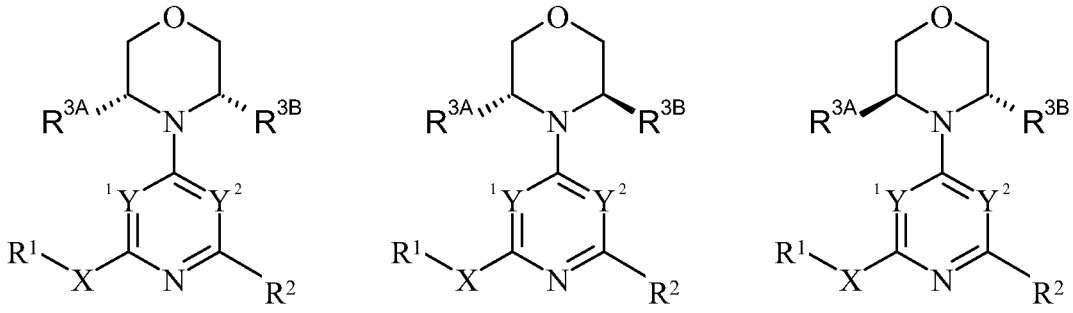
$\mathbf{R^{19}}$ is a group selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, $-CH_2$(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, thiazol-2-yl and 1,2,4-thiadiazol-5-yl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

when $\mathbf{R^{3A}}$ is hydrogen, $\mathbf{R^{3B}}$ is hydrogen, methyl or ethyl; or

when $\mathbf{R^{3A}}$ is methyl, $\mathbf{R^{3B}}$ is methyl.

In a further particular class of compound of formula (IA), (IB) or (IC)



(IA) (IB) (IC)

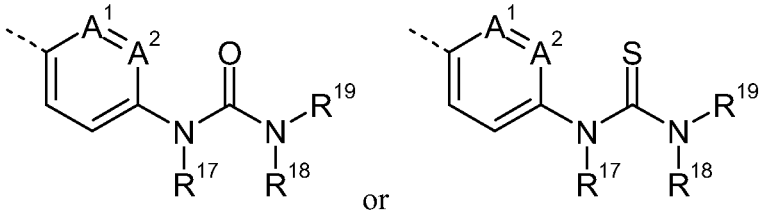
or a pharmaceutically acceptable salt thereof;

X is a $-S(O)_2CR^6R^7-$ linker group;

$\mathbf{^1Y}$ is CH and $\mathbf{Y^2}$ is N;

$\mathbf{R^1}$ is a group selected from methyl, ethyl, cyclopropyl, $-CH_2CH_2CH_2OH$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 5-fluoropyridin-2-yl, pyridin-2-yl, thiazol-2-yl and 4-methylthiazol-2-yl;

$\mathbf{R^2}$ is



or

wherein A^1 and A^2 are CH;

R^{17} is hydrogen;

R^{18} is hydrogen; and

R^{19} is a group selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, $-CH_2$(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, thiazol-2-yl and 1,2,4-thiadiazol-5-yl;

R^6 and R^7 together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

when R^{3A} is hydrogen, R^{3B} is methyl or ethyl; or

when R^{3A} is methyl, R^{3B} is methyl.

Another aspect of the invention provides a compound, or a combination of compounds, selected from any one of the Examples or a pharmaceutically acceptable salt thereof.

In another aspect of the invention there is provided a compound, or a combination of compounds, selected from any one of

3-Ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-Cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propyl-urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
3-(cyclopropylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(1-hydroxypropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(6-methoxypyridin-3-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(4-fluorophenyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(3,4-difluorophenyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(4-methylphenyl)urea,

3-(4-chlorophenyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(4-methoxyphenyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(5-methyl-1,2-oxazol-3-yl)urea,
3-(5-fluoropyridin-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxy-2,2-dimethylpropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-pyrrolidin-1-ylethyl)urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(3,3,3-trifluoro-2-hydroxypropyl)urea,
3-(2-hydroxy-2-methylpropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(oxetan-3-yl)urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-3-yl)urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,
3-(cyanomethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2H-1,2,4-triazol-3-ylmethyl)urea,
3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-cyclobutyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
3-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethyl-urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxy-2,2-dimethylpropyl)urea,
3-(2-cyanoethyl)-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-pyrrolidin-1-ylethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3,3,3-trifluoro-2-hydroxypropyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxy-2-methylpropyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(oxetan-3-yl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-3-yl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-propyl-urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-propyl-urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propyl-urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-propyl-urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea,
1-ethyl-3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
3-cyclobutyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropyl-urea,
3-cyclobutyl-1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,
1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
3-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethyl-urea,
1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,
1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea,
1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea,
1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea,
1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-1-propyl-urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea,
1-ethyl-3-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
3-cyclobutyl-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea,
3-(2-dimethylaminoethyl)-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-ethyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-cyclobutyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-propylurea,

3-(3-hydroxypropyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(1-methylpyrazol-4-yl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-ethylurea,
3-cyclobutyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-propylurea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
3-cyclopropyl-1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]urea,
1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-methylurea,
1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(2-dimethylaminoethyl)urea,
1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(2-hydroxyethyl)urea,
1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]urea,
1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-methylurea,
1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(2-hydroxyethyl)urea,
1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]urea,
1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-methylurea,
3-(2-dimethylaminoethyl)-1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]urea,
1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(2-hydroxyethyl)urea,
1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea,
3-methyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea,
3-(2-dimethylaminoethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea,
3-(2-hydroxyethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea,
1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]urea,
3-methyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]urea,
3-(2-hydroxyethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]urea,
1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]urea,
1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-methylurea,
1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(2-hydroxyethyl)urea,
1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(1-methylpyrazol-4-yl)urea,
3-(2-hydroxyethyl)-1-[5-[4-[1-[4-(2-hydroxyethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]urea,
3-cyclopropyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-ethyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-cyclobutyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,

1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea,

1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

3-(2-cyanoethyl)-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea,

1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-ethyl-1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-cyclopropyl-1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutylurea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea,
1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,
1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,
1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propylurea,
1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-cyclobutyl-1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propylurea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-Benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,
1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,

1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,
1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-1-propylurea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
3-cyclobutyl-1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,
1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutylurea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-propylurea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea
[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,
3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-cyclobutyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea,
3-(2-dimethylaminoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea
N,N-dimethyl-1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide
3-methyl-1-[4-[4-[1-[(3S)-3-methylmorpholine-4-carbonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea
N-cyclopropyl-1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide
N-cyclopropyl-N-methyl-1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide
3-methyl-1-[4-[4-[1-(4-methylpiperazine-1-carbonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea
1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N,N-dimethylcyclopropane-1-carboxamide
3-cyclopropyl-1-[4-[4-[1-[(3S)-3-methylmorpholine-4-carbonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea
N-cyclopropyl-1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide
N-cyclopropyl-1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N-methylcyclopropane-1-carboxamide
3-cyclopropyl-1-[4-[4-[1-(4-methylpiperazine-1-carbonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea
1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N,N-dimethylcyclopropane-1-carboxamide

3-(2-hydroxyethyl)-1-[4-[4-[1-[(3S)-3-methylmorpholine-4-carbonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea

N-cyclopropyl-1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide

N-cyclopropyl-1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N-methylcyclopropane-1-carboxamide,

3-(2-hydroxyethyl)-1-[4-[4-[1-(4-methylpiperazine-1-carbonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-(2-cyanoethyl)-1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,
3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-cyanoethyl)-1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,
3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,

1-ethyl-3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-methylurea,

3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-(1-methylpyrazol-4-yl)urea,

3-(2-hydroxyethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-(1-methylpyrazol-4-yl)-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-methyl-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-ethyl-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-cyclopropyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(2-cyanoethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea,

3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-(5-methylpyrazin-2-yl)urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,3-oxazol-2-yl)urea,

3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3,3,3-trifluoro-2-hydroxypropyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,
3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(oxetan-3-yl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea,
1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-ethyl-3-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-cyclobutyl-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea,
3-(2-hydroxyethyl)-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea,
1-cyclopropyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-methylurea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylcyclopropyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-tert-butyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-cyano-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-hydroxy-N-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]pyrrolidine-1-carboxamide,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylsulfonylethyl)urea,
3-(1,1-dioxothiolan-3-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
2-[[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamoylamino]-N,N-dimethylacetamide,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-cyclopropylurea,
3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-methylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,
3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea,
N-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-hydroxypyrrolidine-1-carboxamide,

2-[[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamoylamino]acetic acid,

2-[[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamoylamino]-N,N-dimethylacetamide,

3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-cyclopropyl-1-methylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-3-yl)urea,

3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-(5-methyl-1,2-oxazol-3-yl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-oxazol-2-yl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2,2-trifluoroethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylimidazol-4-yl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-chloroethyl)urea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,
3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,
3-cyclobutyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-(2-cyanoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,
3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)thiourea,
1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylthiourea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propylthiourea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)thiourea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]thiourea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,
3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylthiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)thiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)thiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)thiourea,
3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylthiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)thiourea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(1H-imidazol-2-ylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(1H-imidazol-2-ylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(1-methylpyrazol-4-yl)-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-cyclobutyl-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(2-cyanoethyl)-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-propylurea,
1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-propan-2-ylurea,
3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,
3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea,
3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea,
3-(2-fluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea,
N-[2-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide,
N-[2-[1-[2-[4-(ethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide,
2-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropyl]sulfonylacetamide,
2-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropyl]sulfonyl-N-methylacetamide,
3-cyclopropyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea,
3-ethyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-cyclopropyl-1-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
N,N-dimethyl-6-[1-[2-[4-(methylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpyridine-3-carboxamide,
6-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-N,N-dimethylpyridine-3-carboxamide,
N,N-dimethyl-3-[1-[2-[4-(methylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpyridine-2-carboxamide,
3-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-N,N-dimethylpyridine-2-carboxamide,
1-[4-[4-[1-(2-methoxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-methylurea,
3-ethyl-1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-fluoroethyl)-1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-ethyl-3-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-ethyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(1-methylpyrazol-4-yl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(2-fluoro-4-methylaminophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclop,ropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea,
1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-(2-fluoroethyl)-1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea,
1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea,
3-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-43-yl)urea,
1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-43-yl)urea
1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-fluoroethyl)-1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-43-yl)urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea,
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea,
3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea,

3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
3-cyclopropyl-1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[3-fluoro-4-(2-hydroxyethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea,
3-(2-fluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea,
1-[4-[4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3R)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[3-(hydroxymethyl)morpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3R,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea,
3-Cyclopropyl-1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2-fluoroethyl)-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-ethyl-3-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-cyclopropyl-1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-(2-fluoroethyl)-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-ethyl-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-ethyl-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea

3-chloro-4-[1-[2-[4-(methylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide

3-chloro-4-[1-[2-[4-(ethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide

3-chloro-4-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide

3-chloro-4-[1-[2-[4-(2-fluoroethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide

3-chloro-4-[1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide

1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

3-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea

1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea

1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea

1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea

1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea

1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea

3-cyclopropyl-1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

3-(2,2-difluoroethyl)-1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,
1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)thiourea,
1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,
1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)thiourea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea,
4-[6-[1-(benzenesulfonyl)cyclopropyl]-2-[4-(ethylcarbamoylamino)phenyl]pyrimidin-4-yl]morpholine-3-carboxamide,

4-[6-[1-(benzenesulfonyl)cyclopropyl]-2-[4-(ethylcarbamoylamino)phenyl]pyrimidin-4-yl]-N,N-dimethylmorpholine-3-carboxamide,

3-cyclopropyl-1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-ethylurea,

1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea

3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea

3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
3-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(3-chloro-4-methylaminophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-[3-chloro-4-(2-hydroxyethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-[3-chloro-4-(2-fluoroethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(3-chloro-4-ethylaminophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyramidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[1-(2-methylaminoethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,
3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea,
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylthiourea,
3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea, and
3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
or a pharmaceutically acceptable salt thereof.

In another aspect of the invention there is provided a compound, or a combination of compounds, selected from any one of
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,
3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-cyclopropyl-1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea, and
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea,

1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,

1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-ethylurea,

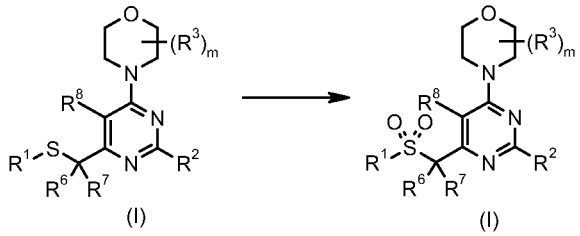
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea, and

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

or a pharmaceutically acceptable salt thereof.

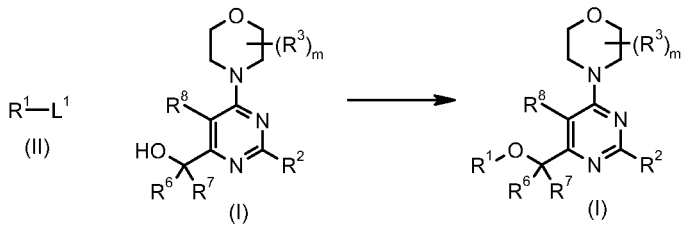
The invention also provides processes for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

A compound of formula (I), wherein X = $-S(O)_2CR^6R^7-$, may be prepared by oxidising a compound of the formula (I), wherein X = SCR^6R^7-, for example by using Oxone® at room temperature in a mixed solvent system of water and ethanol



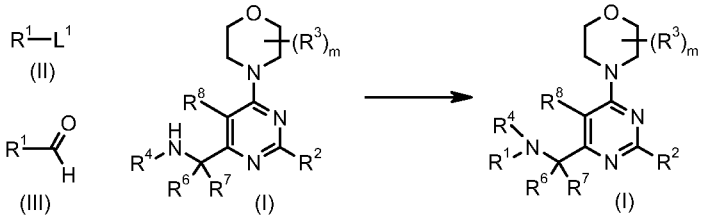
(I) (I)

A compound of formula (I), wherein $R^1X = R^1OCR^6R^7-$, may be prepared by the reaction of a compound of formula (I), wherein $R^1X = HOCR^6R^7-$, with a compound of formula (II), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide.

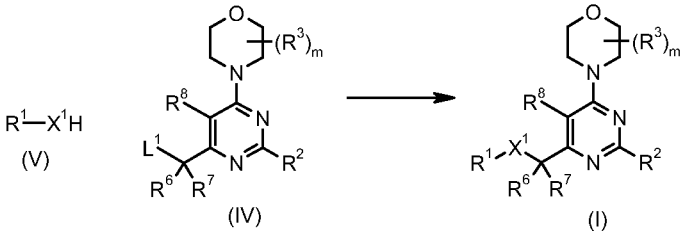


(II) (I) (I)

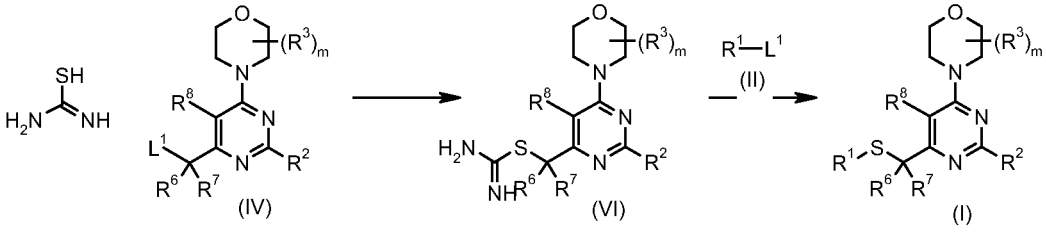
A compound of formula (I), wherein $R^1X = R^1R^4NCR^6R^7$-, may be prepared by the reaction of a compound of formula (I), wherein $R^1X = HR^4NCR^6R^7$-, with a compound of formula (II), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide; or by the reaction of a compound of formula (I), wherein $R^1X = HR^4NCR^6R^7$-, with a compound of formula (III) in the presence of a suitable reducing agent such as $NaCNBH_3$.



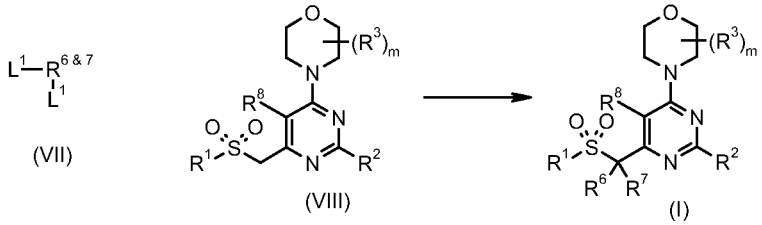
A compound of formula (I), wherein $X^1 = -S(O)_2CR^6R^7$-, $-SCR^6R^7$-, $-OCR^6R^7$-, $-R^4NCR^6R^7$-, $-S(O)CR^6R^7$-, may be prepared by the reaction of a compound of formula (IV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (V) optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide.



A compound of formula (I), wherein $X = -SCR^6R^7$-, may be prepared by the reaction of a compound of formula (IV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with thiourea in a suitable solvent such as ethanol to generate a compound of formula (VI) which is then subsequently reacted with a compound of formula (II) in the presence of a suitable base such as sodium hydroxide and a solvent such as *N,N*-dimethylformamide.

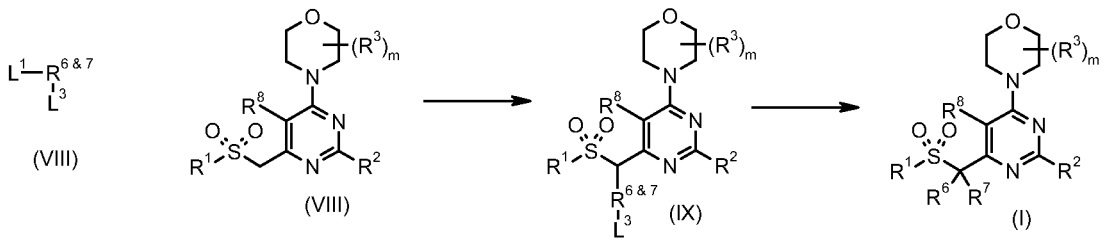


A compound of formula (I), wherein X = -$S(O)_2CR^6R^7$-, may be prepared by the reaction of a compound of formula (VIII) with a compound of formula (VII), wherein $R^{6\ \&\ 7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide.



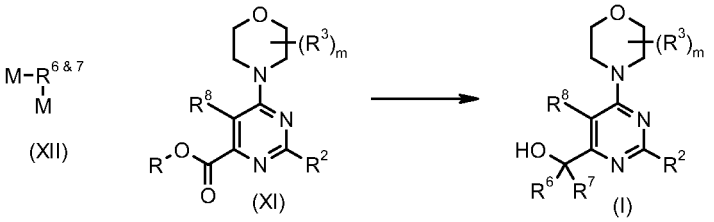
(VII) (VIII) (I)

A compound of formula (I), wherein X = -$S(O)_2CR^6R^7$-, may be prepared by the reaction of a compound of formula (VIII) with a compound of formula (IX), wherein $R^{6\ \&\ 7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), and L^3 is a group which can be transformed to a suitable leaving group (such as halo, tosyl, mesyl) at a later stage, to give a compound of formula (X) in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide, and subsequently converting L^3 to an appropriate leaving group (such as halo, tosyl, mesyl etc.) and then exposing to a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide.



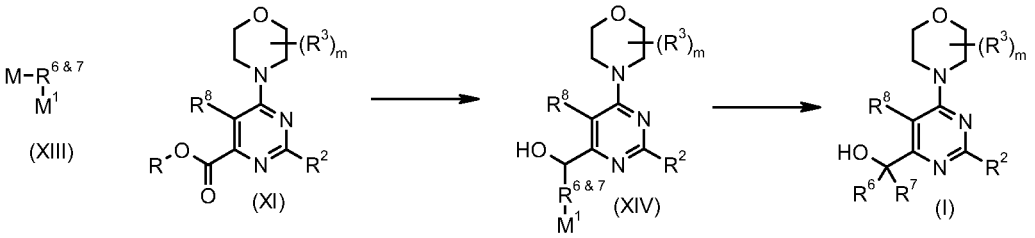
(VIII) (VIII) (IX) (I)

A compound of formula (I), wherein $R^1X = HOCR^6R^7$-, may be prepared by the reaction of a compound of formula (XI), with suitable organometallic reagent of fomula (XII) wherein $R^{6\,\&\,7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, such as the grignard reagent in a suitable solvent.



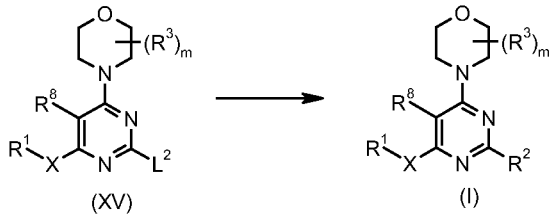
(XII) (XI) (I)

A compound of formula (I), wherein $R^1X = HOCR^6R^7$-, may be prepared by the reaction of a compound of formula (XI), with suitable organometallic reagent of fomula (XIII) wherein $R^{6\,\&\,7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and M^1 is a group which can be transformed into a suitable organometallic reagent (such as a grignard reagent) at a later date, such as the grignard reagent in a suitable solvent, to give a compound of formula (XIV), and then subsequent conversion of M^1 to a suitable organometallic reagent and subsequent reaction.



(XIII) (XI) (XIV) (I)

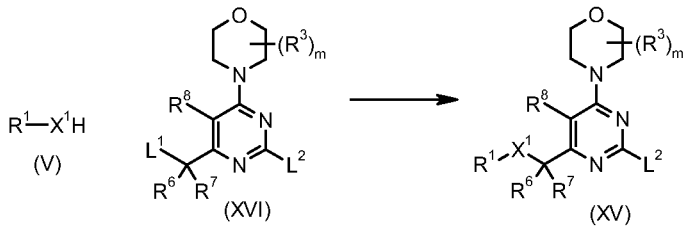
A compound of formula (I) may be prepared from a compound of formula (XV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (I) may be prepared from a compound of formula (XIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.



(XV) (I)

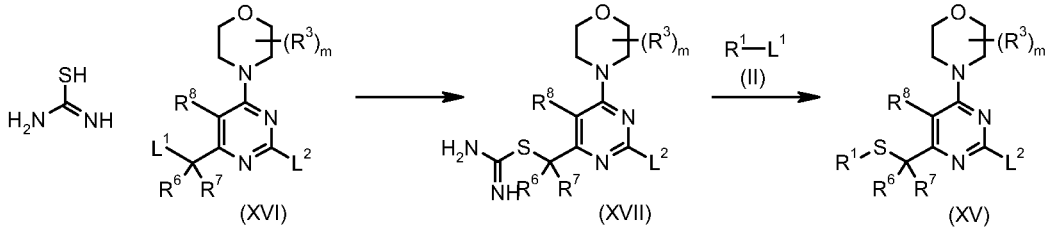
It will be appreciated that a compound of formula (XV) may be transformed into another compound of formula (XV) by techniques such as oxidation, alkylation, reductive amination etc., either listed above or otherwise known in the literature.

A compound of formula (XV), wherein X^1 = $-S(O)_2CR^6R^7-$, $-SCR^6R^7-$, $-OCR^6R^7-$, $-R^4NCR^6R^7-$, $-S(O)CR^6R^7-$, may be prepared by the reaction of a compound of formula (XVI), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (V) optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide.



(V) (XVI) (XV)

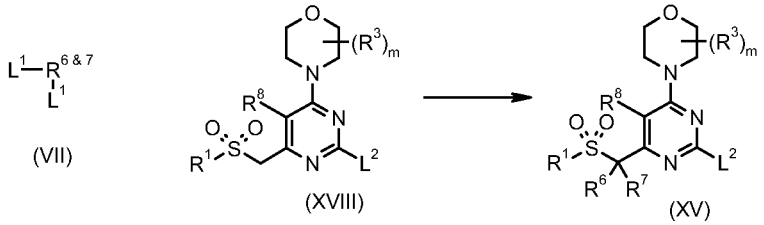
A compound of formula (XV), wherein X = $-SCR^6R^7-$, may be prepared by the reaction of a compound of formula (XVI), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with thiourea in a suitable solvent such as ethanol to generate a compound of formula (XVII) which is then subsequently reacted with a compound of formula (II) in the presence of a suitable base such as sodium hydroxide and a solvent such as *N,N*-dimethylformamide.



(XVI) (XVII) (II) (XV)

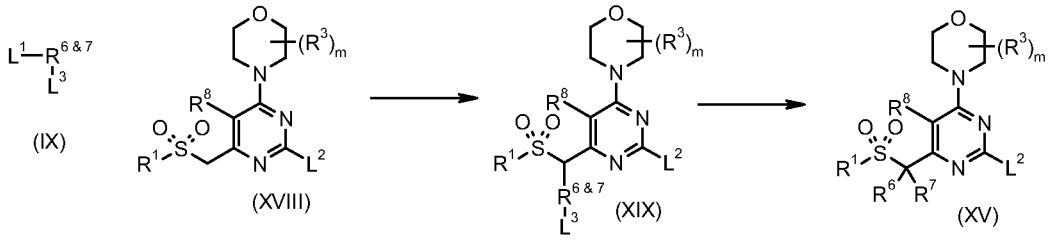
A compound of formula (XV), wherein X = $-S(O)_2CR^6R^7-$, may be prepared by the reaction of a compound of formula (XVIII), wherein X = $-S(O)_2CH_2-$, with a compound of formula (VII), wherein $R^{6\ \&\ 7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), in the presence of a suitable base such as sodium hydride or

potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide.



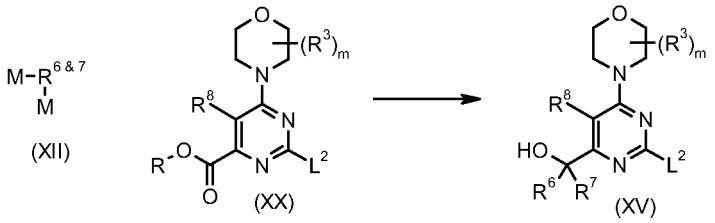
(VII) (XVIII) (XV)

A compound of formula (XV), wherein X = $-S(O)_2CR^6R^7-$, may be prepared by the reaction of a compound of formula (XVIII), wherein X = $-S(O)_2CH_2-$, with a compound of formula (IX), wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), and L^3 is a group which can be transformed to a suitable leaving group (such as halo, tosyl, mesyl) at a later stage, to give a compound of formula (XIX) in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide, and subsequently converting L^3 to an appropriate leaving group (such as halo, tosyl, mesyl etc.) and then exposing to a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide.

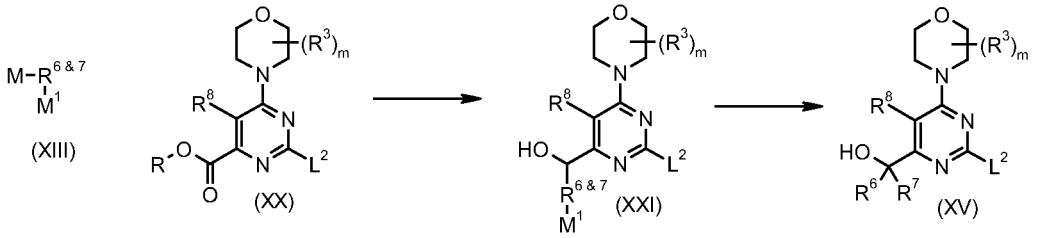


(IX) (XVIII) (XIX) (XV)

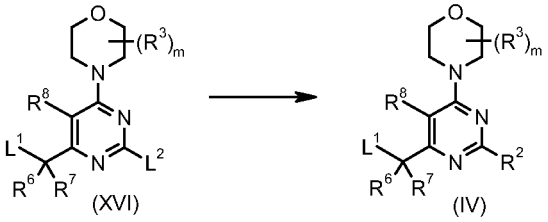
A compound of formula (XV), wherein R^1X = $HOCR^6R^7-$, may be prepared by the reaction of a compound of formula (XX), with suitable organometallic reagent of fomula (XII) wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, such as the grignard reagent in a suitable solvent.



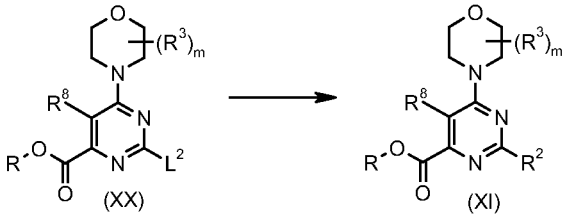
A compound of formula (XV), wherein $R^1X = HOCR^6R^7$-, may be prepared by the reaction of a compound of formula (XX), with suitable organometallic reagent of fomula (XIII) wherein $R^{6\ \&\ 7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and M^1 is a group which can be transformed into a suitable organometallic reagent (such as a grignard reagent) at a later date, such as the grignard reagent in a suitable solvent, to give a compound of formula (XXI), and then subsequent conversion of M^1 to a suitable organometallic reagent and subsequent reaction.



A compound of formula (IV) may be prepared from a compound of formula (XVI), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.) and L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (IV) may be prepared from a compound of formula (XVI), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.

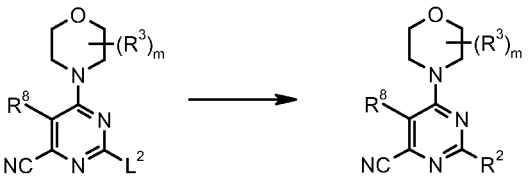


A compound of formula (XI) may be prepared from a compound of formula (XX), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.) and R is a hydrogen or C_{1-4} alkyl group, with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (XI) may be prepared from a compound of formula (XX), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.



(XX) (XI)

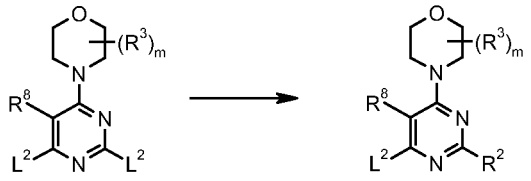
A compound of formula (XXII) may be prepared from a compound of formula (XXIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (XXII) may be prepared from a compound of formula (XXIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.



(XXIII) (XXII)

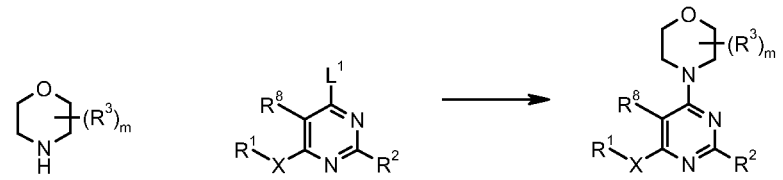
A compound of formula (XXIV) may be prepared from a compound of formula (XXV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent

such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (XXIV) may be prepared from a compound of formula (XXV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.



(XXV) (XXIV)

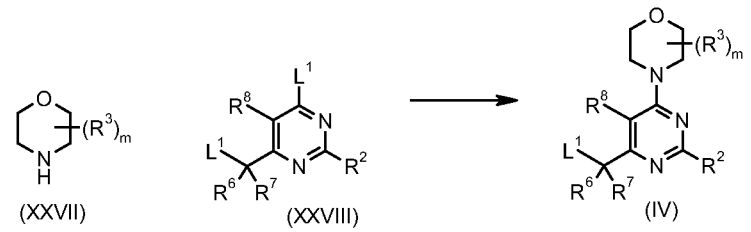
A compound of formula (I), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), may be prepared by the reaction of a compound of formula (XXVI) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



(XXVII) (XXVI) (I)

It will be appreciated that a compound of formula (XXV) may be transformed into another compound of formula (XXV) by techniques such as oxidation, alkylation, reductive amination etc., either listed above or otherwise known in the literature.

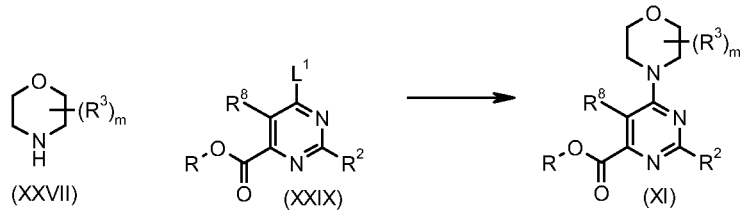
A compound of formula (IV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), may be prepared by the reaction of a compound of formula (XXVIII) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



(XXVII) (XXVIII) (IV)

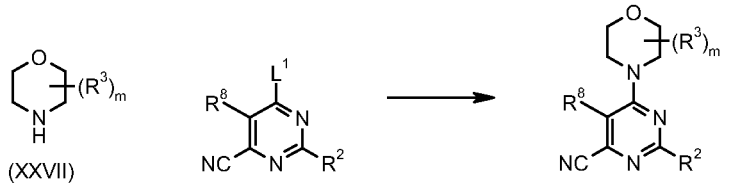
A compound of formula (XI), wherein R is a hydrogen or a C_{1-4} alkyl group, may be prepared by the reaction of a compound of formula (XXIX), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) with a compound of formula (XXVII) optionally in the

presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



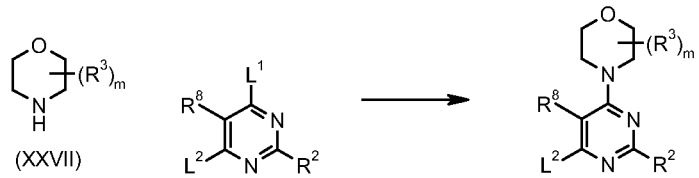
(XXVII) (XXIX) (XI)

A compound of formula (XXII) may be prepared by the reaction of a compound of formula (XXX), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



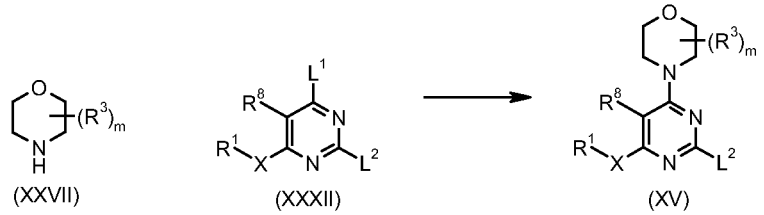
(XXVII) (XXX) (XXII)

A compound of formula (XXIV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXXI), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



(XXVII) (XXXI) (XXIV)

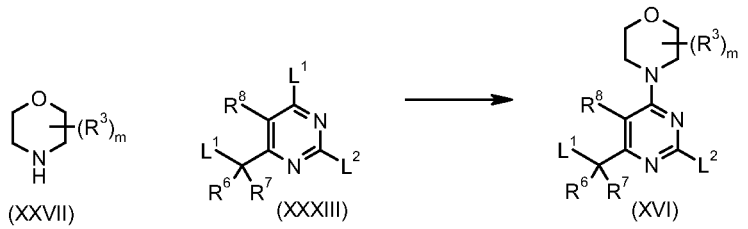
A compound of formula (XV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXXII), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



(XXVII) (XXXII) (XV)

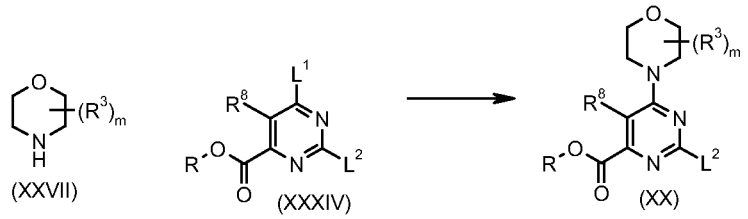
It will be appreciated that a compound of formula (XXXII) may be transformed into another compound of formula (XXXII) by techniques such as oxidation, alkylation, reductive amination etc., either listed above or otherwise known in the literature.

A compound of formula (XVI), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) and L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXXIII) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



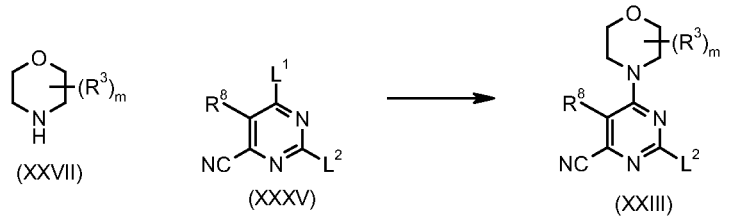
(XXVII) (XXXIII) (XVI)

A compound of formula (XX), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.) and R is a hydrogen or a C_{1-4} alkyl group, may be prepared by the reaction of a compound of formula (XXXIV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



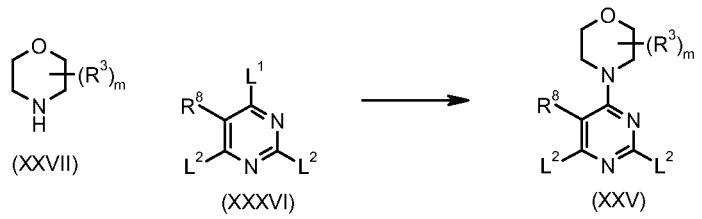
(XXVII) (XXXIV) (XX)

A compound of formula (XXIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXXV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



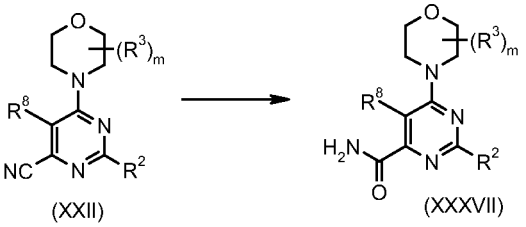
(XXVII) (XXXV) (XXIII)

A compound of formula (XXV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXXVI), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



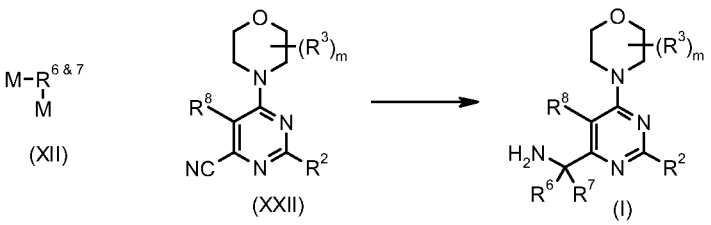
(XXVII) (XXXVI) (XXV)

A compound of formula (XXXVII), wherein $R^1X = H_2NC(O)$-, may be prepared from a compound of formula (XXII) by hydrolysis with, for example, sodium hydroxide in a suitable solvent such as a water ethanol mix.



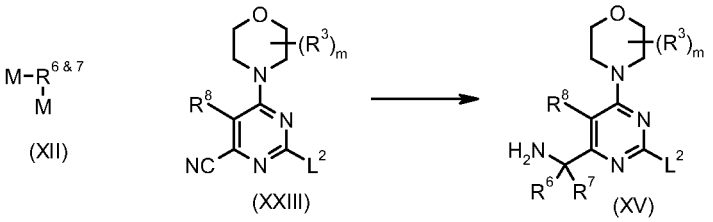
(XXII) (XXXVII)

A compound of formula (I), wherein $R^1X = H_2NCR^6R^7$-, may be prepared by the reaction of a compound of formula (XXII), with suitable organometallic reagent of fomula (XII) wherein $R^{6\ \&\ 7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, such as the grignard reagent or alkyl lithium reagent in a suitable solvent.



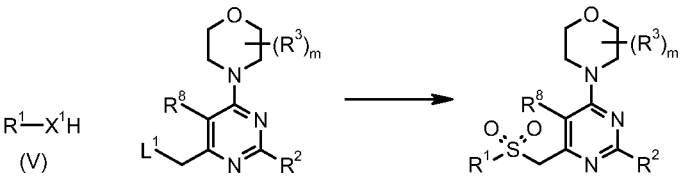
(XII) (XXII) (I)

A compound of formula (XV), wherein $R^1X = H_2NCR^6R^7$-, may be prepared by the reaction of a compound of formula (XXIII), with suitable organometallic reagent of fomula (XII) wherein $R^{6\,\&\,7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, such as the grignard reagent or alkyl lithium reagent in a suitable solvent.



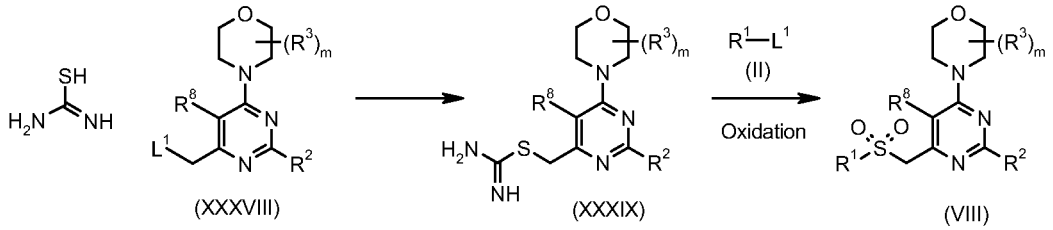
(XII) (XXIII) (XV)

A compound of formula (VIII) may be prepared by the reaction of a compound of formula (XXXVIII), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (V), wherein X^1 = -S-, -SO_2-, optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide. In the case where X^1 = -SH a subsequent oxidation step, for example by using Oxone® at room temperature in a solvent system of water and ethanol, or for example by using 3-chloroperbenzoic acid with dichloromethane as solvent will be required.

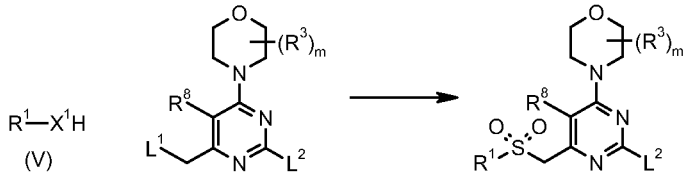


(V) (XXXVIII) (VIII)

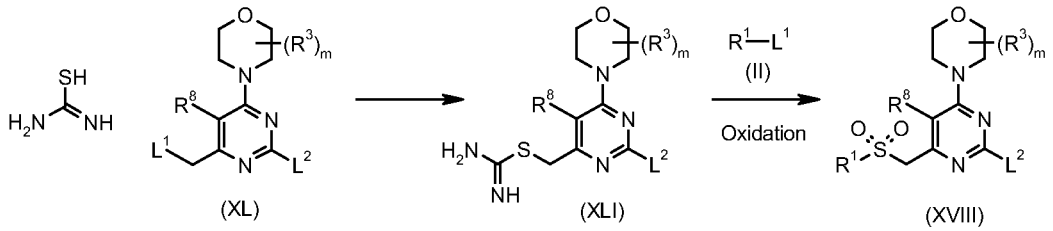
A compound of formula (VIII) may be prepared by the reaction of a compound of formula (XXXVIII), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with thiourea in a suitable solvent such as ethanol to generate a compound of formula (XXXIX) which is then subsequently reacted with a compound of formula (II) in the presence of a suitable base such as sodium hydroxide and a solvent such as *N,N*-dimethylformamide, and subsequently oxidised, for example by using Oxone® at room temperature in a solvent system of water and ethanol, or for example by using 3-chloroperbenzoic acid with dichloromethane as solvent.



A compound of formula (XVIII), wherein L^2 is a leaving group (such as halo, tosyl mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XL), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (V), wherein X^1 = -S-, $-SO_2-$, optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide. In the case where X^1 = -S- a subsequent oxidation step, for example by using Oxone® at room temperature in a solvent system of water and ethanol, or for example by using 3-chloroperbenzoic acid with dichloromethane as solvent will be required.

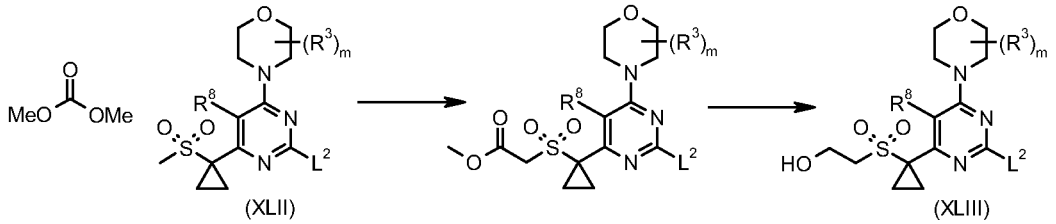


A compound of formula (XVIII), wherein L^2 is a leaving group (such as halo, tosyl mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XL), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with thiourea in a suitable solvent such as ethanol to generate a compound of formula (XLI) which is then subsequently reacted with a compound of formula (II) in the presence of a suitable base such as sodium hydroxide and a solvent such as *N,N*-dimethylformamide, and subsequently oxidised, for example by using Oxone® at room temperature in a solvent system of water and ethanol, or for example by using 3-chloroperbenzoic acid with dichloromethane as solvent.



It will be appreciated that the substituent R^1 present in a compound of formula (I) and formula (XV) can be transformed into another substituent R^1 by a series of chemical

transformations known in the literature, such as oxidation, reduction, nucleophilic or electrophilic reactions, addition and elimination reactions. An example of such a transformation would be the reaction of a compound of formula (XLII), wherein L^2 is a leaving group (such as halo, tosyl mesyl, -SMe, $-S(O)_2Me$ etc.), with an electrophile such as dimethyl carbonate in the presence of a base such as sodium hydride in a suitable solvent such as tetrahydrofuran, followed by a reduction, such as the conversion to a mixed anhydride followed by treatment with a hydride source, to give a compound of formula (XLIII)

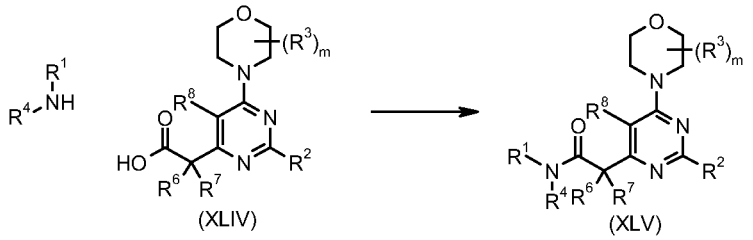


(XLII) (XLIII)

It will be appreciated that the R^2 group may be introduced and subsequently converted to another group of the formula R^2 at a subsequent stage in the synthesis using methods known in the literature. For example, but not limited to, an R^2 containing an alkyl or aryl amine (which may be suitably protected as, for example, a nitro or t-butoxycarbamate) may be introduced at any stage and then converted, for instance, to a urea by reaction with a suitable isocyanate (or by activation to a suitable group, such as isocyanate or phenoxycarbamate, and subsequent reaction with an amine); or to a thiourea by reaction with a suitable isothiocyanate (or by activation to a suitable group, such as an isothiocyanate, and subsequent reaction with an amine); or to an amide or sulphonamide by reaction with a suitably activated carboxylic acid or sulphonic acid derivative; or by other methods known in the literature.

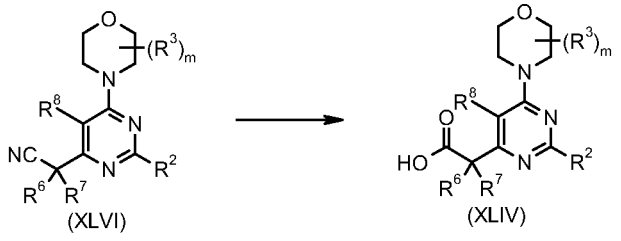
It will be appreciated that where R^6 and R^7, together with the carbon to which they are attached, form a 3-10 membered heterocyclic ring containing a nitrogen atom that the nitrogen atom may be suitably protected (for example a t-butoxycarbamate or benzyl group) and that the protecting group may be removed and if necessary a further reaction performed on the nitrogen (for example an alkylation, reductive amination or amidation) at any stage in the synthesis.

A compound of formula (XLV) may be prepared by the reaction of an amine of formula R^1R^4NH with a compound of formula (XLIV) in the presence of a suitable coupling agent, such as HATU, or following suitable activation of (XLIV), such as the conversion to an acid chloride.



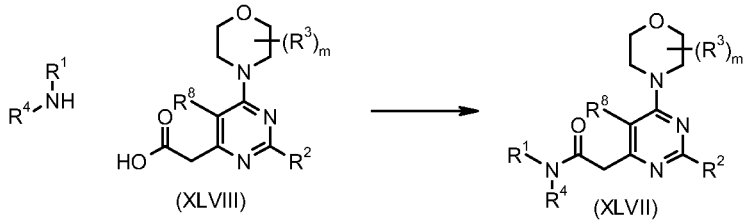
(XLIV) (XLV)

A compound of formula (XLIV) may be prepared from a compound of formula (XLVI) by hydrolysis, for example with sodium hydroxide in a suitable solvent such as an ethanol:water mix.



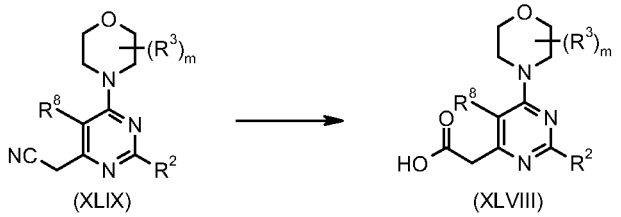
(XLVI) (XLIV)

A compound of formula (XLVII) may be prepared by the reaction of an amine of formula R^1R^4NH with a compound of formula (XLVIII) in the presence of a suitable coupling agent, such as HATU, or following suitable activation of (XLVIII), such as the conversion to an acid chloride.



(XLVIII) (XLVII)

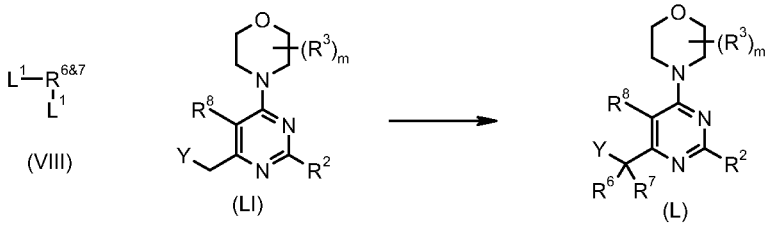
A compound of formula (XLIX) may be prepared from a compound of formula (XLVIII) by hydrolysis, for example with sodium hydroxide in a suitable solvent such as an ethanol:water mix.



(XLIX) (XLVIII)

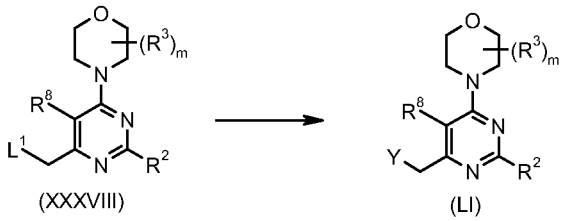
A compound of formula (L), wherein Y = $R^1R^4NC(O)$-, ROC(O)-, NC-, may be prepared by the reaction of a compound of formula (VIII) with a compound of formula (LI), wherein $R^{6\ \&\ 7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon

may be optionally replaced with O, N or S, and wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide.



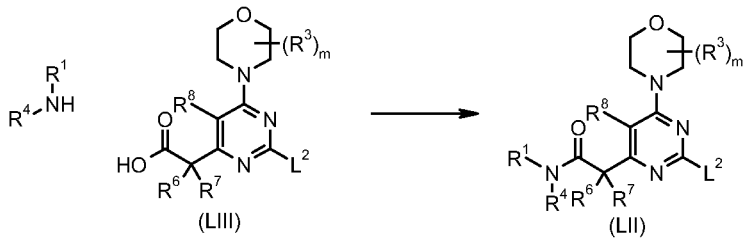
(VIII) (LI) (L)

A compound of formula (LI), wherein Y = NC-, HOC(O)-, may be prepared by the reaction of a compound of formula (XXXVIII) with a suitable nucleophile, such as for example sodium cyanide or for example tris(phenylthio)methane anion followed by a suitable hydrolysis.



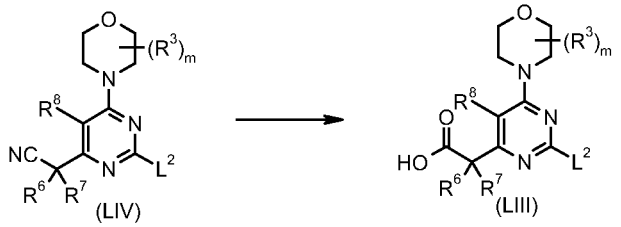
(XXXVIII) (LI)

A compound of formula (LII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), may be prepared by the reaction of an amine of formula R^1R^4NH with a compound of formula (LIII) in the presence of a suitable coupling agent, such as HATU, or following suitable activation of (LIII), such as the conversion to an acid chloride.

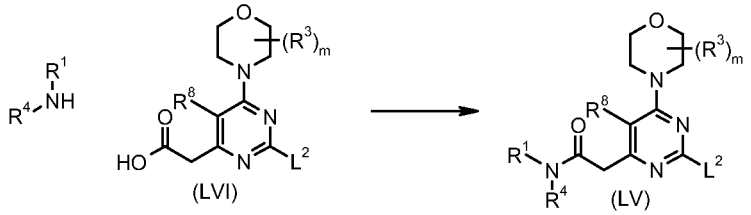


(LIII) (LII)

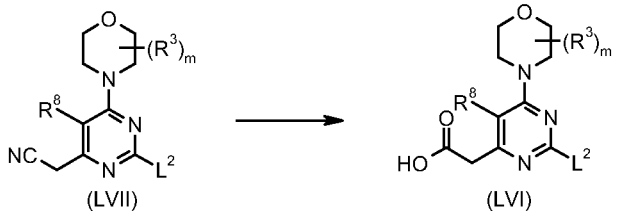
A compound of formula (LIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), may be prepared from a compound of formula (LIV) by hydrolysis, for example with sodium hydroxide in a suitable solvent such as an ethanol:water mix.



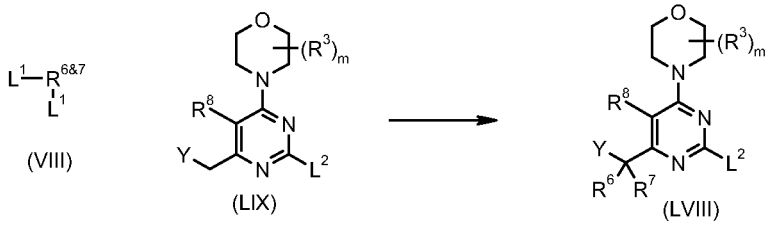
A compound of formula (LV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), may be prepared by the reaction of an amine of formula R^1R^4NH with a compound of formula (LVI) in the presence of a suitable coupling agent, such as HATU, or following suitable activation of (LVI), such as the conversion to an acid chloride.



A compound of formula (LVI), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), may be prepared from a compound of formula (LVII) by hydrolysis, for example with sodium hydroxide in a suitable solvent such as an ethanol:water mix.

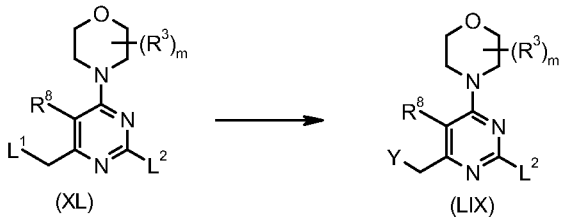


A compound of formula (LVIII), wherein Y = $R^1R^4NC(O)$-, ROC(O)-, NC-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), may be prepared by the reaction of a compound of formula (VIII) with a compound of formula (LIX), wherein $R^{6\,\&\,7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide.



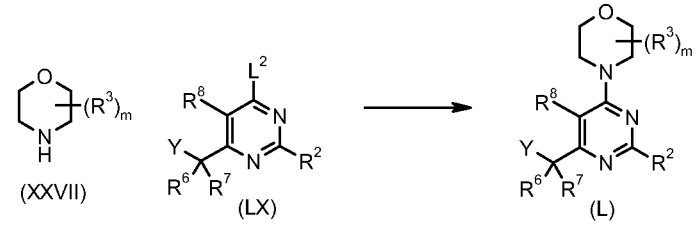
(VIII) (LIX) (LVIII)

A compound of formula (LIX), wherein Y = NC-, HOC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), may be prepared by the reaction of a compound of formula (XL) with a suitable nucleophile, such as for example sodium cyanide or for example tris(phenylthio)methane anion followed by a suitable hydrolysis.



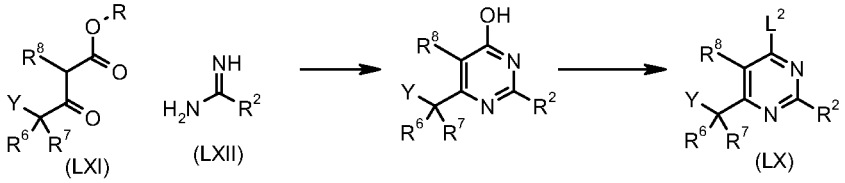
(XL) (LIX)

A compound of formula (L), wherein Y = NC-, ROC(O)-, may be prepared by the reaction of a compound of formula (XXVII) with a compound of formula (LX), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.

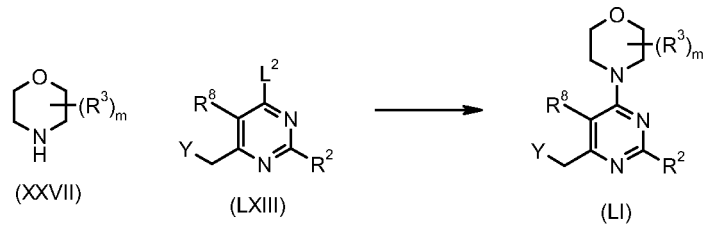


(XXVII) (LX) (L)

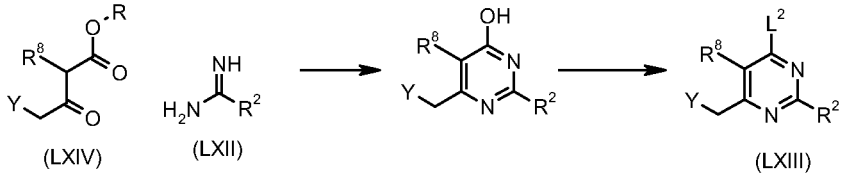
A compound of formula (LX), wherein Y = NC-, ROC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.) may be prepared by the reaction of a compound of formula (LXI) with a compound of formula (LXII) and subsequent conversion of the OH group to a suitable leaving group, such as by reaction with *N*-phenyltrifluoromethanesulfonimide in the presence of a suitable base such as DBU and a suitable solvent such as dichloromethane.



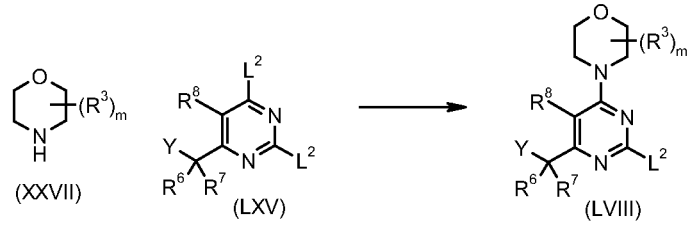
A compound of formula (LI), wherein Y = NC-, ROC(O)-, may be prepared by the reaction of a compound of formula (XXVII) with a compound of formula (LXIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



A compound of formula (LXIII), wherein Y = NC-, ROC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.) may be prepared by the reaction of a compound of formula (LXIV) with a compound of formula (LXII) and subsequent conversion of the OH group to a suitable leaving group, such as by reaction with *N*-phenyltrifluoromethanesulfonimide in the presence of a suitable base such as DBU and a suitable solvent such as dichloromethane.

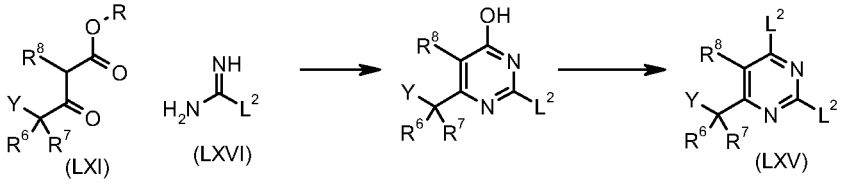


A compound of formula (LVIII), wherein Y = NC-, ROC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.) may be prepared by the reaction of a compound of formula (XXVII) with a compound of formula (LXV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



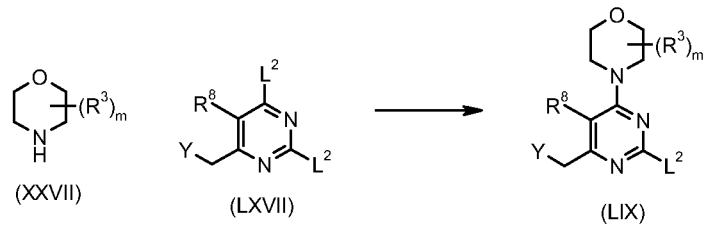
(XXVII) (LXV) (LVIII)

A compound of formula (LXV), wherein Y = NC-, ROC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.) may be prepared by the reaction of a compound of formula (LXI) with a compound of formula (LXVI) and subsequent conversion of the OH group to a suitable leaving group, such as by reaction with *N*-phenyltrifluoromethanesulfonimide in the presence of a suitable base such as DBU and a suitable solvent such as dichloromethane.



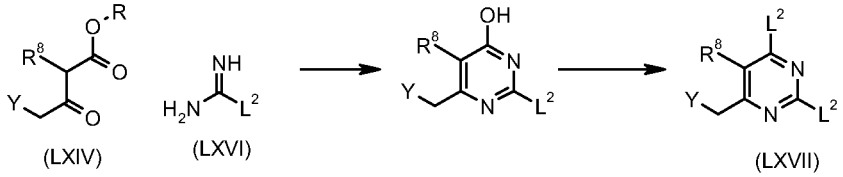
(LXI) (LXVI) (LXV)

A compound of formula (LIX), wherein Y = NC-, ROC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.) may be prepared by the reaction of a compound of formula (XXVII) with a compound of formula (LXVII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.), optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



(XXVII) (LXVII) (LIX)

A compound of formula (LXVII), wherein Y = NC-, ROC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.) may be prepared by the reaction of a compound of formula (LXIV) with a compound of formula (LXVI) and subsequent conversion of the OH group to a suitable leaving group, such as by reaction with *N*-phenyltrifluoromethanesulfonimide in the presence of a suitable base such as DBU and a suitable solvent such as dichloromethane.



(LXIV) (LXVI) (LXVII)

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. For example compounds of formula (I) may be converted into further compounds of formula (I) by standard aromatic substitution reactions or by conventional functional group modifications. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulfinyl or alkylsulfonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl

group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Many of the intermediates defined herein are novel and these are provided as a further feature of the invention.

Biological Assays

The following assays can be used to measure the effects of the compounds of the present invention as mTOR kinase inhibitors, as PI3 kinase inhibitors, as inhibitors *in vitro* of the activation of PI3 kinase signalling pathways and as inhibitors *in vitro* of the proliferation of MDA-MB-468 human breast adenocarcinoma cells.

(a)(i) *In Vitro* mTOR Kinase Assay

The assay used AlphaScreen technology (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) to determine the ability of test compounds to inhibit phosphorylation by recombinant mTOR.

A C-terminal truncation of mTOR encompassing amino acid residues 1362 to 2549 of mTOR (EMBL Accession No. L34075) was stably expressed as a FLAG-tagged fusion in HEK293 cells as described by Vilella-Bach *et al.*, Journal of Biochemistry, 1999, 274, 4266-4272. The HEK293 FLAG-tagged mTOR (1362-2549) stable cell line was routinely maintained at 37°C with 5% CO_2 up to a confluency of 70-90% in Dulbecco's modified Eagle's growth medium (DMEM; Invitrogen Limited, Paisley, UK Catalogue No. 41966-029) containing 10% heat-inactivated foetal calf serum (FCS; Sigma, Poole, Dorset, UK, Catalogue No. F0392), 1% L-glutamine (Gibco, Catalogue No. 25030-024) and 2 mg/ml Geneticin (G418 sulfate; Invitrogen Limited, UK Catalogue No. 10131-027). Following expression in the mammalian HEK293 cell line, expressed protein was purified using the FLAG epitope tag using standard purification techniques.

Test compounds were prepared as 10 mM stock solutions in DMSO and diluted into water as required to give a range of final assay concentrations. Aliquots (2 µl) of each compound dilution were placed into a well of a Greiner 384-well low volume (LV) white polystyrene plate (Greiner Bio-one). A 30 µl mixture of recombinant purified mTOR enzyme, 1 µM biotinylated peptide substrate (Biotin-Ahx-Lys-Lys-Ala-Asn-Gln-Val-Phe-Leu-Gly-Phe-Thr-Tyr-Val-Ala-Pro-Ser-Val-Leu-Glu-Ser-Val-Lys-Glu-NH_2; Bachem UK Ltd), ATP (20 µM) and a buffer solution [comprising Tris-HCl pH7.4 buffer (50 mM), EGTA (0.1 mM), bovine serum albumin (0.5 mg/mL), DTT (1.25 mM) and manganese chloride (10 mM)] was agitated at room temperature for 90 minutes.

Control wells that produced a maximum signal corresponding to maximum enzyme activity were created by using 5% DMSO instead of test compound. Control wells that produced a minimum signal corresponding to fully inhibited enzyme were created by adding

EDTA (83 mM) instead of test compound. These assay solutions were incubated for 2 hours at room temperature.

Each reaction was stopped by the addition of 10 µl of a mixture of EDTA (50 mM), bovine serum albumin (BSA; 0.5 mg/mL) and Tris-HCl pH7.4 buffer (50 mM) containing p70 S6 Kinase (T389) 1A5 Monoclonal Antibody (Cell Signalling Technology, Catalogue No. 9206B) and AlphaScreen Streptavidin donor and Protein A acceptor beads (200 ng; Perkin Elmer, Catalogue No. 6760002B and 6760137R respectively) were added and the assay plates were left for about 20 hours at room temperature in the dark. The resultant signals arising from laser light excitation at 680 nm were read using a Packard Envision instrument.

Phosphorylated biotinylated peptide is formed *in situ* as a result of mTOR mediated phosphorylation. The phosphorylated biotinylated peptide that is associated with AlphaScreen Streptavidin donor beads forms a complex with the p70 S6 Kinase (T389) 1A5 Monoclonal Antibody that is associated with Alphascreen Protein A acceptor beads. Upon laser light excitation at 680 nm, the donor bead : acceptor bead complex produces a signal that can be measured. Accordingly, the presence of mTOR kinase activity results in an assay signal. In the presence of an mTOR kinase inhibitor, signal strength is reduced.

mTOR enzyme inhibition for a given test compound was expressed as an IC_{50} value.

(a)(ii) *In Vitro* mTOR Kinase Assay (Echo)

The assay used AlphaScreen technology (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) to determine the ability of test compounds to inhibit phosphorylation by recombinant mTOR.

A C-terminal truncation of mTOR encompassing amino acid residues 1362 to 2549 of mTOR (EMBL Accession No. L34075) was stably expressed as a FLAG-tagged fusion in HEK293 cells as described by Vilella-Bach *et al.*, Journal of Biochemistry, 1999, 274, 4266-4272. The HEK293 FLAG-tagged mTOR (1362-2549) stable cell line was routinely maintained at 37°C with 5% CO_2 up to a confluency of 70-90% in Dulbecco's modified Eagle's growth medium (DMEM; Invitrogen Limited, Paisley, UK Catalogue No. 41966-029) containing 10% heat-inactivated foetal calf serum (FCS; Sigma, Poole, Dorset, UK, Catalogue No. F0392), 1% L-glutamine (Gibco, Catalogue No. 25030-024) and 2 mg/ml Geneticin (G418 sulfate; Invitrogen Limited, UK Catalogue No. 10131-027). Following expression in the mammalian HEK293 cell line, expressed protein was purified using the FLAG epitope tag using standard purification techniques.

Test compounds were prepared as 10 mM stock solutions in DMSO and diluted in into waterDMSO as required to give a range of final assay concentrations. Aliquots (120nl2 µl) of each compound dilution were acoustically dispensedplaced using a Labcyte Echo 550 into a well of a Greiner 384-well low volume (LV) white polystyrene plate (Greiner Bio-one). A 1230 µl mixture of recombinant purified mTOR enzyme, 1 µM biotinylated peptide substrate (Biotin-Ahx-Lys-Lys-Ala-Asn-Gln-Val-Phe-Leu-Gly-Phe-Thr-Tyr-Val-Ala-Pro-Ser-Val-Leu-Glu-Ser-Val-Lys-Glu-NH_2; Bachem UK Ltd), ATP (20 µM) and a buffer solution [comprising Tris-HCl pH7.4 buffer (50 mM), EGTA (0.1 mM), bovine serum albumin (0.5 mg/mL), DTT (1.25 mM) and manganese chloride (10 mM)] was incubated at room temperature for 12090 minutes.

Control wells that produced a maximum signal corresponding to maximum enzyme activity were created by using 1005% DMSO instead of test compound. Control wells that produced a minimum signal corresponding to fully inhibited enzyme were created by adding LY294002EDTA (100uM83 mM) compound. These assay solutions were incubated for 2 hours at room temperature.

Each reaction was stopped by the addition of 510 µl of a mixture of EDTA (50 mM), bovine serum albumin (BSA; 0.5 mg/mL) and Tris-HCl pH7.4 buffer (50 mM) containing p70 S6 Kinase (T389) 1A5 Monoclonal Antibody (Cell Signalling Technology, Catalogue No. 9206B) and AlphaScreen Streptavidin donor and Protein A acceptor beads (200 ng; Perkin Elmer, Catalogue No. 6760002B and 6760137R respectively) were added and the assay plates were left overnight at room temperature in the dark. The resultant signals arising from laser light excitation at 680 nm were read using a Packard Envision instrument.

Phosphorylated biotinylated peptide is formed *in situ* as a result of mTOR mediated phosphorylation. The phosphorylated biotinylated peptide that is associated with AlphaScreen Streptavidin donor beads forms a complex with the p70 S6 Kinase (T389) 1A5 Monoclonal Antibody that is associated with Alphascreen Protein A acceptor beads. Upon laser light excitation at 680 nm, the donor bead : acceptor bead complex produces a signal that can be measured. Accordingly, the presence of mTOR kinase activity results in an assay signal. In the presence of an mTOR kinase inhibitor, signal strength is reduced.

mTOR enzyme inhibition for a given test compound was expressed as an IC_{50} value.

(b)(i) *In Vitro* PI3K Enzyme Assay

The assay used AlphaScreen technology (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) to determine the ability of test compounds to inhibit phosphorylation by recombinant Type I PI3K enzymes of the lipid PI(4,5)P2.

DNA fragments encoding human PI3K catalytic and regulatory subunits were isolated from cDNA libraries using standard molecular biology and PCR cloning techniques. The selected DNA fragments were used to generate baculovirus expression vectors. In particular, full length DNA of each of the p110α, p110β and p110δ Type Ia human PI3K p110 isoforms (EMBL Accession Nos. HSU79143, S67334, Y10055 for p110α, p110β and p110δ respectively) were sub-cloned into a pDEST10 vector (Invitrogen Limited, Fountain Drive, Paisley, UK). The vector is a Gateway-adapted version of Fastbac1 containing a 6-His epitope tag. A truncated form of Type Ib human PI3K p110γ isoform corresponding to amino acid residues 144-1102 (EMBL Accession No. X8336A) and the full length human p85α regulatory subunit (EMBL Accession No. HSP13KIN) were also sub-cloned into pFastBac1 vector containing a 6-His epitope tag. The Type Ia p110 constructs were co-expressed with the p85α regulatory subunit. Following expression in the baculovirus system using standard baculovirus expression techniques, expressed proteins were purified using the His epitope tag using standard purification techniques.

DNA corresponding to amino acids 263 to 380 of human general receptor for phosphoinositides (Grp1) PH domain was isolated from a cDNA library using standard molecular biology and PCR cloning techniques. The resultant DNA fragment was sub-cloned into a pGEX 4T1 *E. coli* expression vector containing a GST epitope tag (Amersham Pharmacia Biotech, Rainham, Essex, UK) as described by Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245). The GST-tagged Grp1 PH domain was expressed and purified using standard techniques.

Test compounds were prepared as 10 mM stock solutions in DMSO and diluted into water as required to give a range of final assay concentrations. Aliquots (2 μl) of each compound dilution were placed into a well of a Greiner 384-well low volume (LV) white polystyrene plate (Greiner Bio-one, Brunel Way, Stonehouse, Gloucestershire, UK Catalogue No. 784075). A mixture of each selected recombinant purified PI3K enzyme (15 ng), DiC8-PI(4,5)P2 substrate (40 μM; Cell Signals Inc., Kinnear Road, Columbus, USA, Catalogue No. 901), adenosine triphosphate (ATP; 4 μM) and a buffer solution [comprising Tris-HCl pH7.6

buffer (40 mM, 10 µl), 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS; 0.04%), dithiothreitol (DTT; 2 mM) and magnesium chloride (10 mM)] was agitated at room temperature for 20 minutes.

Control wells that produced a minimum signal corresponding to maximum enzyme activity were created by using 5% DMSO instead of test compound. Control wells that produced a maximum signal corresponding to fully inhibited enzyme were created by adding wortmannin (6 µM; Calbiochem / Merck Bioscience, Padge Road, Beeston, Nottingham, UK, Catalogue No. 681675) instead of test compound. These assay solutions were also agitated for 20 minutes at room temperature.

Each reaction was stopped by the addition of 10 µl of a mixture of EDTA (100 mM), bovine serum albumin (BSA, 0.045 %) and Tris-HCl pH7.6 buffer (40 mM).

Biotinylated-DiC8-PI(3,4,5)P3 (50 nM; Cell Signals Inc., Catalogue No. 107), recombinant purified GST-Grp1 PH protein (2.5 nM) and AlphaScreen Anti-GST donor and acceptor beads (100 ng; Packard Bioscience Limited, Station Road, Pangbourne, Berkshire, UK, Catalogue No. 6760603M) were added and the assay plates were left for about 5 to 20 hours at room temperature in the dark. The resultant signals arising from laser light excitation at 680 nm were read using a Packard AlphaQuest instrument.

PI(3,4,5)P3 is formed *in situ* as a result of PI3K mediated phosphorylation of PI(4,5)P2. The GST-Grp1 PH domain protein that is associated with AlphaScreen Anti-GST donor beads forms a complex with the biotinylated PI(3,4,5)P3 that is associated with Alphascreen Streptavidn acceptor beads. The enymatically-produced PI(3,4,5)P3 competes with biotinylated PI(3,4,5)P3 for binding to the PH domain protein. Upon laser light excitation at 680 nm, the donor bead : acceptor bead complex produces a signal that can be measured. Accordingly, PI3K enzme activity to form PI(3,4,5)P3 and subsequent competition with biotinylated PI(3,4,5)P3 results in a reduced signal. In the presence of a PI3K enzyme inhibitor, signal strength is recovered.

PI3K enzyme inhibition for a given test compound was expressed as an IC_{50} value.

(b)(ii) *In Vitro* PI3K Enzyme Assay (Echo)

The assay used AlphaScreen technology (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) to determine the ability of test compounds to inhibit phosphorylation by recombinant Type I PI3K enzymes of the lipid PI(4,5)P2.

DNA fragments encoding human PI3K catalytic and regulatory subunits were isolated from cDNA libraries using standard molecular biology and PCR cloning techniques. The selected DNA fragments were used to generate baculovirus expression vectors. In particular, full length DNA of each of the p110α, p110β and p110δ Type Ia human PI3K p110 isoforms (EMBL Accession Nos. HSU79143, S67334, Y10055 for p110α, p110β and p110δ respectively) were sub-cloned into a pDEST10 vector (Invitrogen Limited, Fountain Drive, Paisley, UK). The vector is a Gateway-adapted version of Fastbac1 containing a 6-His epitope tag. A truncated form of Type Ib human PI3K p110γ isoform corresponding to amino acid residues 144-1102 (EMBL Accession No. X8336A) and the full length human p85α regulatory subunit (EMBL Accession No. HSP13KIN) were also sub-cloned into pFastBac1 vector containing a 6-His epitope tag. The Type Ia p110 constructs were co-expressed with the p85α regulatory subunit. Following expression in the baculovirus system using standard baculovirus expression techniques, expressed proteins were purified using the His epitope tag using standard purification techniques.

DNA corresponding to amino acids 263 to 380 of human general receptor for phosphoinositides (Grp1) PH domain was isolated from a cDNA library using standard molecular biology and PCR cloning techniques. The resultant DNA fragment was sub-cloned into a pGEX 4T1 *E. coli* expression vector containing a GST epitope tag (Amersham Pharmacia Biotech, Rainham, Essex, UK) as described by Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245). The GST-tagged Grp1 PH domain was expressed and purified using standard techniques.

Test compounds were prepared as 10 mM stock solutions in DMSO and diluted in DMSO to wateras required to give a range of final assay concentrations. Aliquots (120nl2 μl) of each compound dilution were acoustically dispensed using a Labcyte Echo 550 placed into a well of a Greiner 384-well low volume (LV) white polystyrene plate (Greiner Bio-one, Brunel Way, Stonehouse, Gloucestershire, UK Catalogue No. 784075). A mixture of each selected recombinant purified PI3K enzyme (15 ng), DiC8-PI(4,5)P2 substrate (40 μM; Cell Signals Inc., Kinnear Road, Columbus, USA, Catalogue No. 901), adenosine triphosphate (ATP; 4 μM) and a buffer solution [comprising Tris-HCl pH7.6 buffer (40 mM, 10 μl), 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS; 0.04%), dithiothreitol

(DTT; 2 mM) and magnesium chloride (10 mM)] was agitatedincubated at room temperature for 20 minutes.

Control wells that produced a minimum signal corresponding to maximum enzyme activity were created by using 1005% DMSO instead of test compound. Control wells that produced a maximum signal corresponding to fully inhibited enzyme were created by adding Wwortmannin (6 μM; Calbiochem / Merck Bioscience, Padge Road, Beeston, Nottingham, UK, Catalogue No. 681675) instead of test compound. These assay solutions were also incubatedagitated for 20 minutes at room temperature.

Each reaction was stopped by the addition of 10 10μl of a mixture of EDTA (100 mM), bovine serum albumin (BSA, 0.045 %) and Tris-HCl pH7.6 buffer (40 mM).

Biotinylated-DiC8-PI(3,4,5)P3 (50 nM; Cell Signals Inc., Catalogue No. 107), recombinant purified GST-Grp1 PH protein (2.5 nM) and AlphaScreen Anti-GST donor and acceptor beads (100 ng; Packard Bioscience Limited, Station Road, Pangbourne, Berkshire, UK, Catalogue No. 6760603M) were added and the assay plates were left for about 5 to overnight

20 hours at room temperature in the dark. The resultant signals arising from laser light excitation at 680 nm were read using a Packard AlphaQuest instrument.

PI(3,4,5)P3 is formed *in situ* as a result of PI3K mediated phosphorylation of PI(4,5)P2. The GST-Grp1 PH domain protein that is associated with AlphaScreen Anti-GST donor beads forms a complex with the biotinylated PI(3,4,5)P3 that is associated with Alphascreen Streptavidn acceptor beads. The enymatically-produced PI(3,4,5)P3 competes with biotinylated PI(3,4,5)P3 for binding to the PH domain protein. Upon laser light excitation at 680 nm, the donor bead : acceptor bead complex produces a signal that can be measured. Accordingly, PI3K enzme activity to form PI(3,4,5)P3 and subsequent competition with biotinylated PI(3,4,5)P3 results in a reduced signal. In the presence of a PI3K enzyme inhibitor, signal strength is recovered.

PI3K enzyme inhibition for a given test compound was expressed as an IC_{50} value.

(c) *In Vitro* phospho-Ser473 Akt assay

This assay determines the ability of test compounds to inhibit phosphorylation of Serine 473 in Akt as assessed using Acumen Explorer technology (Acumen Bioscience Limited), a plate reader that can be used to rapidly quantitate features of images generated by laser-scanning.

A MDA-MB-468 human breast adenocarcinoma cell line (LGC Promochem, Teddington, Middlesex, UK, Catalogue No. HTB-132) was routinely maintained at 37°C with 5% CO_2 up to a confluency of 70–90% in DMEM containing 10% heat-inactivated FCS and 1% L-glutamine.

For the assay, the cells were detached from the culture flask using 'Accutase' (Innovative Cell Technologies Inc., San Diego, CA, USA; Catalogue No. AT104) using standard tissue culture methods and resuspended in media to give $1.7x10^5$ cells per mL. Aliquots (90 µl) were seeded into each of the inner 60 wells of a black Packard 96 well plate (PerkinElmer, Boston, MA, USA; Catalogue No. 6005182) to give a density of ~15000 cells per well. Aliquots (90 µl) of culture media were placed in the outer wells to prevent edge effects. The cells were incubated overnight at 37°C with 5% CO_2 to allow them to adhere.

On day 2, the cells were treated with test compounds and incubated for 2 hours at 37°C with 5% CO_2. Test compounds were prepared as 10 mM stock solutions in DMSO and serially diluted as required with growth media to give a range of concentrations that were 10-fold the required final test concentrations. Aliquots (10 µl) of each compound dilution were placed in a well (in triplicate) to give the final required concentrations. As a minimum reponse control, each plate contained wells having a final concentration of 100 µM LY294002 (Calbiochem, Beeston, UK, Catalogue No. 440202). As a maximum response control, wells contained 1% DMSO instead of test compound. Following incubation, the contents of the plates were fixed by treatment with a 1.6% aqueous formaldehyde solution (Sigma, Poole, Dorset, UK, Catalogue No. F1635) at room temperature for 1 hour.

All subsequent aspiration and wash steps were carried out using a Tecan 96 well plate washer (aspiration speed 10 mm/sec). The fixing solution was removed and the contents of the plates were washed with phosphate-buffered saline (PBS; 50 µl; Gibco, Catalogue No. 10010015). The contents of the plates were treated for 10 minutes at room temperature with an aliquot (50 µl) of a cell permeabilisation buffer consisting of a mixture of PBS and 0.5% Tween-20. The 'permeabilisation' buffer was removed and non-specific binding sites were blocked by treatment for 1 hour at room temperature of an aliquot (50 µl) of a blocking buffer consisting of 5% dried skimmed milk ['Marvel' (registered trade mark); Premier Beverages, Stafford, GB] in a mixture of PBS and 0.05% Tween-20. The 'blocking' buffer was removed and the cells were incubated for 1 hour at room temperature with rabbit anti phospho-Akt

(Ser473) antibody solution (50 µl per well; Cell Signalling, Hitchin, Herts, U.K., Catalogue No 9277) that had been diluted 1:500 in 'blocking' buffer. Cells were washed three times in a mixture of PBS and 0.05% Tween-20. Subsequently, cells were incubated for 1 hour at room temperature with Alexafluor488 labelled goat anti-rabbit IgG (50 µl per well; Molecular Probes, Invitrogen Limited, Paisley, UK, Catalogue No. A11008) that had been diluted 1:500 in 'blocking' buffer. Cells were washed 3 times with a mixture of PBS and 0.05% Tween-20. An aliquot of PBS (50 µl) was added to each well and the plates were sealed with black plate sealers and the fluorescence signal was detected and analysed.

Fluorescence dose response data obtained with each compound were analysed and the degree of inhibition of Serine 473 in Akt was expressed as an IC_{50} value.

(d) *In Vitro* MDA-MB-468 human breast adenocarcinoma Proliferation Assay

This assay determines the ability of test compounds to inhibit cell proliferation as assessed using Cellomics Arrayscan technology. A MDA-MB-468 human breast adenocarcinoma cell line (LGC Promochem, Catalogue No. HTB-132) was routinely maintained as described in Biological Assay (b) herein.

For the proliferation assay, the cells were detached from the culture flask using Accutase and seeded into the inner 60 wells of a black Packard 96 well plate at a density of 8000 cells per well in 100 µl of complete growth media. The outer wells contained 100 µl of sterile PBS. The cells were incubated overnight at 37°C with 5% CO_2 to allow them to adhere.

On day 2, the cells were treated with test compounds and incubated for 48 hours at 37°C with 5% CO_2. Test compounds were prepared as 10 mM stock solutions in DMSO and serially diluted as required with growth media to give a range of test concentrations. Aliquots (50 µl) of each compound dilution were placed in a well and the cells were incubated for 2 days at 37°C with 5% CO_2. Each plate contained control wells without test compound.

On day 4, BrdU labelling reagent (Sigma, Catalogue No. B9285) at a final dilution of 1:1000 was added and the cells were incubated for 2 hours at 37°C. The medium was removed and the cells in each well were fixed by treatment with 100 µl of a mixture of ethanol and glacial acetic acid (90% ethanol, 5% glacial acetic acid and 5% water) for 30 minutes at room temperature. The cells in each well were washed twice with PBS (100 µl). Aqueous hydrochloric acid (2M, 100 µl) was added to each well. After 20 minutes at room temperature, the cells were washed twice with PBS. Hydrogen peroxide (3%, 50 µl; Sigma, Catalogue No.

H1009) was added to each well. After 10 minutes at room temperature, the wells were washed again with PBS.

BrdU incorporation was detected by incubation for 1 hour at room temperature with mouse anti-BrdU antibody (50 µl; Caltag, Burlingame, CA, US; Catalogue No. MD5200) that was diluted 1:40 in PBS containing 1% BSA and 0.05% Tween-20. Unbound antibody was removed with two washes of PBS. For visualisation of incorporated BrdU, the cells were treated for 1 hour at room temperature with PBS (50 µl) and 0.05% Tween-20 buffer containing a 1:1000 dilution of Alexa fluor 488–labelled goat anti-mouse IgG. For visualisation of the cell nucleus, a 1:1000 dilution of Hoechst stain (Molecular Probes, Catalogue No. H3570) was added. Each plate was washed in turn with PBS. Subsequently, PBS (100 µl) was added to each well and the plates were analysed using a Cellomics array scan to assess total cell number and number of BrdU positive cells.

Fluorescence dose response data obtained with each compound were analysed and the degree of inhibition of MDA-MB-468 cell growth was expressed as an IC_{50} value.

Although the pharmacological properties of the compounds of formula (I) vary with structural change as expected, in general, it is believed that activity possessed by compounds of formula (I) may be demonstrated at the following concentrations or doses in one or more of the above tests (a) to (d) :-

Test (a)(i):- IC_{50} versus mTOR kinase at less than 10 µM, in particular 0.001 - 0.5 µM for many compounds; for example 2b the IC_{50} was measured on three occasions, the values were 0.059, 0.005 and 0.023µM.

Test (b)(i):- IC_{50} versus p110γ Type Ib human PI3K at less than 10 µM, in particular 0.001 - 0.5 µM for many compounds; and IC_{50} versus p110α Type Ia human PI3K at less than 10 µM, in particular 0.001 - 0.5 µM for many compounds;
for example 2b the IC50 was measured, the value was 1.044 µM.

Test (c):- IC_{50} versus Serine 473 in Akt at less than 10 µM, in particular 0.1 - 20 µM for many compounds); for example 2b the IC_{50} was measured on two occasions, the values were 0.052 and 0.025 µM.

Test (d):- IC_{50} at less than 20 µM.

The following examples were tested in enzyme assay Test (a)(ii):

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
1	0.00276	23l	0.00888	52	0.0184
1a	0.00279	23m	0.0577	52a	0.0103
2	0.0015	24	0.00517	52b	0.0307
2a	0.0932	25	0.00155	52c	0.0296
2b	0.000169	25a	0.00224	52d	0.00588
2c	0.00186	25b	0.000817	53	0.00218
2d	0.0239	25c	0.00385	53a	0.00229
2e	0.279	25d	0.00152	53b	0.000669
2f	0.00433	25e	0.000277	53c	0.000688
2g	0.000231	25f	0.0547	53d	0.0031
2h	0.000272	25g	0.00143	53e	0.00198
2i	0.00207	25h	0.000993	53f	0.00634
2j	0.012	25i	0.001	54	0.00217
2k	0.00381	25j	0.00576	54a	0.00918
2l	0.0116	25k	0.00292	54b	0.00317
2m	0.00589	25l	0.000956	54c	0.00453
2n	0.00844	25m	0.00025	54d	0.00882
2o	0.000403	26	0.00605	54e	0.00762
2p	0.0027	26a	0.00672	54f	0.0107
2q	0.000379	26b	0.0039	55	0.00296
2r	0.00103	26c	0.119	55a	0.0213
2s	0.00155	26d	0.0012	55b	0.0161
2t	0.000656	26e	0.00395	55c	0.0189
2u	0.00118	26f	0.00457	55d	0.0351
2v	0.00866	26g	0.00746	55e	0.0204
2w	0.0685	26h	0.004	55f	0.0156
2x	0.00164	27	0.00111	56	0.00231
2y	0.23	27a	0.00388	56a	0.00226
2z	0.0181	27b	0.00425	56b	0.00165

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
2aa	0.0274	27c	0.014	56c	0.00623
2ab	0.0553	27d	0.00307	56d	0.0043
2ac	0.00641	27e	0.000351	57	0.0119
2ad	0.000705	27f	0.000997	57a	0.0104
2ae	0.00072	27g	0.0213	57b	0.00457
2af	0.0462	27h	0.000244	57c	0.00695
2ag	0.0149	27i	0.00302	57d	0.01
3	0.00195	27j	0.00761	57e	0.00728
3a	0.00445	27k	0.00462	57f	0.0106
3b	0.00385	27l	0.00112	57g	0.0585
3c	0.0124	27m	0.00144	58	0.00115
3d	0.0135	28	0.00187	58a	0.00339
3e	0.00166	28a	0.00253	58b	0.002
3f	0.0214	28b	0.00149	58c	0.00327
3g	0.00126	28c	0.00847	58d	0.00293
3h	0.0165	28d	0.00237	58e	0.00256
3i	0.000932	28e	0.000434	58f	0.00267
3j	0.00422	28f	0.0674	58g	0.0102
3k	0.00227	28g	0.00118	59	0.00882
3l	0.00257	28h	0.00093	59a	0.0222
3m	0.000497	28i	0.00153	59b	0.00993
3n	0.0396	28j	0.00557	59c	0.0226
3o	0.00596	28k	0.000954	59d	0.032
3p	0.193	28l	0.000442	59e	0.293
3q	0.00839	29	0.0042	59f	0.0491
3r	0.0488	30	0.025	59g	0.101
3s	0.0263	31	0.00452	60	0.012
3t	0.00479	31a	0.00265	60a	0.0191
3u	0.000604	31b	0.00497	60b	0.00862

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
3w	0.00089	31c	0.00131	60c	0.00695
4	0.000699	31d	0.00955	60d	0.0183
4a	0.00217	31e	0.00107	60e	0.0116
4b	0.00203	31f	0.0016	60f	0.0173
4c	0.0169	31g	0.00323	61	0.0269
4d	0.01	31h	0.000209	61a	0.0326
4e	0.000767	31i	0.00326	61b	0.0136
4f	0.01	31j	0.00103	61c	0.0211
4g	0.0626	31k	0.00191	61d	0.0438
4h	0.00146	31l	0.214	61e	0.0237
4i	0.0115	31m	0.00591	61f	0.0328
4j	0.00379	32	0.00315	62	0.00205
4k	0.00905	32a	0.0425	62a	0.0393
4l	0.00369	32b	0.00829	62b	0.00546
4m	0.00245	32c	0.00288	62c	0.0375
4n	0.0392	32d	0.0131	62d	0.022
5	0.000802	33	0.00929	63	0.0725
5a	0.000289	33a	0.0584	64	0.00785
5b	0.00052	33b	0.012	64a	0.0052
5c	0.00681	33c	0.00258	64b	0.00678
5d	0.00274	33d	0.133	64c	0.00215
5e	0.000864	34	0.00405	64d	0.0067
5f	0.00485	34a	0.0387	64e	0.00537
5g	0.0668	34b	0.0109	64f	0.00521
5h	0.00234	34c	0.00345	64g	0.0342
5i	0.00988	34d	0.0863	64h	0.00148
5j	0.000173	35	0.00531	64i	0.00135
5k	0.00333	35a	0.00552	64j	0.0012
5l	0.000237	35b	0.000577	64k	0.00144

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
5m	0.000604	35c	0.108	64l	0.00111
5n	0.00828	35d	0.00411	64m	0.0408
6	0.001	36a	0.142	64n	0.0161
6a	0.00293	36b	0.00179	64o	0.00345
6b	0.00612	36c	0.114	64p	0.00398
6c	0.00321	36d	0.00317	64q	0.00467
6d	0.000874	36e	0.00667	64r	0.00418
6e	0.0673	36f	0.00278	64s	0.00296
6f	0.000794	36g	0.00841	64t	0.0114
6g	0.00225	36h	0.00314	64u	0.0139
6h	0.000799	36i	0.0518	64v	0.146
6i	0.00462	36j	0.018	64w	0.0161
6j	0.00593	36k	0.0131	64x	0.00761
6k	0.00186	36l	0.0428	64y	0.0125
6l	0.00119	36m	0.0347	64z	0.00866
6m	0.000936	36n	0.0248	64aa	0.00388
7	0.00315	36o	0.00358	64ab	0.0094
7a	0.00231	36p	0.00161	64ac	0.00529
7b	0.0181	36q	0.0889	64ad	0.00298
7c	0.00646	36r	0.00733	64ae	0.00213
7d	0.0038	36s	0.00475	64af	0.00339
7e	0.00212	36t	0.194	64ag	0.00281
7f	0.00915	36u	0.00922	64ah	0.00684
7g	0.211	36v	0.467	64ai	0.00567
7h	0.0116	36w	0.11	64aj	0.00778
7i	0.0182	36x	0.182	64ak	0.00161
7j	0.0105	36y	0.00131	64al	0.00558
7k	0.00482	36z	0.00208	65	0.03
7l	0.00913	36aa	0.0749	65a	0.00688

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
7m	0.00504	36ab	0.011	65b	0.00342
8	0.000959	36ac	0.00441	65c	0.0151
8a	0.00096	36ad	0.0323	65d	0.00448
8b	0.00123	36ae	0.0151	65e	0.0114
8c	0.00185	36af	0.00275	66	0.00303
8d	0.00134	36ag	0.0013	66a	0.00415
8e	0.000342	36ah	0.00247	66b	0.0246
8f	0.00882	36ai	0.00561	67	0.001
8g	0.0784	36aj	0.00255	68	0.00141
8h	0.00176	36ak	0.00245	68a	0.00174
8i	0.0198	36al	0.0161	69	0.00788
8j	0.000751	36am	0.0259	70	0.002
8k	0.0173	36an	0.0104	71	0.0182
8l	0.00813	36ao	0.014	72	0.00432
8m	0.00136	36ap	0.0156	73	0.00744
9	0.0018	36aq	0.0157	74	0.00237
9a	0.0129	36ar	0.00945	74a	0.00398
9b	0.0215	36as	0.00911	74b	0.00244
9c	0.0483	36at	0.00639	74c	0.00314
9d	0.0151	36au	0.0121	74d	0.00279
9e	0.00187	36av	0.00995	74e	0.00506
9f	0.144	36aw	0.0164	74f	0.00399
9g	0.00127	36ax	0.0211	74g	0.00433
9h	0.0057	36ay	0.00117	74h	0.00321
9i	0.0024	36az	0.00105	74i	0.00925
9j	0.046	36ba	0.00167	75	0.029
9k	0.0115	36bb	0.00513	75a	0.0435
9l	0.00395	36bc	0.00285	75b	0.0381
9m	0.00401	36bd	0.00258	75c	0.0339

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
10	0.00448	36be	0.00376	75d	0.0399
10a	0.0395	36bf	0.00457	75e	0.037
10b	0.0266	36bg	0.00189	75f	0.0608
10c	0.147	36bh	0.00137	76	0.00687
10d	0.0432	36bi	0.00231	76a	0.00407
10e	0.00691	36bj	0.00106	76b	0.00719
10f	0.174	36bk	0.00433	76c	0.00319
10g	0.00156	36bl	0.00333	76d	0.00924
10h	0.0268	36bm	0.00193	76e	0.00566
10i	0.00591	36bn	0.00637	76f	0.00678
10j	0.11	36bo	0.0176	77	0.00821
10k	0.0502	36bp	0.00198	77a	0.00524
10l	0.0183	36bq	0.00131	77b	0.0086
10m	0.00497	36br	0.00188	77c	0.00437
11	0.00165	36bs	0.00264	77d	0.0101
11a	0.0059	36bt	0.00188	77e	0.00517
11b	0.00333	36bu	0.00118	77f	0.00919
11c	0.0247	36bv	0.00264	78	0.0418
11d	0.00642	36bw	0.00909	78a	0.0153
11e	0.00197	36bx	0.00269	78b	0.0333
11f	0.00337	36by	0.012	78c	0.0209
11g	0.313	36bz	0.0143	78d	0.0175
11h	0.00913	36ca	0.31	78e	0.0239
11i	0.0294	36cb	0.163	78f	0.0291
11j	0.0122	36cc	0.129	79	0.0186
11k	0.00332	36cd	0.147	79a	0.0222
11l	0.00356	36ce	0.42	79b	0.0109
11m	0.00437	36cf	0.286	79c	0.0299
12	0.00421	36cg	0.136	79d	0.0161

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
12a	0.00167	36ch	0.208	79e	0.0259
12b	0.00271	36ci	0.0386	79f	0.0398
12c	0.00751	36cj	0.00333	80	0.0197
12d	0.00155	36ck	2.62	80a	0.0146
12e	0.00459	36cl	0.0681	80b	0.0103
12f	0.35	36cm	0.00946	80c	0.00921
12g	0.00273	36cn	0.0858	80d	0.00951
12h	0.00392	36co	1.62	80e	0.0143
12i	0.000771	36cp	1.26	81	0.0137
12j	0.00167	36cq	0.114	82	0.00939
12k	0.0043	36cr	0.0435	82a	0.0265
12l	0.00138	36cs	1.17	82b	0.00757
12m	0.0101	36ct	0.00157	82c	0.0185
12n	0.238	36cu	0.0686	82d	0.0243
12o	0.00509	36v	0.259	82e	0.0208
12p	0.0014	36cw	0.0493	82f	0.0273
12q	0.00162	36cx	0.284	83	0.00346
12r	0.000991	36cy	0.0478	83a	0.00483
12s	0.117	36cz	0.0384	83b	0.0114
12t	0.0366	36da	0.0331	83c	0.0124
13	0.00357	36db	0.0209	83d	0.0472
13a	0.00341	36dc	0.00989	84	0.00956
13b	0.0037	36dd	0.00291	84a	0.00909
13c	0.00173	36de	0.00389	84b	0.00385
13d	0.00351	36df	0.00712	84c	0.00829
13e	0.0301	36dg	0.0164	84d	0.00959
13f	0.386	36dh	0.0034	84e	0.00818
13g	0.00479	36di	0.00923	84f	0.0134
13h	0.0106	36dj	0.00891	85	0.00477

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
13i	0.00275	36dk	0.00905	85a	0.00313
13j	0.0178	36dl	0.00399	85b	0.00526
13k	0.0179	36dm	0.0298	85c	0.00509
13l	0.0108	36dn	0.0138	85d	0.00323
13m	0.0532	36do	0.0277	85e	0.0183
13n	0.997	36dp	0.0106	85f	0.0202
13o	0.0287	36dq	0.0245	85g	0.0259
13p	0.00202	36dr	0.294	85h	0.0426
13q	0.00192	36ds	0.000973	85i	0.0153
13r	0.00198	36dt	0.00037	85j	0.0124
13s	0.00846	36du	0.0152	86	0.00247
13t	0.172	36dv	0.0043	86a	0.00522
13u	0.00477	36dw	0.00624	86b	0.00725
14	0.0465	36dx	0.00262	86c	0.00247
14a	0.0136	36dy	0.00636	86d	0.00382
14b	1.39	36dz	0.00277	86e	0.00223
14c	0.0401	36ea	0.00884	86f	0.00345
14d	0.0143	36eb	0.00311	87	0.00487
14e	0.11	36ec	0.00321	87a	0.0887
14f	0.189	36ed	0.00704	87b	0.0177
14g	0.0857	36ee	0.00958	87c	0.00775
14h	0.14	36ef	0.00841	87d	0.0177
14i	0.0339	36eg	0.00877	87e	0.0103
14j	0.0129	37a	0.026	87f	0.00907
14k	0.275	37b	0.0124	88	0.0321
14l	0.0137	37c	0.0033	88a	0.00448
14m	0.0143	37d	0.00439	88b	0.0567
14n	0.0363	37e	0.0049	88c	0.047
14o	0.0217	37f	0.12	88d	0.004

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
14p	0.537	37g	0.0179	88e	0.131
14q	0.0265	37h	0.0198	89	0.485
14r	0.0103	37i	0.00379	90	0.0189
14s	0.122	37j	0.0309	91	0.00498
14t	0.197	37k	0.0161	91a	0.00198
14u	0.123	37l	0.032	91b	0.00521
14v	0.0823	37m	0.0506	91c	0.00368
14w	0.208	37n	0.0393	91d	0.00356
14x	0.63	37o	0.033	92	0.00793
14y	0.152	37p	0.00534	92a	0.00551
14z	0.171	37q	0.00294	92b	0.00746
14aa	0.0186	37r	0.00162	92c	0.0078
15	0.00154	37s	0.00756	92d	0.00807
15a	0.000591	37t	0.00889	92e	0.00599
16	0.00142	37u	0.000395	92f	0.00625
16a	0.0101	37v	0.00549	93	0.00505
16b	0.00577	37w	0.00137	93a	0.00303
16c	0.0016	37x	0.00944	93b	0.0023
16d	0.00364	37y	0.00686	93c	0.0029
16e	0.0214	37z	0.00481	93d	0.000818
16f	0.0212	37aa	0.00567	93e	0.00541
16g	0.0176	37ab	0.00488	94a	0.0136
16h	0.186	37ac	0.0438	94b	0.0122
16i	0.845	37ad	0.00263	94c	0.0118
17	0.00116	37ae	0.00952	94d	0.011
17a	0.000942	37af	0.0233	94e	0.0135
17b	0.000584	37ag	0.0134	94f	0.0151
17c	0.00179	38	0.00131	94g	0.0127
18	0.00135	38a	0.000918	94h	0.0116

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
18a	0.00714	39	0.000351	94i	0.0121
18b	0.0147	39a	0.000502	94j	0.00605
18c	0.032	40	0.00436	94k	0.0106
18d	0.0151	40a	0.00221	95a	0.0139
18e	0.000654	41	0.0308	95b	0.019
18f	0.12	42	0.000705	95c	0.00706
18g	0.00123	42a	0.00261	95d	0.0126
18h	0.00664	42b	0.00535	95e	0.016
18i	0.00555	42c	0.0036	95f	0.0109
18j	0.0303	42d	0.000607	95g	0.0164
18k	0.0113	42e	0.00257	95h	0.013
18l	0.0102	42f	0.00264	95i	0.00479
18m	0.00315	42g	0.00401	95j	0.0131
19	0.00131	42h	0.00412	95k	0.0272
19a	0.00425	43	0.00539	95l	0.00109
19b	0.00119	43a	0.00479	95m	0.00202
19c	0.0214	43b	0.00751	95n	0.000668
19d	0.00318	43c	0.0288	95o	0.00473
19e	0.00135	43d	0.011	95p	0.00543
19f	0.0804	43e	0.188	95q	0.00168
19g	0.000274	43f	0.0392	95r	0.00631
19h	0.00246	43g	0.029	96a	0.0177
19i	0.00152	43h	0.133	96b	0.0268
19j	0.0199	43i	0.102	96c	0.0272
19k	0.00415	43j	0.012	96d	0.0209
19l	0.00152	43k	0.0257	96e	0.00862
19m	0.000944	43l	0.0236	97	0.0882
20	0.0128	43m	0.00531	98a	0.011
20a	0.0163	43n	0.0119	98b	0.00413

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
20b	0.874	43o	0.0157	98c	0.0267
20c	0.00559	43p	0.0555	98d	0.00441
20d	0.0133	43q	0.028	98e	0.00335
21	0.0253	43r	0.0577	98f	0.00229
21a	0.0378	43s	0.00629	98g	0.0127
21b	0.0133	43t	0.00545	98h	0.00362
21c	0.0234	44	0.0234	98i	0.0285
22	0.503	45	0.00717	98j	0.00374
23	0.00492	46	0.00456	98k	0.00246
23a	0.00459	46a	0.0126	98l	0.00789
23b	0.197	47	0.0155	99a	0.0438
23c	0.000831	47a	0.0054	99b	0.0316
23d	0.00534	47b	0.0149	99c	0.239
23e	0.00876	48	0.00072	99d	0.219
23f	0.0199	48a	0.00116	99e	0.0317
23g	1.21	49	0.00187	99f	0.00589
23h	0.00808	49a	0.00267	99g	0.0152
23i	0.0254	50	0.0104	99h	0.0782
23j	0.0314	50a	0.00794	99i	0.0594
23k	1.14	51	0.00332	99j	0.0124

Compounds may be further selected on the basis of further biological or physical properties which may be measured by techniques known in the art and which may be used in the assessment or selection of compounds for therapeutic or prophylactic application.

The compounds of the present invention are advantageous in that they possess pharmacological activity. In particular, the compounds of the present invention modulate (in particular, inhibit) mTOR kinase and/or phosphatidylinositol-3-kinase (PI3K) enzymes, such as the Class Ia PI3K enzymes (*e.g.* PI3Kalpha, PI3Kbeta and PI3Kdelta) and the Class Ib PI3K enzyme (PI3Kgamma). More particularly compounds of the present invention modulate (in

particular, inhibit) mTOR kinase. More particularly compounds of the present invention modulate (in particular, inhibit) one or more PI3K enzyme. The inhibitory properties of compounds of formula (I) may be demonstrated using the test procedures set out herein and in the experimental section. Accordingly, the compounds of formula (I) may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are mediated by mTOR kinase and/or one or more PI3K enzyme(s), and in particular by mTOR kinase.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in association with a pharmaceutically acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 1 mg to 1 g of active agent (more suitably from 1 to 250 mg, for example from 1 to 100 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of formula I will naturally vary according to the nature and severity of the disease state, the age and sex of the animal or patient and the route of administration, according to well known principles of

medicine.

In using a compound of formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 1 mg/kg to 100 mg/kg body weight is received, given if required in divided doses. In general, lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 1 mg/kg to 25 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 1 mg/kg to 25 mg/kg body weight will be used. Typically, unit dosage forms will contain about 10 mg to 0.5 g of a compound of this invention.

As stated herein, it is known that mTOR kinase and the PI3K enzymes have roles in tumourigenesis as well as numerous other diseases. We have found that the compounds of formula (I) possess potent anti-tumour activity which it is believed is obtained by way of inhibition of mTOR kinase and/or one or more of the PI3K enzymes.

Accordingly, the compounds of the present invention are of value as anti-tumour agents. Particularly, the compounds of the present invention are of value as anti-proliferative, apoptotic and/or anti-invasive agents in the containment and/or treatment of solid and/or liquid tumour disease. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are sensitive to inhibition of mTOR and/or one or more of the PI3K enzymes such as the Class Ia PI3K enzymes and the Class Ib PI3K enzyme. Further, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are mediated alone or in part by mTOR and/or one or more of the PI3K enzymes such as the Class Ia PI3K enzymes and the Class Ib PI3K enzyme. The compounds may thus be used to produce an mTOR enzyme inhibitory effect in a warm-blooded animal in need of such treatment. Certain compounds may be used to produce an PI3K enzyme inhibitory effect in a warm-blooded animal in need of such treatment.

As stated herein, inhibitors of mTOR kinase and/or one or more PI3K enzymes should be of therapeutic value for the treatment of proliferative disease such as cancer and in particular solid tumours such as carcinoma and sarcomas and the leukaemias and lymphoid malignancies and in particular for treatment of, for example, cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate, and of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and

vulva, and of leukaemias [including acute lymphoctic leukaemia (ALL) and chronic myelogenous leukaemia (CML)], multiple myeloma and lymphomas.

Anti-cancer effects which are accordingly useful in the treatment of cancer in a patient include, but are not limited to, anti-tumour effects, the response rate, the time to disease progression and the survival rate. Anti-tumour effects of a method of treatment of the present invention include but are not limited to, inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment, slowing of disease progression. Anti-cancer effects include prophylactic treatment as well as treatment of existing disease.

A mTOR kinase inhibitor, or a pharmaceutically acceptable salt thereof, may also be useful for the treatment patients with cancers, including, but not limited to, haematologic malignancies such as leukaemia, multiple myeloma, lymphomas such as Hodgkin's disease, non-Hodgkin's lymphomas (including mantle cell lymphoma), and myelodysplastic syndromes, and also solid tumours and their metastases such as breast cancer, lung cancer (non-small cell lung cancer (NSCL), small cell lung cancer (SCLC), squamous cell carcinoma), endometrial cancer, tumours of the central nervous system such as gliomas, dysembryoplastic neuroepithelial tumour, glioblastoma multiforme, mixed gliomas, medulloblastoma, retinoblastoma, neuroblastoma, germinoma and teratoma, cancers of the gastrointestinal tract such as gastric cancer, oesophagal cancer, hepatocellular (liver) carcinoma, cholangiocarcinomas, colon and rectal carcinomas, cancers of the small intestine, pancreatic cancers, cancers of the skin such as melanomas (in particular metastatic melanoma), thyroid cancers, cancers of the head and neck and cancers of the salivary glands, prostate, testis, ovary, cervix, uterus, vulva, bladder, kidney (including renal cell carcinoma, clear cell and renal oncocytoma), squamous cell carcinomas, sarcomas such as osteosarcoma, chondrosarcoma, leiomyosarcoma, soft tissue sarcoma, Ewing's sarcoma, gastrointestinal stromal tumour (GIST), Kaposi's sarcoma, and paediatric cancers such as rhabdomyosarcomas and neuroblastomas.

The compounds of the present invention and the methods of treatment comprising the administering or use of a mTOR kinase inhibitor, or a pharmaceutically acceptable salt thereof, are expected to be particularly useful for the treatment of patients with lung cancer, prostate cancer, melanoma, ovarian cancer, breast cancer, endometrial cancer, kidney cancer, gastric

cancer, sarcomas, head and neck cancers, tumours of the central nervous system and their metastases, and also for the treatment of patients with acute myeloid leukaemia.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use as a medicament in a warm-blooded animal such as man.

According to a further aspect of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further aspect of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the production of an apoptotic effect in a warm-blooded animal such as man.

According to a further feature of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in a warm-blooded animal such as man as an anti-invasive agent in the containment and/or treatment of proliferative disease such as cancer.

According to a further aspect of the invention, there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further aspect of the invention, there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for the production of an apoptotic effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the production of an apoptotic effect in a warm-blooded animal such as man.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the

manufacture of a medicament for use in a warm-blooded animal such as man as an anti-invasive agent in the containment and/or treatment of proliferative disease such as cancer.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the prevention or treatment of proliferative disease such as cancer in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of proliferative disease such as cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the prevention or treatment of those tumours which are sensitive to inhibition of mTOR kinase and/or one or more PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells.

According to a further feature of this aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of mTOR kinase and/or one or more PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) that are involved in the signal transduction

steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of mTOR kinase and/or one or more PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in providing a mTOR kinase inhibitory effect and/or a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect).

According to a further feature of this aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in providing a mTOR kinase inhibitory effect and/or a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect).

According to a further aspect of the invention there is also provided a method for providing a mTOR kinase inhibitory effect and/or a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect) which comprises administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases.

According to a further feature of the invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of solid tumours such as carcinoma and sarcomas and the leukaemias and lymphoid malignancies.

According to a further feature of the invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of

cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate.

According to a further feature of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

According to a further feature of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, endometrium, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

According to a further feature of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of lung cancer, prostate cancer, melanoma, ovarian cancer, breast cancer, endometrial cancer, kidney cancer, gastric cancer, sarcomas, head and neck cancers, tumours of the central nervous system and their metastases, and also for the treatment acute myeloid leukaemia.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of of solid tumours such as carcinoma and sarcomas and the leukaemias and lymphoid malignancies.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the

manufacture of a medicament for use in the treatment of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of lung cancer, prostate cancer, melanoma, ovarian cancer, breast cancer, endometrial cancer, kidney cancer, gastric cancer, sarcomas, head and neck cancers, tumours of the central nervous system and their metastases, and also for the treatment acute myeloid leukaemia.

According to a further feature of the invention there is provided a method for treating cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a method for treating solid tumours such as carcinoma and sarcomas and the leukaemias and lymphoid malignancies in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a method for treating cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a method for treating cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a method for treating lung cancer, prostate cancer, melanoma, ovarian cancer, breast cancer, endometrial cancer, kidney cancer, gastric cancer, sarcomas, head and neck cancers, tumours of the central nervous system and their metastases, and acute myeloid leukaemia in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

As stated herein, the *in vivo* effects of a compound of formula (I) may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of formula (I).

The invention further relates to combination therapies wherein a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of formula (I) is administered concurrently or sequentially or as a combined preparation with another treatment of use in the control of oncology disease.

In particular, the treatment defined herein may be applied as a sole therapy or may involve, in addition to the compounds of the invention, conventional surgery or radiotherapy or chemotherapy. Accordingly, the compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of cancer.

Suitable agents to be used in combination include :-

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea and gemcitabine); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like paclitaxel and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecins);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin),

progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341) and *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661), and metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™] and the anti-erbB1 antibody cetuximab [C225]); such inhibitors also include, for example, tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033) and erbB2 tyrosine kinase inhibitors such as lapatinib), inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)) and inhibitors of cell signalling through MEK and/or Akt kinases;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin)];

(vi) vascular damaging agents such as combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense agent;

(viii) gene therapy approaches, including approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapeutic approaches, including *ex-vivo* and *in-vivo* approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

The invention will now be further explained by reference to the following illustrative examples.

Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received.

In the examples ^{1}H NMR spectra were recorded on a Bruker DPX 300 (300 MHz), Bruker DRX 400 (400 MHz) instrument or a Bruker DRX 500 (500 MHz) instrument. The central peaks of chloroform-d (δ_H 7.27 ppm), dimethylsulfoxide-d_6 (δ_H 2.50 ppm) or acetone-d_6 (δ_H 2.05 ppm) were used as internal references. The following abbreviations have been used:

s, singlet; d, doublet;

t, triplet; q, quartet; m, multiplet; br, broad.

Column chromatography was carried out using silica gel (0.04-0.063 mm, Merck). In general, a Kromasil KR-100-5-C18 reversed-phase column (250 x 20 mm, Akzo Nobel) was used for preparative HPLC with mixtures of acetonitrile and water [containing 0.1% trifluoroacetic acid (TFA)] used as the eluent at a flow rate of 10 mL/min.

The following methods were used for liquid chromatography (LC) / mass spectral (MS) analysis :-

HPLC: Agilent 1100 or Waters Alliance HT (2790 & 2795)

Mass Spectrometer: Waters ZQ ESCi

HPLC Column

The standard HPLC column used is the Phemonenex Gemini C18 5μm, 50 x 2 mm.

Acidic HPLC Methods

The mobile phases used are: Mobile phase A: Water

Mobile Phase B: Acetonitrile

Mobile Phase C: 1% Formic Acid in 50:50 Water:MeCN (v/v)

Each method is followed by a rapid equilibration using a 5 mL flow rate for 0.45 min.

Four generic HPLC methods are available:

5 Minute Monitor Acidic method

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
4	0	95	5	6	1.1
4.5	0	95	5	6	1.1

Early Acidic method for early eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
4	57.5	37.5	5	6	1.1
4.5	57.5	37.5	5	6	1.1

Mid Acidic method for middle eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
0.01	67.5	27.5	5	6	1.1
4.5	27.5	67.5	5	6	1.1

Late Acidic method for late eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
0.01	27.5	67.5	5	6	1.1
4.5	5	95	5	6	1.1

Basic HPLC methods

In some instances the standard acidic methods may be unsuitable for either the compound ionisation or the chromatography separation required. In such cases four comparable Basic HPLC methods are available.

The mobile phases used are: Mobile phase A: Water

Mobile Phase B: Acetonitrile

Mobile Phase D: 0.1% 880 Ammonia in acetonitrile

Each method is followed by a rapid equilibration using a 5 mL flow rate for 0.45 min.

Minute Monitor Basic method

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase D:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
4	0	95	5	6	1.1
4.5	0	95	5	6	1.1

Early Basic method for early eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase D:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
4	57.5	37.5	5	6	1.1
4.5	57.5	37.5	5	6	1.1

Mid Basic method for middle eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase D:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
0.01	67.5	27.5	5	6	1.1
4.5	27.5	67.5	5	6	1.1

Late Basic method for late eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
0.01	27.5	67.5	5	6	1.1
4.5	5	95	5	6	1.1

The following method was used for liquid chromatography (LC) / mass spectral (MS) analysis :- Instrument: Agilent 1100; Column: Waters 'Symmetry' 2.1 x 30 mm; Mass Spectral analysis using chemical ionisation (APCI); Flow rate: 0.7 mL/min; Absorption Wavelength: 254 nm; Solvent A: water + 0.1% TFA; Solvent B: acetonitrile + 0.1% TFA ; Solvent Gradient: 15-95% Solvent B for 2.7 minutes followed by 95% Solvent B for 0.3 minutes.

The following methods were used for LC analysis :-

Method A :- Instrument: Agilent 1100; Column: Kromasil C18 reversed-phase silica, 100 x 3 mm, 5μm particle size; Solvent A: 0.1% TFA/water, Solvent B: 0.08% TFA/acetonitrile; Flow Rate: 1 mL/min; Solvent Gradient: 10-100% Solvent B for 20 minutes followed by 100% Solvent B for 1 minute; Absorption Wavelengths: 220, 254 and 280 nm. In general, the retention time of the product was noted.

Method B :- Instrument: Agilent 1100; Column: Waters 'Xterra' C8 reversed-phase silica, 100 x 3 mm, 5μm particle size; Solvent A: 0.015M ammonia in water, Solvent B: acetonitrile; Flow Rate: 1 ml/min, Solvent Gradient: 10-100% Solvent B for 20 minutes followed by 100% Solvent B for 1 minute; Absorption Wavelength: 220, 254 and 280 nm. In general, the retention time of the product was noted.

The following abbreviations are used herein or within the following illustrative examples :-

HPLC	High Performance Liquid Chromatography
HBTU	*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate;
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate;
HOBT	1-hydroxybenzotriazole;
HOAT	1-hydroxy-7-azabenzotriazole;
NMP	*N*-methylpyrrolidin-2-one;
DMSO	dimethylsulfoxide;
DMF	*N*,*N*-dimethylformamide;
DMA	*N*,*N*-dimethylacetamide;
THF	tetrahydrofuran;
DME	1,2-dimethoxyethane;
DCCI	dicyclohexylcarbodiimide;

MeOH methanol;

MeCN acetonitrile;

DCM dichloromethane;

DIPEA *N*,*N*-diisopropylethylamine;

DBU 1,8-diazabicyclo[5.4.0]undec-7-ene;

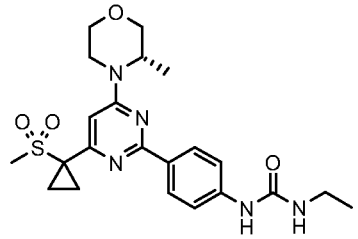
RT room temperature (approximately 17 to 25ºC);

tR retention time;

m/z mass/charge ratio.

The chemical names were generated by software which used the Lexichem Toolkit (v. 1.60) from OpenEye Scientific Software (www.eyesopen.com) to generate IUPAC conforming names.

Example 1: 3-Ethyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



To a solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine (200 mg, 0.60 mmol) in ethanol was added toluene (1.00 mL), water (1.00 mL), [4-(3-ethylureido)phenyl]boronic acid, pinacol ester (262 mg, 0.90 mmol), tri-potassium orthophosphate (448 mg, 2.11 mmol) and palladiumbis(tri-*tert*-butylphosphine) (18.55 mg, 0.04 mmol). The reaction was degassed then purged with nitrogen and heated at 80°C for 2 hours. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (5 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 0 to 10% (3.5M ammonia in methanol) in DCM, to give the desired material as a white solid (109 mg).

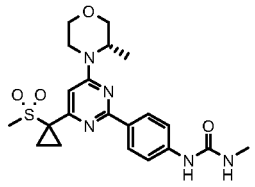
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, m), 1.23 (3H, d), 1.56 (2H, s), 1.67 (2H, s), 3.14 (2H, t), 3.22 (1H, m), 3.30 (3H, s), 3.48 (1H, t), 3.63 (1H, m), 3.76 (1H,

d), 3.97 (1H, d), 4.21 (1H, d), 4.57 (1H, s), 6.16 (1H, t), 6.76 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.66 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 460 ; HPLC tR = 1.83 min

mTOR Kinase Assay (Echo): 0.00276μM

The following compound was made in an analogous fashion from the appropriate boronic ester.

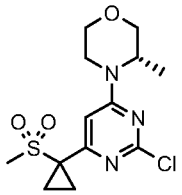
Example	Structure	NAME	LCMS MH+	Retention time (min)
1a		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	446	1.68

Example 1a: ^{1}H NMR (400.132 MHz, DMSO) δ 1.23 (3H, d), 1.31 (3H, s), 1.56 (2H, m), 1.67 (2H, m), 2.66 (3H, d), 3.22 (1H, m), 3.48 (1H, m), 3.63 (1H, m), 3.76 (1H, d), 3.97 (1H, m), 4.21 (1H, d), 4.57 (1H, s), 6.07 (1H, m), 6.76 (1H, s), 7.51 (2H, d), 8.19 (2H, d), 8.75 (1H, s)

mTOR Kinase Assay (Echo): 0.00279μM

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine is described below.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine



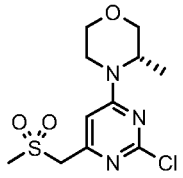
2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (1.2 g, 3.9 mmol) was dissolved in DMF (20 mL) and sodium *tert*-butoxide (755 mg, 7.85 mmol) was added to the reaction, followed by dibromoethane (738 mg, 3.9 mmol). The reaction was stirred at RT for 4 hours then at 60°C overnight. Further sodium *tert*-butoxide (378 mg, 3.9

mmol) was added to the reaction, followed by dibromoethane (369 mg, 1.9 mmol) and the reaction stirred at 60°C a further 24 hours. DCM (20 mL) was added and the reaction washed with 2M aqueous hydrochloric acid (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude solid was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM, to give the desired material (400 mg, 31 %).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (d, 3H), 1.51 (m, 2H), 1.64 (m, 2H), 3.18 (s, 3H), 3.22 (m, 1H), 3.43 (m, 1H), 3.58 (m, 1H), 3.72 (d, 1H), 3.93 (m, 1H), 4.05 (d, 1H), 4.41 (s, 1H), 6.93 (s, 1H)

LCMS Spectrum: m/z (ESI+)(M+H)+ 332, HPLC tR = 1.6 min

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine

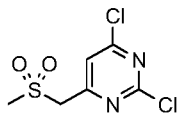


2,4-Dichloro-6-(methylsulfonylmethyl)pyrimidine (30 g, 0.13 mol) was dissolved in dichloromethane and stirred (under nitrogen) at -5°C. Triethylamine (17.4 mL, 0.13 mol) was added to give a clear brown solution. (3*S*)-3-Methylmorpholine was dissolved in dichloromethane and added dropwise keeping the reaction below -5°C. The cooling bath was then removed and the mixture stirred for 1 hour. The reaction mixture was heated at reflux for 2 hours, then the reaction mixture was washed with water, dried then evaporated. The crude material was purified by preparative HPLC to give the desired material as a solid (19.3 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.21 - 1.23 (m, 3H), 3.11 (s, 3H), 3.19 - 3.26 (m, 1H), 3.42 - 3.49 (m, 1H), 3.58 - 3.62 (1H, m), 3.73 (d, 1H), 3.92 - 3.96 (m, 2H), 4.27 - 4.31 (m, 1H), 4.45 (s, 2H), 6.92 (s, 1H)

LCMS Spectrum: MH+ 306, retention time 1.42 min, Method 5 Min Acid

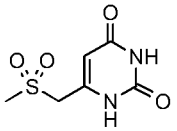
2,4-Dichloro-6-(methylsulfonylmethyl)pyrimidine



6-(Methylsulfonylmethyl)-1*H*-pyrimidine-2,4-dione (132 g, 0.65 mol) was added to phosphorus oxychloride (1.2 L) and the mixture heated to reflux for 16 hours, then cooled to

room temperature. The excess phosphorus oxychloride was removed *in vacuo*, the residue azeotroped with toluene (2 x 500 mL) and dissolved in dichloromethane. This mixture was then poured slowly onto ice (4 L) and stirred for 20 minutes, then extracted with dichloromethane (3 x 1 L) (the insoluble black material was filtered off and discarded) and ethyl acetate (2 x 1 L). The extracts were combined, dried, then evaporated to leave the desired material as a dark brown solid (51 g). The material was used without further purification.
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.13 (s, 3H), 4.79 (s, 2H), 7.87 (s, 1H)
LCMS Spectrum: MH+ 239, retention time 1.21 min, Method 5 Min Acid

6-(Methylsulfonylmethyl)-1*H*-pyrimidine-2,4-dione

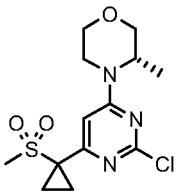


6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (175 g, 1.09 mol) was dissolved in DMF (2 L) and methanesulphinic acid sodium salt (133.5 g, 1.31 mol) was added. The reaction was heated to 125°C for 2 hours then allowed to cool and the suspension filtered and concentrated *in vacuo* to give a yellow solid. The crude material was washed with water, filtered, then triturated with toluene. The solid was filtered then triturated with isohexane to leave the desired compound as a yellow solid (250 g). The material was used without further purification.

6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione is a commercially available material.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine can also be prepared by the method described below.

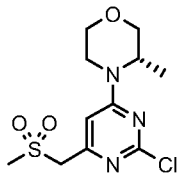
2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine



Sodium hydroxide (50%w/w solution) (115 g, 2877.88 mmol) was addedto 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (16 g, 52.33 mmol), 1,2-

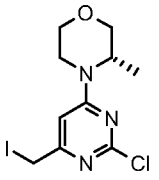
dibromoethane (13.53 ml, 156.98 mmol) and tetrabutylammonium bromide (1.687 g, 5.23 mmol) in toluene (128 mL) and the resulting suspension stirred at RT for 4 hours. Water was added and the mixture was extracted twice with toluene. The toluene was dried over $MgSO_4$, filtered and evaporated. The crude product,15g was purified by flash silicachromatography, elution gradient 0to 20% ethyl acetate in DCM, to give the desired material (13 g) as a white solid which was identical to previous samples.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine



Methanesulfinic acid, sodium salt (11.75 g, 115.11 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (37 g, 104.64 mmol), in acetonitrile (900 mL) and the resulting solution stirred at 85°Cfor 24 hours. The organic layers were combined and washed with water (3 x 100 mL), dried over $MgSO_4$, filtered, and the solvent was removed by evaporation to give the crude product as a dark brown oil, which solidifed (36 g). The crude solidwas purified by flash silicachromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material (22 g) as a cream solid which was identical to previous samples.

2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

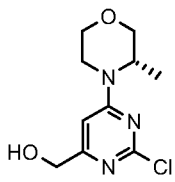


Methanesulfonyl chloride (0.245 mL, 3.14 mmol) was added dropwise over a period of 5 minutes to a solution of triethylamine (0.875 mL, 6.28 mmol) and [2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (510 mg, 2.09 mmol) in DCM (30 mL) at 0ºC under nitrogen. The resulting solution was stirred at RT for 45 minutes. The reaction mixture was diluted with water (20 mL). The organic layer was dried ($MgSO_4$) and filtered. Sodium

Iodide (1569 mg, 10.46 mmol) was added and the reaction was heated to 50°C for 20 hours. The reaction mixture was filtered and evaporated to afford the desired material (761 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 1.19 - 1.25 (3H, m), 3.18 - 3.22 (1H, m), 3.40 - 3.47 (1H, m), 3.57 - 3.60 (1H, m), 3.71 (1H, d), 3.90 - 3.94 (1H, m), 3.96 - 3.98 (1H, m), 4.28 - 4.32 (3H, m), 6.94 (1H, s).
LCMS Spectrum: m/z (ESI+) (M+H)+ = 354; HPLC tR = 2.10 min.

2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine can also be prepared by the dropwise addition of methanesulfonyl chloride (91 mL, 1169.52 mmol) to [2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (190 g, 779.68 mmol) and triethylamine (163 mL, 1169.52 mmol) in DCM (2293 mL) at 0°C under air. The resulting solution was allowed to warm up slowly to RT over a period of 4 hours. The reaction mixture was quenched with water, extracted with DCM and the organic layer dried over $MgSO_4$, filtered and evaporated to afford [2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methyl methanesulfonate as a yellow gum (251 g). Sodium iodide (234 g, 1560.07 mmol) was added to this material in acetone (3679 mL) and the resulting suspension stirred at RT for 16 hours. The reaction mixture was evaporated to dryness and redissolved in DCM and washed three times with water then with a saturated aqueous solution of sodium thiosulphate. The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude desired product (270 g). This was purified by chromatography to give an off white solid which was further triturated with ether to give the desired material which was identical to previous samples.

[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol



Methyl 2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate (3.15 g) was dissolved in dry THF (20 mL) and cooled to 0°C under nitrogen. A solution of lithium borohydride (2.0M in THF, 6.09mL) was added dropwise and the solution allowed to warm to RT and stirred for 1 hour. The reaction was quenched with water (20 mL) then evaporated to dryness, the residue dissolved in ethyl acetate (150 mL) and washed with water (150 mL)

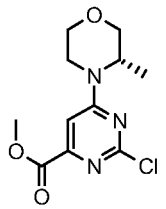
followed by brine (50 mL). The organics were evaporated to dryness to give to the desired material as a white solid (2.44 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 1.20 - 1.21 (3H, m), 3.18 - 3.22 (1H, m), 3.40 - 3.47 (1H, m), 3.56 - 3.60 (1H, m), 3.71 (1H, d), 3.91 - 3.94 (1H, m), 3.98 (1H, d), 4.35 (3H, d), 5.51 (1H, t), 6.74 (1H, s).

Mass Spectrum; M+H$^+$ 244.

[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol can also be prepared by the dropwise addition of lithium borohydride (2M in THF) (454 mL, 908.17 mmol) over a period of 15 minutes to a solution of methyl 2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate (235 g, 864.92 mmol) in the THF (4701 mL) at 0°C. The mixture was stirred at RT for 2 hours then water (1500 mL) was added slowly. A white solid formed which was decanted off and the THF was removed under vacuum. To the residue was added more water (500 mL), and extracted with ethyl acetate (3 x 700 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a white solid which was identical to previous samples.

Methyl 2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate



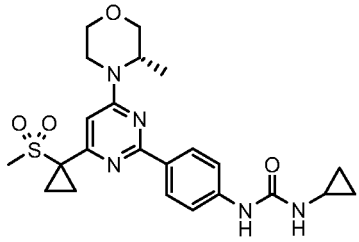
Methyl 2,6-dichloropyrimidine-4-carboxylate (5 g) was dissolved in DCM (120 mL). (3*S*)-3-Methylmorpholine (2.49 g) dissolved in triethylamine (3.70 mL) and DCM (10 mL) was added dropwise to the solution over 10 minute. The reaction was left to stir at room temperature for 1 hour. The reaction was then evaporated to dryness and dissolved in DCM (300 mL). The organics were washed once with water (150 mL) and dried ($MgSO_4$), filtered and evaporated. The crude material was chromatographed on silica, eluting with 2.5% methanol in DCM, to give the desired material as a white solid (3.15 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 1.22 - 1.24 (3H, m), 3.25 (1H, d), 3.41 - 3.48 (1H, m), 3.57 - 3.61 (1H, m), 3.71 (1H, d), 3.87 (3H, s), 3.91 - 3.95 (1H, m), 4.25 (1H, s), 4.45 (1H, s), 7.29 (1H, s).

Mass Spectrum; $M+H^+$ 272.

Methyl 2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate can also be prepared by the addition of methyl 2,6-dichloropyrimidine-4-carboxylate (250 g, 1207.65 mmol) to the DCM (2500 mL).Triethylamine (185 mL, 1328.41 mmol) was added and the reaction cooled to 0ºC. (3*S*)-3-Methylmorpholine (128 g, 1268.03 mmol) dissolved in DCM (300 mL), was added dropwise over 30 minutes and the mixture stirred at 5º overnight. Water (800 mL) was added, the phases separated and the aquoeus layer extracted with DCM (300 mL). The combined organics were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated to a cream solid. The crude solid was dissolved in hot ethyl acetate (3 volumes) then isohexane (5 volumes) added the mixture left to cool with stirring over the weekend to give the desired material as a solid which was identical to previous samples.

Example 2: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



To a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (200 mg, 0.39 mmol) in DMF (2 mL) was added triethylamine (0.164 mL, 1.18 mmol) followed by cyclopropylamine (0.136 mL, 1.97 mmol) and the reaction heated at 50°C for 2 hours.

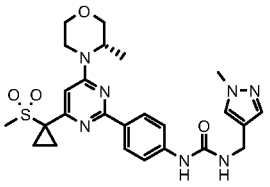
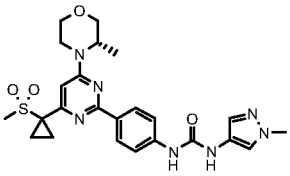
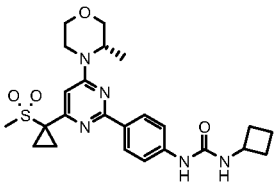
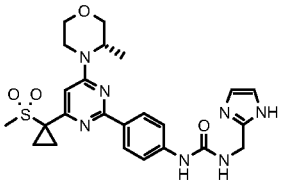
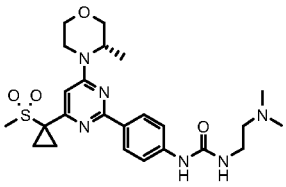
The solvent was removed under reduced pressure to give the crude product which was purified by flash silica chromatography, elution gradient 0 to 10% (3.5M ammonia in methanol) in DCM, to give the desired product as a white solid (168 mg).

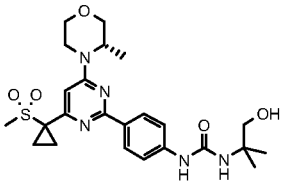
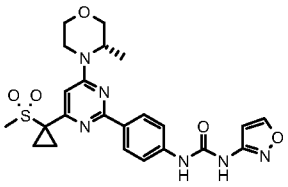
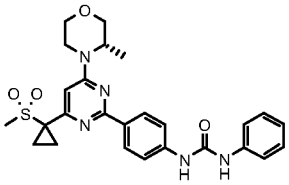
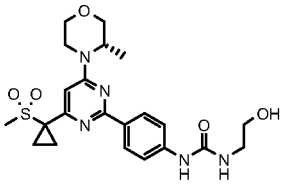
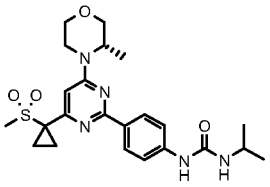
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.42 (2H, m), 0.65 (2H, m), 1.24 (3H, d), 1.56 (2H, m), 1.67 (2H, m), 2.56 (3H, m), 3.21 (1H, m), 3.48 (1H, m), 3.63 (1H, m), 3.78 (1H, d), 3.97 (1H, m), 4.21 (1H, d), 4.57 (1H, s), 6.43 (1H, d), 6.77 (1H, s), 7.51 (2H, d), 8.20 (2H, d), 8.54 (1H, s)

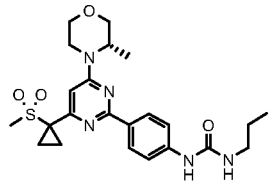
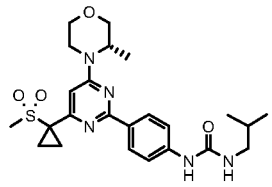
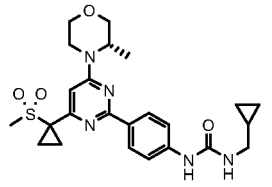
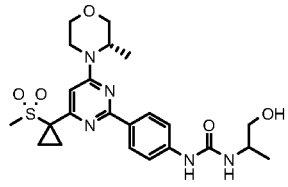
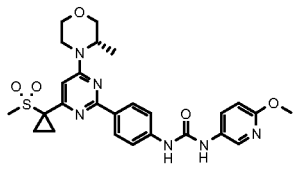
LCMS Spectrum: m/z (ESI+)(M+H)+ = 472; HPLC tR = 1.93 min.

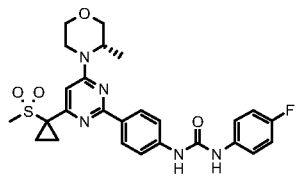
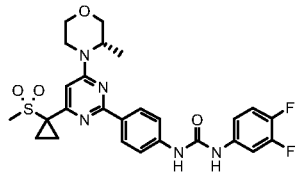
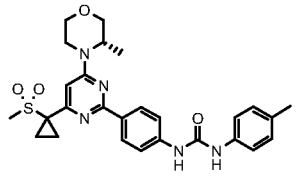
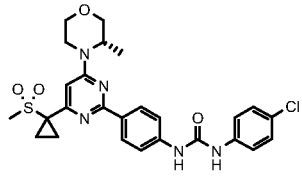
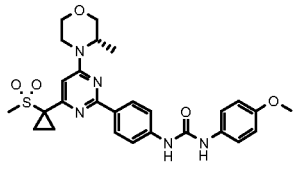
mTOR Kinase Assay (Echo): 0.0015μM

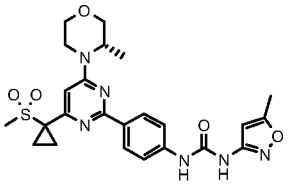
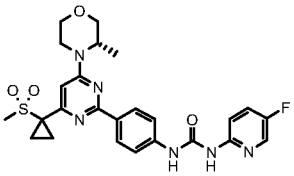
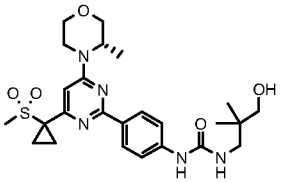
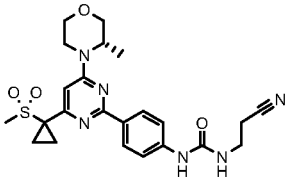
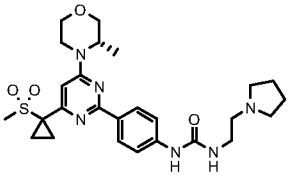
The compounds below were prepared in an analogous fashion using the appropriate amine.

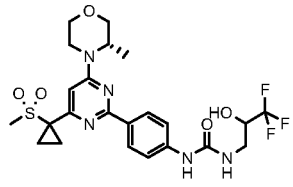
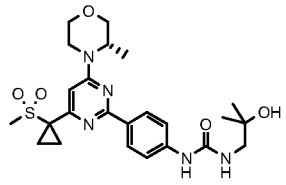
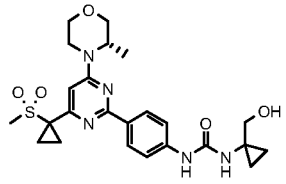
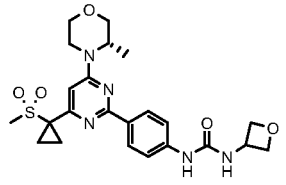
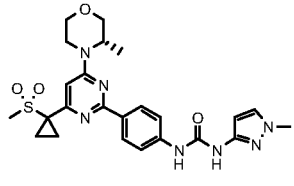
Example	Structure	NAME	LCMS MH+	Retention time (min)
2a		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea	526	1.73
2b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	512	1.75
2c		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	486	2.21
2d		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	512	1.66
2e		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	502	1.89

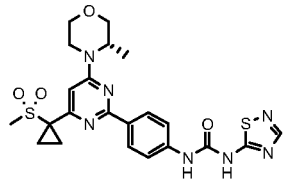
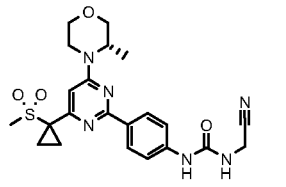
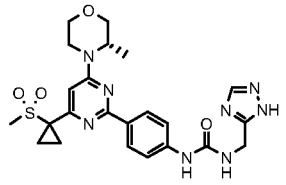
Example	Structure	NAME	LCMS MH+	Retention time (min)
2f		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	503	1.83
2g		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	498	2.03
2h		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea	507	2.35
2i		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	475	1.54
2j		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	473	2.0

Example	Structure	NAME	LCMS MH+	Retention time (min)
2k		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propyl-urea	473	2.02
2l		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	487	2.18
2m		3-(cyclopropylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	485	2.06
2n		3-(1-hydroxypropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	489	1.63
2o		3-(6-methoxypyridin-3-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	538	2.11

Example	Structure	NAME	LCMS MH+	Retention time (min)
2p		3-(4-fluorophenyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	525	2.4
2q		3-(3,4-difluorophenyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	543	2.52
2r		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(4-methylphenyl)urea	521	2.49
2s		3-(4-chlorophenyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	541	2.59
2t		3-(4-methoxyphenyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	537	2.29

Example	Structure	NAME	LCMS MH+	Retention time (min)
2u		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(5-methyl-1,2-oxazol-3-yl)urea	512	2.16
2v		3-(5-fluoropyridin-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	527	2.35
2w		3-(3-hydroxy-2,2-dimethylpropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	518	2.05
2x		3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	485	1.91
2y		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-pyrrolidin-1-ylethyl)urea	529	2.21

Example	Structure	NAME	LCMS MH+	Retention time (min)
2z		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(3,3,3-trifluoro-2-hydroxypropyl)urea	544	2.11
2aa		3-(2-hydroxy-2-methylpropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	530	1.91
2ab		3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	502	1.81
2ac		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(oxetan-3-yl)urea	488	2.25
2ad		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-3-yl)urea	512	2.11

Example	Structure	NAME	LCMS MH+	Retention time (min)
2ae		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	515	1.43
2af		3-(cyanomethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	471	1.54
2ag		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2H-1,2,4-triazol-3-ylmethyl)urea	513	1.58

Both **Example 2** and **Example 1a** can be prepared in an analogous fashion to that described above but using THF as a solvent. **Example 1a** can also be prepared in an analogous fashion to that described above but using NMP as a solvent.

Example 2a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.56 (2H, s), 1.67 (2H, s), 3.21 (1H, m), 3.48 (1H, t), 3.63 (1H, d), 3.76 (4H, m), 3.80 (3H, s), 3.97 (1H, d), 4.13 (2H, d), 4.20 (1H, s), 4.57 (1H, s), 6.42 (1H, t), 6.77 (1H, s), 7.35 (1H, s), 7.51 (2H, d), 7.59 (1H, s), 8.20 (2H, d), 8.70 (1H, s)

mTOR Kinase Assay (Echo): 0.0932μM

Example 2b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.66 - 1.69 (2H, m), 3.21 (1H, dt), 3.27 - 3.29 (1H, m), 3.29 (3H, s), 3.49 (1H, dt), 3.64 (1H, dd), 3.79 (3H, s), 3.98 (1H, dd), 4.22 (1H, d), 4.58 (1H, s), 6.78 (1H, s), 7.38 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.23 (2H, d), 8.38 (1H, s), 8.84 (1H, s)

mTOR Kinase Assay (Echo): 0.000169μM

Example 2c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.24 (3H, d), 1.54-1.69 (6H, m), 1.81-1.91 (2H, m), 2.18-2.25 (2H, m), 3.17-3.24 (1H, td), 3.29 (3H, s), 3.45-3.52 (1H, td),

3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.10-4.23 (2H, m), 4.57 (1H, bs), 6.45-6.47 (1H, d), 6.77 (1H, s), 7.47-7.50 (2H, d), 8.18-8.21 (2H, d), 8.57 (1H, s).

mTOR Kinase Assay (Echo): 0.00121μM

Example 2d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.66 (2H, q), 1.67-1.69 (2H, q), 3.17-3.25 (1H, td), 3.30 (3H, s), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.32-4.34 (2H, d), 4.57 (1H, bs), 6.61-6.64 (1H, t), 6.77 (1H, s), 6.77 (2H, bs), 7.51-7.54 (2H, d), 8.21-8.22 (2H, d), 8.94 (1H, s), 11.84 (1H, bs).

mTOR Kinase Assay (Echo): 0.0239μM

Example 2e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.24 (3H, d), 1.54-1.58 (2H, q), 1.66-1.69 (2H, q), 2.19 (6H, s), 2.33-2.36 (2H, t), 3.18-3.22 (2H, t), 3.20-3.25 (1H, td), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 6.15-6.18 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.90 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.279μM

Example 2f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25(9H, d), 1.54-1.58 (2H, q), 1.66-1.69 (2H, q), 3.17-3.25 (1H, td), 3.39-3.40 (2H, d), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-4.00 (1H, dd), 4.20-4.23 (1H, d), 4.56 (1H, bs), 4.94-4.97 (1H, t), 6.01 (1H, s), 6.77 (1H, s), 7.45-7.47 (2H, d), 8.18-8.20 (2H, d), 8.74 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.00433μM

Example 2g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.19-3.26 (1H, td), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.81 (1H, s), 6.87-6.88 (1H, d), 7.57-7.59 (2H, d), 8.27-8.29 (2H, d), 8.75-8.76 (1H, d), 9.08 (1H,s), 9.62 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.000137μM

Example 2h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.18-3.26 (1H, td), 3.31 (3H, s), 3.46-3.53 (1H, td), 3.63-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.59 (1H, bs), 6.79 (1H, s), 6.98-7.01 (1H, t), 7.28-7.32 (2H, t), 7.46-7.48 (2H, d), 7.57-7.59 (2H, d), 8.25-8.27 (2H, d), 8.71 (1H, s), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.000272μM

Example 2i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.24 (3H, d), 1.54-1.58 (2H, q), 1.65-1.70 (2H, q), 3.16-3.25 (1H, td), 3.16-3.21 (2H, q), 3.45-3.52 (1H, td), 3.45-3.49 (2H, q), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 4.72-4.74 (1H, t), 6.25-6.27 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.82 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.00207μM

Example 2j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11-1.12 (6H, d), 1.23-1.24 (3H, d), 1.54-1.58 (2H, q), 1.66-1.69 (2H, q), 3.17-3.25 (1H, td), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.74-3.82 (2H, m), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 6.06-6.07 (1H, d), 6.77 (1H, s), 7.48-7.50 (2H, d), 8.19-8.21 (2H, d), 8.54 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.012μM

Example 2k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87-0.91 (3H, t), 1.23-1.25 (3H, d), 1.42-1.51 (2H, m), 1.54-1.58 (2H, q), 1.66-1.69 (2H, q), 3.05-3.09 (2H, q), 3.17-3.25 (1H, td), 3.45-3.52 (1H, td), 3.61-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 6.19-6.22 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.66 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.00406μM

Example 2l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88-0.90 (6H, d), 1.23-1.25 (3H, d), 1.54-1.58 (2H, q), 1.66-1.68 (2H, q), 1.67-1.76 (1H, m), 2.93-2.96 (2H, t), 3.17-3.25 (1H, td), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 6.24-6.27 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.66 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.0116μM

Example 2m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.18-0.22 (2H, m), 0.42-0.46 (2H, m), 0.93-1.00 (1H, m), 1.23-1.25 (3H, d), 1.54-1.58 (2H, q), 1.66-1.69 (2H, q), 2.98-3.01 (2H, t), 3.17-3.25 (1H, td), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 6.25-6.28 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.70 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.00589μM

Example 2n: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08-1.10 (3H, d), 1.23-1.25 (3H, d), 1.54-1.57 (2H, q), 1.66-1.69 (2H, q), 2.98-3.01 (2H, t), 3.18-3.25 (1H, td), 3.30 (3H, s), 3.34-3.43 (2H, m), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.69-3.75 (1H, m), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 4.77-4.80 (1H, t), 6.09-6.11 (1H, d), 6.77 (1H, s), 7.48-7.50 (2H, d), 8.19-8.21 (2H, d), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.00844μM

Example 2o: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.18-3.26 (1H, td), 3.30 (3H, s), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.83 (3H, s), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.79(s, 1H), 6.79-6.81 (1H, d), 7.56-7.58 (2H, d), 7.83-7.86 (1H, dd), 8.21-8.22 (1H, d), 8.25-8.27 (2H, d), 8.62 (1H, s), 8.98 (1H, s).

mTOR Kinase Assay (Echo): 0.000851μM

Example 2p: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.58 (2H, q), 1.66-1.69 (2H, q), 3.18-3.25 (1H, td), 3.30 (3H, s), 3.46-3.52 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.78 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.79(s, 1H), 7.11-7.16 (2H, t), 7.46-7.50 (2H, m), 7.56-7.58 (2H, d), 8.24-8.27 (2H, d), 8.74 (1H, s), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.0027μM

Example 2q: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.18-3.26 (1H, td), 3.30 (3H, s), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.80(s, 1H), 7.14-7.17 (1H, m), 7.32-7.39 (1H, q), 7.56-7.59 (2H, d), 7.65-7.71 (1H, qd), 8.26-8.28 (2H, d), 8.93 (1H, s), 9.00 (1H, s).

mTOR Kinase Assay (Echo): 0.001μM

Example 2r: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 2.26 (3H, s), 3.18-3.26 (1H, td), 3.30 (3H, s), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.79(s, 1H), 7.09-7.12 (2H, d), 7.34-7.36 (2H, d), 7.56-7.58 (2H, d), 8.24-8.27 (2H, d), 8.59 (1H, s), 8.87 (1H, s).

mTOR Kinase Assay (Echo): 0.00066μM

Example 2s: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.18-3.26 (1H, td), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.79(s, 1H), 7.33-7.36 (2H, d), 7.50-7.52

(2H, d), 7.56-7.59 (2H, d), 8.25-8.27 (2H, d), 8.87 (1H, s), 8.97 (1H, s). Note:methyl signal obscured by water peak at 3.29

mTOR Kinase Assay (Echo): 0.00138μM

Example 2t: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.58 (2H, q), 1.67-1.69 (2H, q), 3.18-3.25 (1H, td), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.73 (3H, s), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.79(s, 1H), 6.88-6.90 (2H, d), 7.36-7.38 (2H, d), 7.55-7.57 (2H, d), 8.24-8.26 (2H, d), 8.51 (1H, s), 8.84 (1H, s). Note:methyl signal obscured by water peak at 3.29

mTOR Kinase Assay (Echo): 0.00145μM

Example 2u: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 2.38 (3H, s), 3.18-3.26 (1H, td), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.57 (1H, s), 6.80 (s, 1H), 7.56-7.58 (2H, d), 8.27-8.29 (2H, d), 9.06 (1H, s), 9.47 (1H, s). Note:methyl signal obscured by water peak at 3.29

mTOR Kinase Assay (Echo): 0.00118μM

Example 2v: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.19-3.26 (1H, td), 3.31 (3H, s), 3.46-3.53 (1H, td), 3.63-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.00 (1H, dd), 4.22-4.25 (1H, d), 4.58 (1H, bs), 6.80 (1H, s), 7.60-7.63 (2H, d), 7.72-7.77 (1H, td), 7.79-7.82 (1H, dd), 8.28-8.30 (3H, m), 9.40 (1H, s), 9.89 (1H, s).

mTOR Kinase Assay (Echo): 0.00866μM

Example 2w: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.82 (6H, s), 1.23 (3H, d), 1.54 - 1.57 (2H, m), 3.00 (2H, d), 3.15 (2H, d), 3.18 - 3.24 (1H, m), 3.29 (3H, s), 3.48 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.21 (1H, d), 4.55 - 4.62 (2H, m), 6.24 (1H, t), 6.76 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.77 (1H, s).

mTOR Kinase Assay (Echo): 0.0685μM

Example 2x: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.66 - 1.68 (2H, m), 2.70 (2H, t), 3.21 (1H, dt), 3.27 (3H, s), 3.35 - 3.40 (2H, m), 3.48 (1H, dt), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.22 (1H, d), 4.57 (1H, s), 6.53 (1H, t), 6.77 (1H, s), 7.52 (2H, d), 8.21 (2H, d), 8.93 (1H, s).

mTOR Kinase Assay (Echo): 0.00164μM

Example 2y: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.65 - 1.67 (2H, m), 1.70 - 1.73 (4H, m), 2.46 - 2.50 (4H, m), 3.20 - 3.24 (4H, m), 3.27 (3H, s), 3.48

(1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 3.97 (1H, dd), 4.21 (1H, d), 4.56 (1H, s), 6.19 (1H, t), 6.76 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.23μM

Example 2z: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.66 - 1.68 (2H, m), 3.14 - 3.27 (1H, m), 3.29 (3H, s), 3.45 - 3.56 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.05 - 4.11 (1H, m), 4.21 (1H, d), 4.57 (1H, s), 6.39 (1H, t), 6.49 (1H, d), 6.77 (1H, s), 7.51 (2H, d), 8.21 (2H, d), 8.94 (1H, s).

mTOR Kinase Assay (Echo): 0.0181μM

Example 2aa: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, s), 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.66 - 1.68 (2H, m), 3.06 (2H, d), 3.18 (1H, d), 3.22 (`H, dd), 3.29 (3H, s), 3.48 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.21 (1H, d), 4.52 (1H, s), 4.57 (1H, s), 6.25 (1H, t), 6.76 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.0274μM

Example 2ab: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.63 - 0.67 (2H, m), 0.69 - 0.73 (2H, m), 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.66 - 1.68 (2H, m), 3.18 - 3.24 (1H, m), 3.29 (3H, s), 3.43 - 3.52 (3H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.21 (1H, d), 4.56 (1H, s), 4.83 (1H, s), 6.57 (1H, s), 6.77 (1H, s), 7.48 (2H, d), 8.20 (2H, d), 8.69 (1H, s).

mTOR Kinase Assay (Echo): 0.0553μM

Example 2ac: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.66 - 1.68 (2H, m), 3.17 - 3.24 (1H, m), 3.29 (3H, s), 3.48 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.21 (1H, d), 4.44 (2H, t), 4.56 (1H, s), 4.72 - 4.82 (3H, m), 6.77 (1H, s), 6.95 (1H, d), 7.50 (2H, d), 8.20 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00641μM

Example 2ad: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.66 - 1.69 (2H, m), 3.17 - 3.25 (1H, m), 3.27 (3H, s), 3.49 (1H, dt), 3.64 (1H, dd), 3.74 (3H, s), 3.77 (1H, d), 3.98 (1H, dd), 4.22 (1H, d), 4.57 (1H, s), 6.25 (1H, d), 6.79 (1H, s), 7.54 (1H, t), 7.57 (2H, d), 8.25 (2H, d), 8.92 (1H, s), 9.18 (1H, s).

mTOR Kinase Assay (Echo): 0.000705μM

Example 2ae: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.56 - 1.59 (2H, m), 1.67 - 1.70 (2H, m), 3.17 - 3.23 (1H, m), 3.27 (3H, s), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.24 (1H, d), 4.58 (1H, s), 6.81 (1H, s), 7.64 (2H, d), 8.30 (2H, d), 8.35 (1H, s), 9.46 (1H, s).

mTOR Kinase Assay (Echo): 0.00072μM

Example 2af: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.57 - 1.60 (2H, m), 1.68 - 1.71 (2H, m), 3.18 - 3.24 (1H, m), 3.27 (3H, s), 3.50 (1H, d), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.08 (2H, s), 4.25 (1H, d), 4.61 (1H, s), 6.86 (1H, s), 7.55 (2H, d), 8.14 (1H, s), 8.35 (2H, d), 8.44 (1H, d).

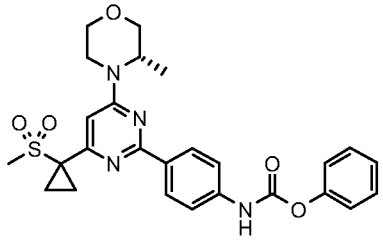
mTOR Kinase Assay (Echo): 0.0462μM

Example 2ag: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.66 - 1.68 (2H, m), 3.18 (1H, d), 3.22 (1H, dd), 3.49 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.21 (1H, d), 4.38 (2H, s), 4.44 (1H, s), 4.57 (1H, s), 6.66 (1H, d), 6.77 (1H, s), 7.52 (2H, d), 8.19 (1H, d), 8.21 (2H, d), 8.95 (1H, s), 13.83 (1H, s), 13.83 (1H, s).

mTOR Kinase Assay (Echo): 0.0149μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate



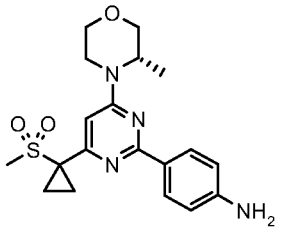
To a solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (1.35 g, 3.48 mmol) in 1,4-Dioxane (17.4 mL) was added sodium bicarbonate (0.438 g, 5.21 mmol) and phenyl chloroformate (0.437 mL, 3.48 mmol) and the reaction stirred at RT for 2 hours. The reaction mixture was diluted with DCM (20 mL), and washed with water (20 mL), the organic layer dried (MgSO4), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (1.058 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 1.24 (3H, d), 1.57 (2H, m), 1.68 (2H, m), 3.23 (1H, m), 3.49 (1H, m), 3.58 (3H, s), 3.64 (1H, m), 3.77 (1H, d), 3.97 (1H, m), 4.23 (1H,

d), 4.58 (1H, s), 6.81 (1H, s), 7.25 (2H, d), 7.30 (1H, d), 7.45 (2H, m), 7.64 (2H, d), 8.30 (2H, d), 10.44 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 509; HPLC tR = 2.48 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline

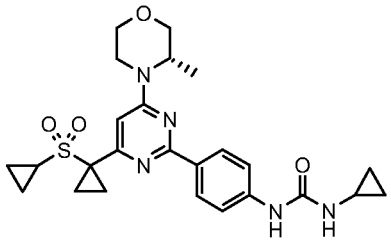


To a solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine (1.52 g, 4.58 mmol) in DMF (0.24 mL), DME (9.33 mL), water (4.0 mL) and ethanol (2.67 mL) was added 4-(*tert*-butoxycarbonylamino)phenylboronic acid (1.629 g, 6.87 mmol), sodium carbonate (5.73 mL, 11.45 mmol), and dichlorobis(triphenylphosphine)palladium(II) (0.161 g, 0.23 mmol) and the suspension heated at 80°C for 2 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate (10 mL) and washed with water (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was dissolved in DCM (6.67 mL) and trifluoroacetic acid (0.353 mL, 4.58 mmol) added and the reaction was stirred at RT for 16 hours. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% (7.5N ammonia in methanol) in DCM, to give the desired material as a beige solid (1.283 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 1.24 (3H, d), 1.55 (2H, m), 1.67 (2H, m), 3.23 (1H, m), 3.27 (3H, s), 3.47 (1H, m), 3.63 (1H, m), 3.77 (1H, d), 3.97 (1H, m), 4.24 (1H, s), 4.58 (1H, s), 5.75 (1H, s), 6.68 (2H, d), 8.04 (2H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 389; HPLC tR = 1.82 min.

Example 3: 3-Cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



[4-(3-Cyclopropylureido)phenyl]boronic acid, pinacol ester (199 mg, 0.66 mmol), 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (189mg, 0.53 mmol), dichlorobis(triphenylphosphine)palladium(II) (37.1 mg, 0.05 mmol) and sodium carbonate (1.32 mL, 2.64 mmol) were dissolved in a solution of 18% DMF in DME:Water:Ethanol 7:3:2 (4 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 20 minutes in the microwave reactor and cooled to RT. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol and pure fractions were evaporated to dryness to afford a crude product. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the desired material as a colourless gum (69.0 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 0.91 - 0.97 (1H, m), 0.94 (1H, s), 1.02 - 1.04 (2H, m), 1.23 (3H, t), 1.55 - 1.58 (2H, m), 1.64 - 1.66 (2H, m), 2.56 (1H, s), 2.98 - 3.02 (1H, m), 3.18 (1H, d), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.17 - 4.21 (1H, m), 4.53 (1H, s), 6.42 (1H, d), 6.85 (1H, s), 7.49 - 7.51 (2H, m), 8.20 - 8.22 (2H, m), 8.53 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 498; HPLC tR = 1.95 min.

mTOR Kinase Assay (Echo): 0.00195μM

Example 3, 3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea, may also be prepared as described below.

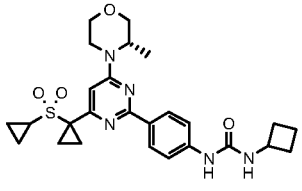
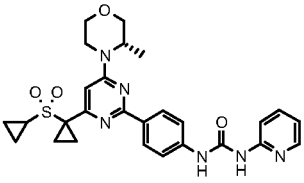
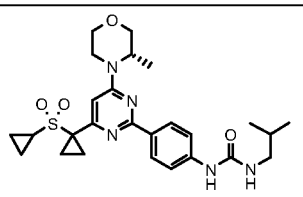
To a solution of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.28 mmol) in DMF (2

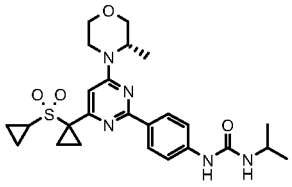
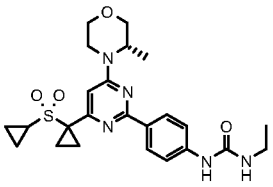
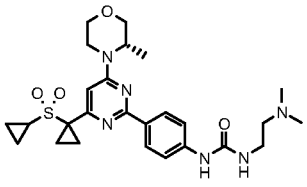
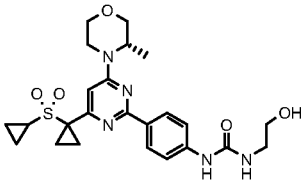
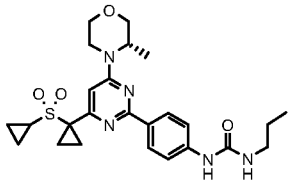
mL) was added triethylamine (0.177 mL, 0.84 mmol) followed by cyclopropylamine (0.097 mL, 1.40mmol) and the reaction heated at 50°C for 2 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (103 mg).

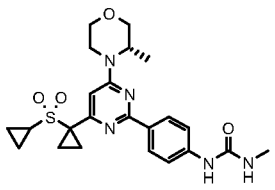
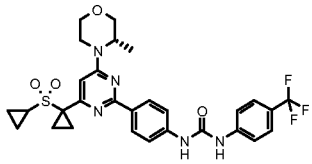
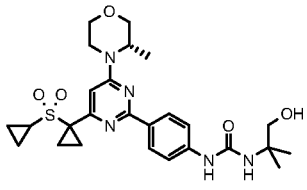
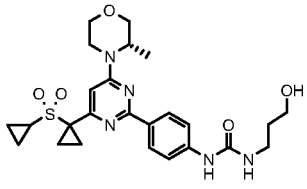
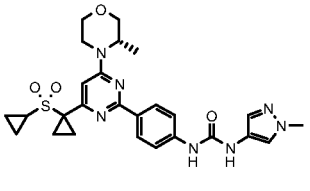
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 0.90 - 0.97 (2H, m), 1.02 - 1.04 (2H, m), 1.24 (3H, d), 1.56 - 1.60 (2H, m), 1.65 (2H, d), 2.60 (1H, t), 2.96 - 3.02 (1H, m), 3.20 - 3.24 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.42 (1H, d), 6.85 (1H, s), 7.50 (2H, d), 8.21 (2H, d), 8.53 (1H, s)

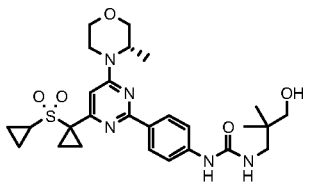
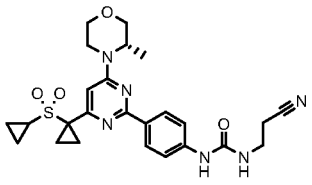
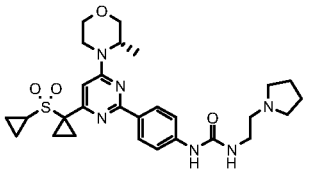
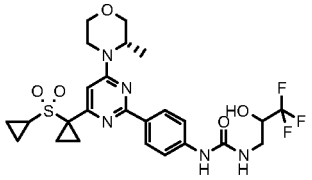
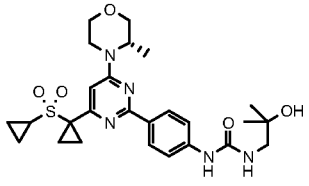
LCMS Spectrum: m/z (ESI+)(M+H)+ = 498; HPLC tR = 2.13 min.

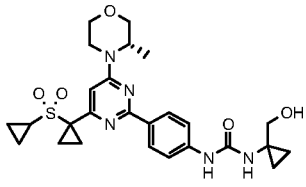
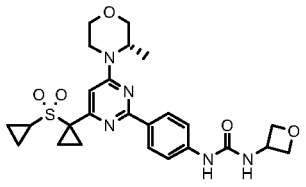
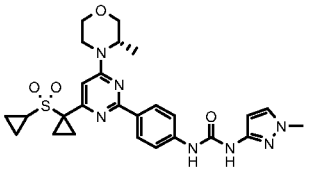
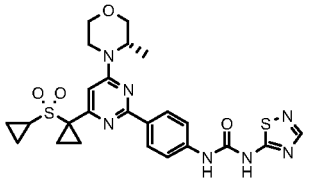
The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
3a		3-cyclobutyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	512	2.38
3b		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	535	2.58
3c		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	514	2.46

Example	Structure	NAME	LCMS MH+	Retention time (min)
3d		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	500	2.28
3e		3-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethyl-urea	486	2.12
3f		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	529	2.04
3g		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	502	1.79
3h		3-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea	500	2.29

Example	Structure	NAME	LCMS MH+	Retention time (min)
3i		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	472	1.96
3j		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	602	3.00
3k		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea	530	2.10
3l		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	516	1.83
3m		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	538	2.00

Example	Structure	NAME	LCMS MH+	Retention time (min)
3n		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxy-2,2-dimethylpropyl)urea	544	2.02
3o		3-(2-cyanoethyl)-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	511	1.92
3p		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-pyrrolidin-1-ylethyl)urea	555	2.17
3q		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3,3,3-trifluoro-2-hydroxypropyl)urea	570	2.01
3r		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxy-2-methylpropyl)urea	530	1.91

Example	Structure	NAME	LCMS MH+	Retention time (min)
3s		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea	528	1.91
3t		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(oxetan-3-yl)urea	514	1.92
3u		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-3-yl)urea	538	2.22
3w		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	542	1.50

Example 3a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.90 - 0.97 (2H, m), 1.02 - 1.04 (2H, m), 1.23 (3H, d), 1.56 - 1.59 (2H, m), 1.63 (2H, d), 1.65 (2H, d), 1.83 (1H, d), 1.86 (1H, t), 2.17 - 2.25 (2H, m), 2.97 - 3.01 (1H, m), 3.17 - 3.24 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.11 - 4.17 (1H, m), 4.20 (1H, s), 4.53 (1H, d), 6.45 (1H, d), 6.84 (1H, s), 7.46 - 7.48 (2H, m), 8.20 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.00445μM

Example 3b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.88 - 0.98 (2H, m), 0.99 - 1.06 (2H, m), 1.25 (3H, d), 1.57 - 1.62 (2H, m), 1.65 - 1.68 (2H, m), 2.99 - 3.05 (1H, m), 3.19 - 3.23 (1H, m), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.21 (1H, d),

4.54 (1H, d), 6.88 (1H, s), 7.02 - 7.05 (1H, m), 7.56 (1H, d), 7.63 (2H, d), 7.75 - 7.77 (1H, m), 8.29 - 8.31 (3H, m), 9.44 (1H, d), 10.58 (1H, s).

mTOR Kinase Assay (Echo): 0.00385μM

Example 3c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.88 - 0.90 (6H, m), 0.94 (2H, t), 1.00 - 1.06 (2H, m), 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.64 - 1.66 (2H, m), 1.67 - 1.74 (1H, m), 2.94 (2H, t), 2.98 - 3.02 (1H, m), 3.20 - 3.24 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.23 (1H, t), 6.84 (1H, s), 7.47 - 7.50 (2H, m), 8.20 - 8.22 (2H, m), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.0124μM

Example 3d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.97 (2H, m), 1.00 - 1.05 (2H, m), 1.11 (6H, d), 1.23 (3H, d), 1.55 - 1.58 (2H, m), 1.64 - 1.66 (2H, m), 2.97 - 3.03 (1H, m), 3.17 - 3.24 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.76 (2H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.05 (1H, d), 6.84 (1H, s), 7.46 - 7.49 (2H, m), 8.19 - 8.22 (2H, m), 8.52 (1H, s).

mTOR Kinase Assay (Echo): 0.0135μM

Example 3e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.94 (2H, t), 1.02 - 1.04 (2H, m), 1.07 (3H, t), 1.23 (3H, d), 1.58 (2H, d), 1.64 - 1.66 (2H, m), 2.98 - 3.02 (1H, m), 3.17 - 3.18 (1H, m), 3.14 - 3.24 (2H, m), 3.47 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.15 (1H, t), 6.84 (1H, s), 7.47 - 7.51 (2H, m), 8.19 - 8.22 (2H, m), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.00166μM

Example 3f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.97 (2H, m), 0.98 - 1.05 (2H, m), 1.23 (3H, d), 1.55 - 1.58 (2H, m), 1.64 - 1.66 (2H, m), 2.18 (6H, s), 2.34 (2H, t), 2.97 - 3.03 (1H, m), 3.19 (3H, q), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.15 (1H, t), 6.84 (1H, s), 7.47 - 7.50 (2H, m), 8.19 - 8.22 (2H, m), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.0214μM

Example 3g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.97 (2H, m), 1.00 - 1.05 (2H, m), 1.23 (3H, d), 1.55 - 1.58 (2H, m), 1.64 - 1.66 (2H, m), 2.97 - 3.03 (1H, m), 3.16 - 3.21 (3H, m), 3.44 - 3.52 (3H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.17 - 4.21 (1H, m), 4.53 (1H, s), 4.72 (1H, t), 6.25 (1H, t), 6.84 (1H, s), 7.47 - 7.50 (2H, m), 8.20 - 8.22 (2H, m), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.00134μM

Example 3h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 (3H, t), 0.91 - 0.95 (2H, m), 1.02 - 1.04 (2H, m), 1.23 (3H, d), 1.41 - 1.50 (2H, m), 1.56 - 1.60 (2H, m), 1.64 - 1.66 (2H, m), 2.98 - 3.02 (1H, m), 3.04 - 3.09 (2H, m), 3.20 - 3.24 (1H, m), 3.47 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.20 (1H, t), 6.84 (1H, s), 7.47 - 7.50 (2H, m), 8.20 - 8.22 (2H, m), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.0165μM

Example 3i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.95 (2H, m), 1.02 - 1.05 (2H, m), 1.23 (3H, d), 1.56 - 1.60 (2H, m), 1.63 - 1.66 (2H, m), 2.66 (3H, d), 2.98 - 3.02 (1H, m), 3.17 - 3.24 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.05 (1H, t), 6.84 (1H, s), 7.48 - 7.51 (2H, m), 8.19 - 8.22 (2H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.000932μM

Example 3j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.98 (2H, m), 1.01 - 1.05 (2H, m), 1.25 (3H, d), 1.57 - 1.62 (1H, m), 1.61 (1H, d), 1.65 - 1.68 (2H, m), 2.97 - 3.04 (1H, m), 3.22 - 3.26 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.21 (1H, d), 4.55 (1H, s), 6.87 (1H, s), 7.57 - 7.59 (2H, m), 7.63 - 7.70 (4H, m), 8.29 (2H, d), 9.04 (1H, s), 9.13 (1H, s).

mTOR Kinase Assay (Echo): 0.00422μM

Example 3k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.94 (2H, t), 1.04 (2H, d), 1.23 (6H, d), 1.24 (3H, d), 1.56 - 1.59 (2H, m), 1.64 - 1.66 (2H, m), 2.98 - 3.02 (1H, m), 3.18 (1H, d), 3.39 (2H, d), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.52 (1H, s), 4.95 (1H, t), 6.00 (1H, s), 6.84 (1H, s), 7.43 - 7.47 (2H, m), 8.19 - 8.21 (2H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00227μM

Example 3l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.94 (2H, m), 1.01 - 1.05 (2H, m), 1.23 (3H, d), 1.55 - 1.58 (2H, m), 1.60 -1.61 (2H, m), 1.65 (1H, m), 2.98 - 3.02 (1H, m), 3.17 (1H, d), 3.18 - 3.23 (2H, m), 3.45 - 3.49 (3H, m), 3.50 (1H, d), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.17 (1H, s), 4.47 (1H, t), 4.53 (1H, s), 6.20 (1H, t), 6.84 (1H, s), 7.48 - 7.50 (2H, m), 8.21 (2H, d), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00257μM

Example 3m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.95 (2H, m), 1.02 - 1.05 (2H, m), 1.24 (3H, d), 1.57 - 1.60 (2H, m), 1.65 - 1.67 (2H, m), 2.98 - 3.02 (1H, m), 3.18 (1H, t), 3.46 - 3.50 (1H, m), 3.63 - 3.66 (1H, m), 3.76 (1H, s), 3.79 (3H, s), 3.96 - 4.00 (1H, m), 4.18 (1H, s), 4.53 (1H, s), 6.86 (1H, s), 7.38 - 7.38 (1H, m), 7.55 (2H, t), 7.76 (1H, s), 8.25 (2H, d), 8.38 (1H, s), 8.83 (1H, s).

mTOR Kinase Assay (Echo): 0.000497μM

Example 3n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.81 (6H, s), 0.91 - 0.95 (2H, m), 1.01 - 1.05 (2H, m), 1.23 (3H, d), 1.56 - 1.60 (3H, m), 1.63 - 1.66 (2H, m), 2.98 - 3.02 (2H, m), 3.15 (2H, d), 3.21 (1H, dt), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 4.19 (1H, d), 4.53 (1H, s), 4.61 (1H, t), 6.26 (1H, t), 6.84 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.0396μM

Example 3o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.90 - 0.95 (2H, m), 1.00 - 1.06 (2H, m), 1.24 (3H, d), 1.56 - 1.60 (2H, m), 1.63 - 1.66 (2H, m), 2.70 (2H, t), 2.96 - 3.03 (1H, m), 3.17 - 3.25 (1H, m), 3.35 - 3.39 (2H, m), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.53 (1H, s), 6.52 (1H, t), 6.85 (1H, s), 7.51 (2H, d), 8.22 (2H, d), 8.91 (1H, s).

mTOR Kinase Assay (Echo): 0.00596μM

Example 3p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.94 (2H, m), 1.02 - 1.04 (2H, m), 1.23 (3H, d), 1.56 - 1.58 (2H, m), 1.64 - 1.67 (2H, m), 1.72 (8H, m), 2.94 - 3.02 (1H, m), 3.18 - 3.24 (5H, m), 3.49 (1H, t), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.19 (1H, d), 4.53 (1H, s), 6.22 (1H, s), 6.84 (1H, s), 7.49 (2H, d), 8.21 (2H, d), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.193μM

Example 3q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.95 (2H, m), 1.00 - 1.06 (2H, m), 1.23 (3H, d), 1.56 - 1.60 (2H, m), 1.63 - 1.66 (2H, m), 2.96 - 3.03 (1H, m), 3.14 - 3.25 (2H, m), 3.46 - 3.55 (2H, m), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.07 - 4.08 (1H, m), 4.19 (1H, d), 4.52 (1H, s), 6.42 (1H, t), 6.49 (1H, s), 6.85 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.95 (1H, s).

mTOR Kinase Assay (Echo): 0.00839μM

Example 3r: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.95 (2H, m), 1.00 - 1.06 (2H, m), 1.10 (6H, s), 1.23 (3H, d), 1.56 - 1.60 (2H, m), 1.61 - 1.66 (2H, m), 2.97 - 3.02 (1H, m), 3.06 (2H, d), 3.22 (1H, dd), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.52 (1H, s), 4.54 (1H, s), 6.24 (1H, t), 6.84 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.0488μM

Example 3s: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.63 - 0.67 (2H, m), 0.69 - 0.73 (2H, m), 0.91 - 0.95 (2H, m), 1.02 - 1.04 (2H, m), 1.23 (3H, d), 1.56 - 1.60 (2H, m), 1.63 - 1.66 (2H, m), 2.97 - 3.03 (1H, m), 3.17 - 3.25 (2H, m), 3.44 (1H, d), 3.46 - 3.52 (1H, m), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.52 (1H, s), 4.83 (1H, s), 6.56 (1H, s), 6.85 (1H, s), 7.47 (2H, d), 8.21 (2H, d), 8.67 (1H, s).

mTOR Kinase Assay (Echo): 0.0263μM

Example 3t: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.95 (2H, m), 1.00 - 1.07 (2H, m), 1.23 (3H, d), 1.56 - 1.61 (2H, m), 1.63 - 1.66 (2H, m), 2.96 - 3.02 (1H, m), 3.21 (1H, dt), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.45 (2H, t), 4.52 (1H, s), 4.72 - 4.83 (3H, m), 6.85 (1H, s), 6.95 (1H, d), 7.49 (2H, d), 8.22 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00479μM

Example 3u: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.95 (2H, m), 1.00 - 1.07 (2H, m), 1.23 (3H, d), 1.56 - 1.61 (2H, m), 1.63 - 1.66 (2H, m), 2.96 - 3.02 (1H, m), 3.21 (1H, dt), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.45 (2H, t), 4.52 (1H, s), 4.72 - 4.83 (3H, m), 6.85 (1H, s), 6.95 (1H, d), 7.49 (2H, d), 8.22 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.000604μM

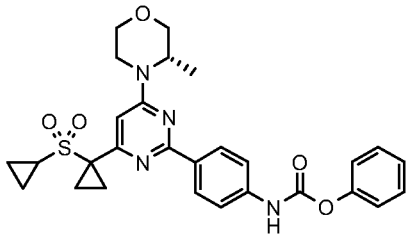
Example 3v: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.94 - 0.96 (2H, m), 1.03 - 1.05 (2H, m), 1.24 (3H, d), 1.57 - 1.59 (2H, m), 1.64 - 1.66 (2H, m), 2.98 - 3.03 (1H, m), 3.19 - 3.25 (1H, m), 3.50 (1H, t), 3.65 (1H, d), 3.74 (3H, s), 3.77 (1H, d), 3.98 (1H, d), 4.21 (1H, d), 4.54 (1H, s), 6.24 (1H, d), 6.86 (1H, s), 7.54 - 7.55 (1H, m), 7.56 (2H, d), 8.26 (2H, d), 8.92 (1H, s), 9.17 (1H, s).

Example 3w: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.96 (2H, m), 1.02 - 1.06 (2H, m), 1.25 (3H, d), 1.58 - 1.60 (2H, m), 1.66 - 1.67 (2H, m), 2.98 - 3.05 (1H, m), 3.20 - 3.23 (1H, m), 3.50 (1H, t), 3.65 (1H, d), 3.78 (1H, d), 3.99 (1H, d), 4.21 (1H, d), 4.55 (1H, s), 6.89 (1H, s), 7.63 (2H, d), 8.31 - 8.36 (3H, m), 9.43 (1H, s).

mTOR Kinase Assay (Echo): 0.00089μM

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

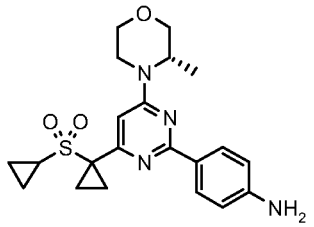


Phenyl chloroformate (0.729 mL, 5.79 mmol) was added dropwise to 4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (2.40 g, 5.79 mmol) and sodium bicarbonate (0.730 g, 8.68 mmol) in dioxane (45 mL) under nitrogen. The resulting suspension was stirred at 20°C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in ethyl acetate (200 mL) and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a white solid (3.03 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d6) δ 0.92 - 0.95 (2H, m), 1.03 - 1.05 (2H, m), 1.25 (3H, d), 1.57 - 1.61 (1H, m), 1.61 (1H, d), 1.65 - 1.68 (2H, m), 2.99 - 3.03 (1H, m), 3.46 - 3.47 (1H, m), 3.49 - 3.53 (1H, m), 3.63 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.22 (1H, d), 4.56 (1H, s), 6.89 (1H, s), 7.26 (1H, t), 7.24 - 7.30 (2H, m), 7.43 - 7.47 (2H, m), 7.60 - 7.65 (2H, m), 8.29 - 8.32 (2H, m), 10.43 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 535; HPLC tR = 2.84 min.

4-[4-(1-Cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



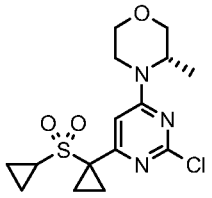
Dichlorobis(triphenylphosphine)palladium(II) (0.524 g, 0.75 mmol) was added to a degassed solution of 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.67 g, 7.46 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.043 g, 9.33 mmol) and sodium carbonate (18.65 mL, 37.31 mmol) in 18% DMF in 7:3:2 DME:Water:Ethanol (20 mL). The resulting solution was stirred at 85°C for 1 hour. The

reaction mixture was concentrated and diluted with DCM (150 mL), and washed with water (100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 2.5% methanol in DCM, to give the desired material as a brown solid (2.40 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d6) δ 0.90 - 0.98 (2H, m), 0.98 - 1.05 (2H, m), 1.22 (3H, d), 1.52 - 1.59 (2H, m), 1.62 - 1.64 (2H, m), 2.95 - 3.02 (1H, m), 3.14 - 3.22 (1H, m), 3.45 - 3.51 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.98 (1H, m), 4.14 - 4.17 (1H, m), 4.48 - 4.51 (1H, m), 5.53 (2H, d), 6.60 (2H, d), 6.75 (1H, s), 8.03 - 8.06 (2H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 415; HPLC tR = 2.13 min.

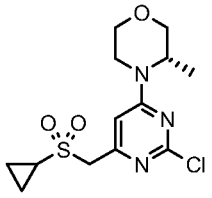
2-Chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



5N Sodium hydroxide solution (1.74 mL, 8.68 mmol) was added to tetrabutylammonium bromide (0.140 g, 0.43 mmol), 1,2-dibromoethane (0.374 mL, 4.34 mmol) and 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.44 g, 4.34 mmol) in DCM (20 mL). The resulting mixture was stirred at 40°C for 2 hours. Additional solid sodium hydroxide (4 g, 0.1 mol) was added directly to the reaction and stirred at 40°C for a further 1 hour. The reaction mixture was diluted with DCM (20 mL) and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material (1.68 g).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 358; HPLC tR = 1.87 min.

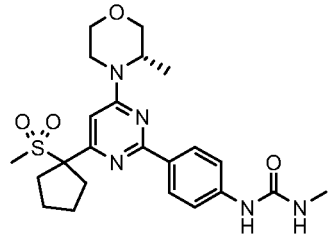
2-Chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Cyclopropanesulfinic acid, sodium salt (381 mg, 2.97 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (700 mg, 1.98 mmol) in acetonitrile (20 mL) at RT. The resulting suspension was stirred at 90°C for 3 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL), and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to gve the desired material as a white solid (458 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 0.95 - 0.98 (2H, m), 1.02 - 1.06 (2H, m), 1.18 - 1.23 (3H, m), 2.77 - 2.83 (1H, m), 3.19 - 3.25 (1H, m), 3.42 - 3.49 (1H, m), 3.58 - 3.62 (1H, m), 3.73 (1H, d), 3.92 - 3.96 (2H, m), 4.30 (1H, s), 4.48 (2H, s), 6.92 (1H, s).
LCMS Spectrum: m/z (ESI+) (M+H)+ = 332; HPLC tR = 1.68 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 4: 3-Methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea

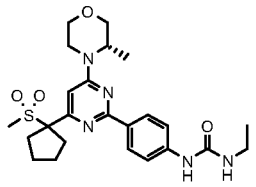
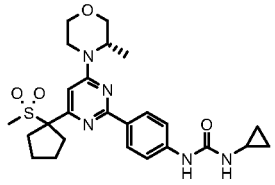
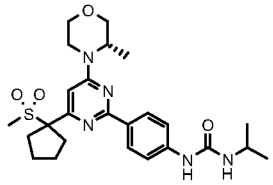
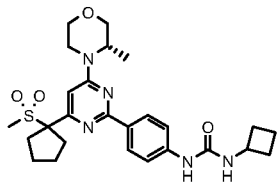
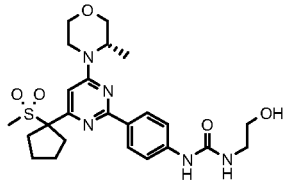


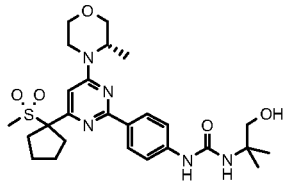
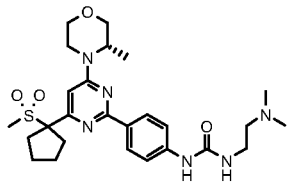
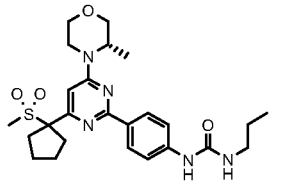
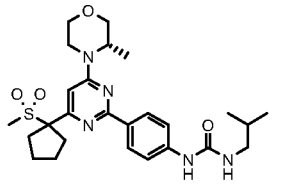
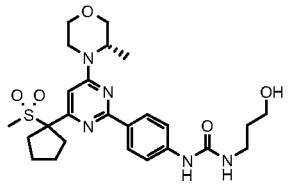
Triethylamine (0.15 mL, 1.1 mmol) was added to a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]carbamate (200 mg, 0.37 mmol) and methylamine (2M in THF, 1.48 mmol) in NMP (2 mL). The reaction was heated at 80°C for 2 hours the purified by prep HPLC, using a mixture of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a solid (126 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.52-1.62 (2H, m), 1.75-1.90 (2H, m), 2.38-2.50 (2H, m), 2.65 (3H, d), 2.65-2.78 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3.64 (1H, d), 3.75 (1H, d), 3.95 (1H, dd), 4.25 (1H, d), 4.55 (1H, s), 6.05 (1H, q), 6.79 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.72 (1H, s).

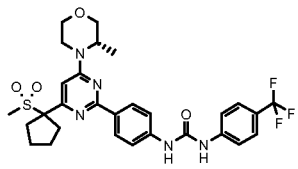
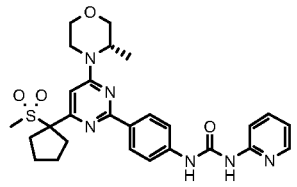
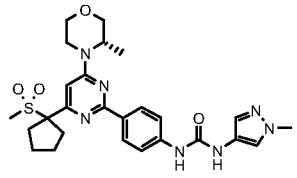
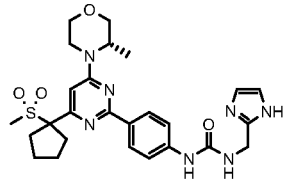
LCMS Spectrum: m/z (ESI+)(M+H)+ = 474; HPLC tR = 1.96 min

mTOR Kinase Assay (Echo): 0.000699μM

The following compounds were prepeared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
4a		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	488	2.13
4b		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	500	2.13
4c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	502	2.29
4d		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	514	2.35
4e		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	504	1.80

Example	Structure	NAME	LCMS MH+	Retention time (min)
4f		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	532	2.09
4g		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	531	2.07
4h		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-propyl-urea	502	2.28
4i		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	517	2.45
4j		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	518	1.84

Example	Structure	NAME	LCMS MH+	Retention time (min)
4k		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	604	2.95
4l		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	537	2.55
4m		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	540	1.99
4n		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	540	1.92

Example 4a: ^{1}H NMR (400.132 MHz, DMSO) δ 1.05 (3H, t), 1.21 (3H, d), 1.50-1.62 (2H, m), 1.78-1.85 (2H, m), 2.35-2.45 (2H, m), 2.65-2.75 (2H, m), 2.89 (3H, s), 3.12 (2H, q), 3.18 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.24 (1H, d), 4.55 (1H, s), 6.15 (1H, t), 6.78 (1H, s), 7.48 (2H, d), 8.22 (2H, d), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.00216μM

Example 4b: ^{1}H NMR (400.132 MHz, DMSO) δ 0.41 (2H, q), 0.62 (2H, q), 1.21 (3H, d), 1.51-1.61 (2H, m), 1.75-1.86 (2H, m), 2.35-2.45 (2H, m), 2.55 (1H, m), 2.65-2.85 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.25 (1H, d), 4.55 (1H, s), 6.41 (1H, d), 6.78 (1H, s), 7.50 (2H, d), 8.25 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.00203μM

Example 4c: ^{1}H NMR (400.132 MHz, DMSO) δ 1.11 (6H, d), 1.21 (3H, d), 1.50-1.62 (2H, m), 1.75-1.85 (2H, m), 2.38-2.50 (3H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, dd), 3.99 (1H, dd), 4.23 (1H, d), 4.55 (1H, s), 6.05 (1H, d), 6.79 (1H, s), 7.48 (2H, d), 8.22 (2H, d), 8.54 (1H, s).

mTOR Kinase Assay (Echo): 0.0169μM

Example 4d: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.65 (4H, m), 1.75-1.90 (4H, m), 2.15-2.20 (2H, m), 2.35-2.50 (2H, m), 2.65-2.80 (2H, m), 2.88 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, dd), 3.95 (1H, dd), 4.15 (1H, q), 4.22 (1H, d), 4.55 (1H, s), 6.42 (1H, d), 6.79 (1H, s), 7.45 (2H, d), 8.22 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.01μM

Example 4e: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.62 (2H, m), 1.78-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.15-3.22 (3H, m), 3.40-3.50 (3H, m), 3.65 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.22 (1H, d), 4.55 (1H, s), 4.71 (1H, t), 6.22 (1H, t), 6.78 (1H, s), 7.45 (2H, d), 8.22 (2H, d), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00119μM

Example 4f: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.62 (2H, m), 1.75-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.35-3.40 (2H, m), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.22 (1H, d), 4.55 (1H, s), 4.95 (1H, t), 6.0 (1H, s), 6.78 (1H, s), 7.45 (2H, d), 8.22 (2H, d), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.01μM

Example 4g: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.60 (2H, m), 1.75-1.85 (2H, m), 2.18 (6H, s), 2.31 (2H, t), 2.38-2.50 (2H, m), 2.65-2.75 (2H, m), 2.89 (3H, s), 3.15-3.22 (3H, m), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, dd), 3.96 (1H, dd), 4.22 (1H, dd), 4.55 (1H, s), 6.15 (1H, t), 6.79 (1H, s), 7.48 (2H, d), 8.22 (2H, d), 8.87 (1H, s).

mTOR Kinase Assay (Echo): 0.0626μM

Example 4h: ^{1}H NMR (400.132 MHz, DMSO) δ 0.88 (3H, t), 1.21 (3H, d), 1.45 (2H, q), 1.50-1.62 (2H, m), 1.75-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.05 (2H, m), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.22 (1H, d), 4.55 (1H, s), 6.20 (1H, t), 6.78 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.62 (1H, s).

mTOR Kinase Assay (Echo): 0.00157μM

Example 4i: ^{1}H NMR (400.132 MHz, DMSO) δ 0.88 (6H, d), 1.21 (3H, d), 1.50-1.62 (2H, m), 1.70 (1H, m), 1.75-1.85 (2H, m), 2.35-2.50 (2H, m), 2.65-2.80 (2H, m), 2.90 (3H, s), 2.94 (2H, t), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, dd), 3.97 (1H, dd), 4.24 (1H, d), 4.54 (1H, s), 6.22 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.0115μM

Example 4j: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.62 (4H, m), 1.75-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.10-3.22 (3H, m), 3.45-3.52 (3H, m), 3.65 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.22 (1H, d), 4.45 (1H, t), 4.55 (1H, s), 6.1991H, t), 6.79 (1H, s), 7.49 (2H, d), 8.22 (2H, d), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00461μM

Example 4k: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.62 (2H, m), 1.75-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3, 22 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.25 (1H, d), 4.55 (1H, s), 6.80 (1H, s), 7.58 (2H, d), 7.62-7.70 (4H, m), 8.30 (2H, d), 9.04 (1H, s), 9.10 (1H, s).

mTOR Kinase Assay (Echo): 0.00905μM

Example 4l: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.55-1.62 (2H, m), 1.78-1.90 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, d), 3.9791H, dd), 4.2591H, d), 4.55 (1H, s), 6.80 (1H, s), 7.02 (1H, dd), 7.58 (1H, d), 7.61 (2H, d), 7.74 (1H, dd), 8.25-8.35 (4H, m), 9.41 (1H, s).

mTOR Kinase Assay (Echo): 0.00369μM

Example 4m: ^{1}H NMR (400.132 MHz, DMSO) δ 1.20 (3H, d), 1.50-1.62 (2H, m), 1.78-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75-40 (4H, m), 3.97 (1H, dd), 4.25 (1H, d), 4.55 (1H, s), 6.80 (1H, s), 7.38 (1H, s), 7.55 (2H, d), 7.73 (1H, s), 8.25 (2H, d), 8.35 (1H, s), 8.85 (1H, s).

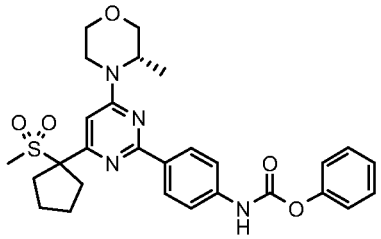
mTOR Kinase Assay (Echo): 0.00245μM

Example 4n: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.62 (2H, m), 1.75-1.85 (2H, m), 2.35-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3, 65 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.24 (1H, d), 4.35 (1H, d), 4.55 (1H, s), 6.65 (1H, t), 6.78 (1H, s), 7.04 (2H, s), 7.52 (2H, d), 8.25 (2H, d), 9.0 (1H, s), 12.6 (1H, s).

mTOR Kinase Assay (Echo): 0.0392μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]carbamate

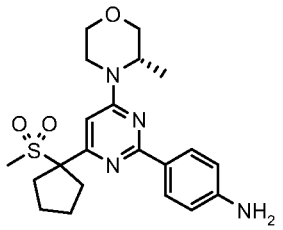


Sodium hydrogen carbonate (1.150 g, 13.68 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]aniline (3.8 g, 9.12 mmol), in dioxane (100 mL) at 21°C under nitrogen. The resulting mixture was cooled to10°C and phenyl chloroformate (1.72 mL, 13.68 mmol) added slowly then the reaction stirred for 3 hours and allowed to warm to RT and left for 16 hours. The reaction mixture was diluted with ethyl acetate (250 mL), and washed with water (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether, iso-hexane and acetone to give the desired material as a white solid (4.50 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.50-1.62 (2h, m), 1.75-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 3.21 (1H, dd), 3.30 (3H, s), 3.50 (1H, dd), 3.63 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.28 (1H, d), 4.57 (1H, s), 6.81 (1H, s), 7.22-7.30 (3Hh, m), 7.43 (2H, dd), 7.61 (1H, d), 8.32 (2H, d), 10.45 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 537 ; HPLC tR = 2.98 min

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]aniline

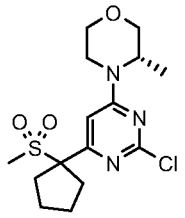


Bis (triphenylphosphine)palladium (II) chloride (0.390 g, 0.56 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidine (4.0g, 11.12 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.17 g, 14.45 mmol) and sodium carbonate (20 mL, 40.0 mmol) in a mixture of DMF (20 mL), DME (50 mL), ethanol (20 mL) and water (20 mL) at RT under nitrogen. The resulting mixture was stirred at 95°C for 12 hours. The reaction mixture was diluted with ethyl acetate (400 mL), washed twice with water (200 mL followed by 250 mL), the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was chromatographed on silica, eluting with 5 - 50% ethyl acetate in iso-hexane, to give a yellow solid which was subsequently triturated with a mixture of diethyl ether and iso-hexane to give the desired material as a white solid (4.25 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.50-1.60 (2H, m), 1.75-1.90 (2H, m), 2.34-2.43 (2H, m), 2.62-2.78 (2H, m), 2.88 (3H, s), 3.18 (1H, dd), 3.48 (1H, dd), 3.65 (1H, dd), 3.75 (1H, dd), 3.95 (1H, dd), 4.20 (1H, d), 4.51 (1H, s), 5.55 (2H, s), 6.62 (2H, d), 6.68 (1H, s), 8.09 (1H, d).

Mass Spectrum: m/z (ESI+)(M+H)+ = 417

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidine

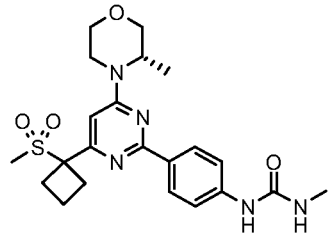


Tetrabutylammonium bromide (0.495 g, 1.54 mmol) was added toa mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6- (methylsulfonylmethyl)pyrimidine (4.7 g, 15.37 mmol), 1, 4-dibromobutane (1.84 mL, 15.37 mmol) and aqueous sodium hydroxide solution (30 mL, 368.9 mmol) in DCM (150 mL) at RT under nitrogen. The resulting mixture was stirred at 40°C for 6 hours. The reaction mixture was diluted with DCM (200 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was chromatographed on silica, eluting with 5 - 50% ethyl acetate in iso-hexane, to give the desired material as a yellow solid (3.90 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.50-1.60 (2H, m), 1.72-1.82 (2H, m), 2.30-2.41 (2H, m,), 2.50-2.60 (2H, m), 2.88 (3H, s), 3.20 (1H, dd), 3.45 (1H, dd), 3.60 (1H, dd), 3.71 (1H, d), 3.94 (1H, dd), 4.0-4.10 (1H, m), 4.42 (1H, s), 6.89 (1H, s).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 360 ; HPLC tR = 2.22 min

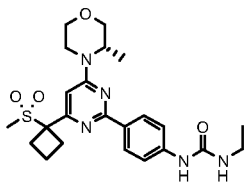
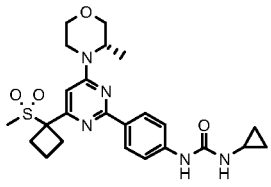
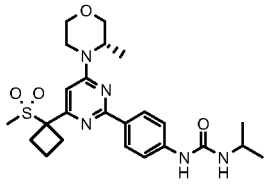
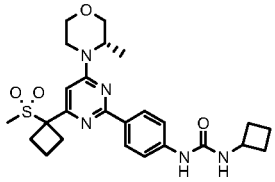
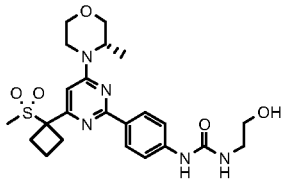
The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine was described earlier.

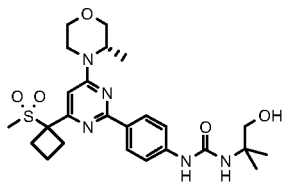
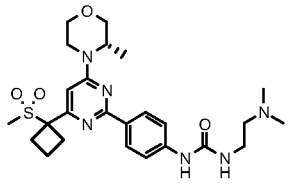
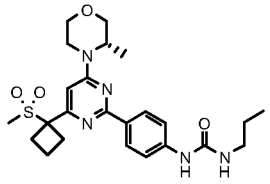
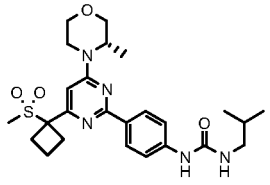
Example 5: 3-Methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea

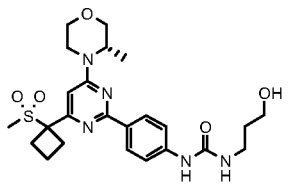
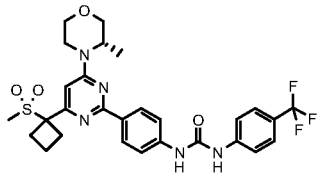
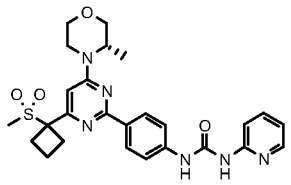
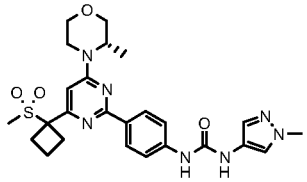


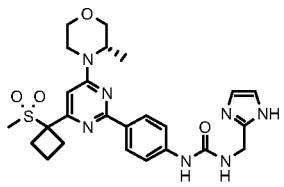
Triethylamine (0.07 mL, 0.48mmol) was added to a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate (86 mg, 0.16 mmol) and methylamine (2M in THF, 0.65 mmol) in NMP (2 mL). The reaction was heated at 80°C for 2 hours the purified by prep HPLC, using a mixture of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a solid (48 mg).
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.91 (2H, m), 2.08 (2H, m), 2.62(3H,d), 2.80 (2H, m), 2.87 (3H, s), 3.21 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.24 (1H, d), 4.60 (1H, s), 6.07 (1H, d), 6.71 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.75 (1H, s).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 460; HPLC tR = 1.5 min
mTOR Kinase Assay (Echo): 0.000802μM

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
5a		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	474	1.98
5b		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	486	2.01
5c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	488	2.15
5d		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	500	2.24
5e		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	490	1.69

Example	Structure	NAME	LCMS MH+	Retention time (min)
5f		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	518	1.97
5g		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	517	1.98
5h		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-propyl-urea	488	2.16
5i		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	502	2.33

Example	Structure	NAME	LCMS MH+	Retention time (min)
5j		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	504	1.73
5k		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	590	2.84
5l		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	523	2.42
5m		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	526	1.88

Example	Structure	NAME	LCMS MH+	Retention time (min)
5n		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	526	1.79

Example 5a: ^{1}H NMR (400.132 MHz, DMSO) δ 1.07 (3H, t), 1.24 (3H, d), 1.91 (2H, m), 2.07 (2H, m), 2.81 (2H, m), 2.87 (3H, s), 3.12 (2H, m), 3.22 (1H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.24 (1H, d), 4.59 (1H, s), 6.16 (1H, t), 6.71 (1H, s), 7.49 (2H, d), 8.22 (2H, d), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.000289μM

Example 5b: ^{1}H NMR (400.132 MHz, DMSO) δ 0.42 (2H, m), 0.65 (2H, m), 1.24 (3H, d), 1.92 (2H, m), 2.08 (2H, m), 2.56 (2H, m), 2.80 (2H, m), 2.88 (3H, s), 3.21 (1H, td), 3.54 (1H, s), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.24 (1H, d), 4.59 (1H, s), 6.45 (1H, s), 6.72 (1H, s), 7.51 (2H, d), 8.22 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.000383μM

Example 5c: ^{1}H NMR (400.132 MHz, DMSO) δ 1.11 (6H, d), 1.24 (3H, d), 1.86 - 1.96 (2H, m), 2.03 - 2.13 (2H, m), 2.76 - 2.84 (2H, m), 2.86 (3H, s), 3.21 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.73 - 3.80 (2H, m), 3.98 (1H, dd), 4.25 (1H, d), 4.61 (1H, s), 6.05 (1H, d), 6.72 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.54 (1H, s).

mTOR Kinase Assay (Echo): 0.00681μM

Example 5d: ^{1}H NMR (400.132 MHz, DMSO) δ 1.23 (3H, d), 1.58 - 1.67 (3H, m), 1.81 - 1.94 (4H, m), 2.02 - 2.11 (2H, m), 2.20 (2H, m), 2.76 - 2.84 (2H, m), 2.87 (3H, s), 3.21 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.13 (1H, quintet), 4.25 (1H, d), 4.61 (1H, s), 6.45 (1H, d), 6.71 (1H, s), 7.47 (2H, d), 8.21 (3H, d), 8.58 (2H, s).

mTOR Kinase Assay (Echo): 0.00385μM

Example 5e: ^{1}H NMR (400.132 MHz, DMSO) δ 1.24 (3H, d), 1.87 - 1.97 (2H, m), 2.01 - 2.12 (2H, m), 2.77 - 2.85 (2H, m), 2.88 (3H, s), 3.15 - 3.25 (3H, m), 3.43 - 3.54 (3H, m), 3.65

(1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.24 (1H, d), 4.60 (1H, s), 4.72 (1H, t), 6.26 (1H, t), 6.71 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.82 (1H, s).

mTOR Kinase Assay (Echo): 0.000864μM

Example 5f: ^{1}H NMR (400.132 MHz, DMSO) δ 1.25 (14H, s), 1.87 - 1.95 (2H, m), 2.03 - 2.11 (2H, m), 2.76 - 2.83 (7H, m), 2.88 (7H, s), 3.17 - 3.25 (15H, m), 3.39 (2H, d), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.59 (1H, s), 4.95 (1H, t), 6.02 (1H, s), 6.72 (1H, s), 7.44 (2H, d), 8.21 (2H, d), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.00736μM

Example 5g: ^{1}H NMR (400.132 MHz, DMSO) δ 1.24 (3H, d), 1.87 - 1.96 (2H, m), 2.02 - 2.12 (2H, m), 2.21 (6H, s), 2.34 (2H, t), 2.74 - 2.85 (2H, m), 2.88 (3H, s), 3.15 - 3.26 (3H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.24 (1H, d), 4.60 (1H, s), 6.15 (1H, t), 6.72 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.91 (1H, s).

mTOR Kinase Assay (Echo): 0.0668μM

Example 5h: ^{1}H NMR (400.132 MHz, DMSO) δ 0.89 (3H, t), 1.24 (3H, d), 1.40 - 1.51 (2H, m), 1.87 - 1.97 (2H, m), 2.01 - 2.12 (2H, m), 2.76 - 2.84 (2H, m), 2.89 (3H, s), 3.06 (2H, q), 3.17 - 3.27 (1H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.24 (1H, d), 4.57 (1H, s), 6.20 (1H, t), 6.72 (1H, s), 7.49 (2H, d), 8.21 (2H, d), 8.66 (1H, s).

mTOR Kinase Assay (Echo): 0.00234μM

Example 5i: ^{1}H NMR (400.132 MHz, DMSO) δ 0.89 (6H, d), 1.24 (3H, d), 1.65 - 1.75 (2H, m), 1.85 - 1.96 (2H, m), 2.01 - 2.12 (2H, m), 2.75 - 2.84 (2H, m), 2.88 (3H, s), 2.89 - 2.99 (3H, m), 3.16 - 3.26 (1H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.24 (1H, d), 4.56 (1H, s), 6.24 (1H, t), 6.72 (1H, s), 7.49 (2H, d), 8.22 (2H, d), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.00988μM

Example 5j: ^{1}H NMR (400.132 MHz, DMSO) δ 1.24 (3H, d), 1.59 (2H, q), 1.86 - 1.96 (2H, m), 2.02 - 2.14 (2H, m), 2.76 - 2.85 (2H, m), 2.88 (3H, s), 3.13 - 3.26 (3H, m), 3.45 - 3.54 (3H, m), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.24 (1H, d), 4.48 (1H, t), 4.56 (1H, s), 6.20 (1H, t), 6.72 (1H, s), 7.49 (2H, d), 8.21 (2H, d), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.000239μM

Example 5k: mTOR Kinase Assay (Echo): 0.00333μM

Example 5l: mTOR Kinase Assay (Echo): 0.000248μM

Example 5m: ^{1}H NMR (400.132 MHz, DMSO) δ 1.24 (3H, d), 1.87 - 1.98 (2H, m), 2.03 - 2.12 (2H, m), 2.76 - 2.84 (2H, m), 2.88 (3H, s), 3.17 - 3.30 (4H, m), 3.51 (1H, td), 3.65 (1H,

dd), 3.73 - 3.80 (1H, m), 3.98 (1H, dd), 4.25 (1H, d), 4.62 (1H, s), 6.73 (1H, s), 7.39 (1H, s), 7.54 (2H, d), 7.77 (1H, s), 8.27 (2H, d), 8.40 (1H, s), 8.86 (1H, s).

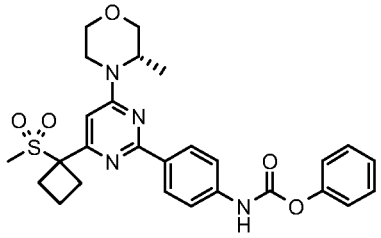
mTOR Kinase Assay (Echo): 0.00069μM

Example 5n: ^{1}H NMR (400.132 MHz, DMSO) δ 1.24 (3H, d), 1.87 - 1.97 (2H, m), 2.03 - 2.12 (2H, m), 2.75 - 2.85 (2H, m), 2.88 (3H, s), 3.21 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.25 (1H, d), 4.32 (2H, d), 4.60 (1H, s), 6.62 (1H, t), 6.98 (2H, s), 7.52 (2H, d), 8.24 (2H, d), 11.88 (1H, s).

mTOR Kinase Assay (Echo): 0.00828μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate

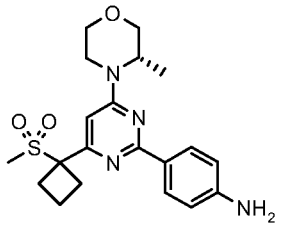


Sodium hydrogen carbonate (0.313 g, 3.73 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]aniline (1 g, 2.48 mmol), in dioxane (20 mL) at RT under nitrogen. The resulting mixture was cooled to 10°C and phenyl chloroformate (0.468 mL, 3.73 mmol) added slowly. The reaction was stirred for 3 hours then diluted with ethyl acetate (150 mL), and washed with water (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The crude solid was triturated with a mixture of diethyl ether, iso-hexane and acetone to give the desired material as a white solid (1.35 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21(3H,d), 1.88-1.96(2H,m), 2.02-2.11(2H,m), 2.75-2.85(2H,m), 2.85(3H,s), 3.21(1H,dd), 3.50(1H,dd), 3.64(1H,d), 3.75(1H,d), 3.98(1H,dd), 4.25(1H,d), 4.57(1H,s), 6.72(1H,s), 7.20-7.30(3H,m), 7.42(2H,dd), 7.61(2H,d), 8.32(2H,m), 10.44(1H,s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 523; HPLC tR = 2.88 min

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]aniline

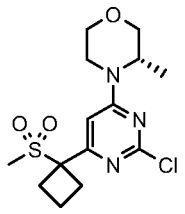


Bis(triphenylphosphine)palladium(II) chloride (0.101 g, 0.14 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidine (1 g, 2.89 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.824 g, 3.76 mmol) and sodium carbonate (5 mL, 10.00 mmol) in a mixture of DMF (5 mL), DME (50 mL), ethanol (20 mL) and water (20 mL) at RT under nitrogen. The resulting mixture was stirred at 95°C for 12 hours. The reaction mixture was diluted with ethyl acetate (400 mL), and washed twice with water (200 mL followed by 250 mL), the organic layer dried (Na_2SO_4), filtered and evaporated. The crude product was chromatographed on silica, eluting with 5 - 60% ethyl acetate in iso-hexane, to give the desired material as a cream solid (0.98 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21(3H,d), 1.85-1.95(2H,m), 2.0-2.10(2H,m), 2.71-2.82(2H,m), 2.82(3H,s), 3.18(1H,dd), 3.50(1H,dd), 3.62(1H,dd), 3.75(1H,d), 3.95(1H,dd), 4.20(1H,d), 4.53(1H,s), 5.55(2H,s), 6.60(3H,d), 8.05(2H,d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 403; HPLC tR = 2.17 min

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidine



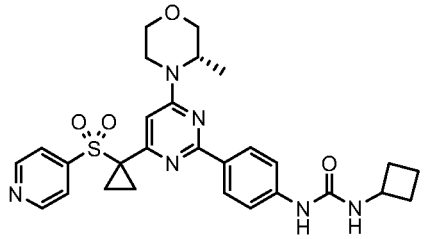
Tetrabutylammonium bromide (0.45 g, 1.40 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (4.27 g, 13.96 mmol), 1,3-dibromopropane (1.42 mL, 13.96 mmol) and aqueous sodium hydroxide solution (30 mL, 368.9 mmol) in DCM (100 mL) at RT under nitrogen. The resulting mixture was stirred at 35°C for 5 hours then diluted with DCM (50 mL), and washed with water (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was

chromatographed on silica, eluting with 5 - 50% ethyl acetate in iso-hexane, to give the desired material (1.0 g).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 346; HPLC tR = 1.92 min

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine was described earlier.

Example 6: 3-Cyclobutyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



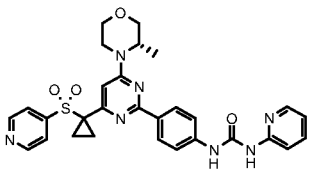
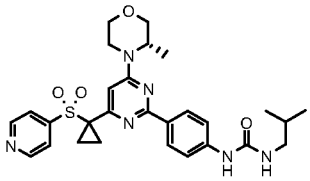
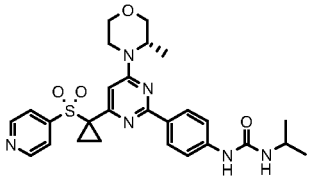
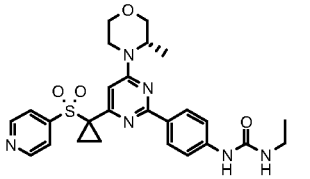
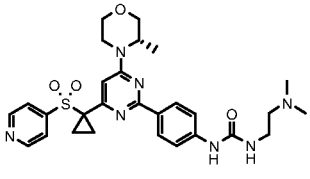
To a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (122 mg, 0.21 mmol) in DMF (2 mL) was added triethylamine (0.088 mL, 0.63 mmol) followed by cyclobutylamine (0.090 mL, 1.05 mmol) and the reaction heated at 50°C overnight. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (90 mg).

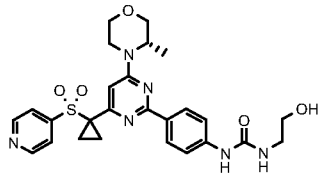
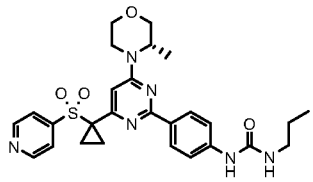
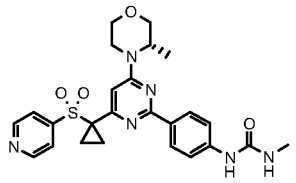
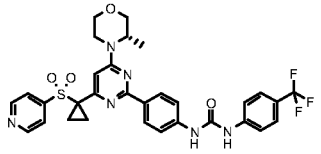
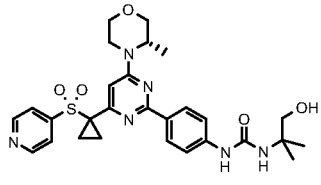
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.20 (3H, d), 1.57-1.70 (4H, m), 1.82-1.91 (2H, m), 1.95-1.98 (2H, q), 2.18-2.25 (2H, m), 3.12-3.20 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.11-4.17 (2H, m), 4.46 (1H, bs), 6.42-6.44 (1H, d), 6.67 (1H, s), 7.33-7.35 (2H, q), 7.65-7.67 (2H, d), 7.76-7.78 (2H, q), 8.53 (1H, s), 8.85-8.87 (2H, q).

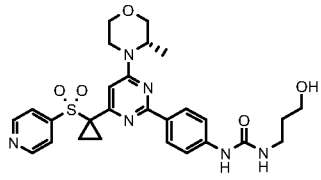
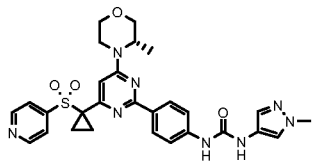
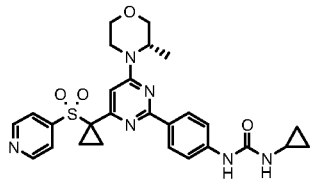
LCMS Spectrum: m/z (ESI+) (M+H)+549 = HPLC tR =2.25 min.

mTOR Kinase Assay (Echo): 0.001μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
6a		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	572	2.44
6b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	551	2.33
6c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	537	2.17
6d		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	523	2.03
6e		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	566	1.32

Example	Structure	NAME	LCMS MH+	Retention time (min)
6f		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	539	1.75
6g		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propyl-urea	537	2.18
6h		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	509	1.89
6i		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	639	2.84
6j		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	567	2.01

Example	Structure	NAME	LCMS MH+	Retention time (min)
6k		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	553	1.80
6l		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	575	1.96
6m		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	535	2.12

Example 6a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21 (3H, d), 1.69-1.72 (2H, q), 1.97-2.00 (2H, q), 3.15-3.22 (1H, td), 3.44-3.51 (1H, td), 3.61-3.64 (1H, dd), 3.74-3.77 (1H, d), 3.95-3.99 (1H, dd), 4.17-4.20 (1H, d), 4.48 (1H, bs), 6.71 (1H, s), 7.02-7.06 (1H, m), 7.49-7.51 (2H, d), 7.56-7.58 (1H, d), 7.74-7.79 (5H, m), 8.30-8.32 (1H, d), 8.88-8.89 (2H, q), 9.43 (1H, s), 10.55 (1H, s).

mTOR Kinase Assay (Echo): 0.00293μM

Example 6b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88-0.90 (6H, d), 1.18-1.20 (3H, d), 1.68-1.74 (3H, m), 1.96-1.98 (2H, q), 2.93-2.96 (2H, t), 3.13-3.20 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.99 (1H, dd), 4.15-4.18 (1H, d), 4.45 (1H, bs), 6.20-6.23 (1H, t), 6.67 (1H, s), 7.34-7.36 (2H, d), 7.65-7.67 (2H, d), 7.77-7.78 (2H, q), 8.62 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.00612μM

Example 6c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11-1.12 (6H, d), 1.18-1.20 (3H, d), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 3.13-3.20 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.82 (2H, m), 3.94-3.98 (1H, dd), 4.14-4.18 (1H, d), 4.46 (1H, bs), 6.02-6.04 (1H, d), 6.67 (1H, s), 7.32-7.36 (2H, q), 7.64-7.67 (2H, q), 7.76-7.78 (2H, q), 8.50 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.00321μM

Example 6d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.05-1.09 (2H, t), 1.18-1.20 (3H, d), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 3.09-3.20 (4H, m), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.15-4.17 (1H, d), 4.46 (1H, bs), 6.12-6.15 (1H, t), 6.67 (1H, s), 7.35-7.37 (2H, q), 7.65-7.67 (2H, d), 7.77-7.78 (2H, q), 8.63 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.000874μM

Example 6e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.20 (3H, d), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 2.18 (6H, s), 2.32-2.35 (2H, t), 3.13-3.21 (3H, m), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.15-4.18 (1H, d), 4.47 (1H, bs), 6.12-6.15 (1H, t), 6.67 (1H, s), 7.34-7.37 (2H, q), 7.65-7.67 (2H, d), 7.76-7.78 (2H, q), 8.86-8.87 (3H, m).

mTOR Kinase Assay (Echo): 0.0673μM

Example 6f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.20 (3H, d), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 3.13-3.20 (3H, m), 3.43-3.50 (3H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.15-4.18 (1H, d), 4.46 (1H, bs), 4.71-4.74 (1H, t), 6.21-6.24 (1H, t), 6.67 (1H, s), 7.34-7.36 (2H, q), 7.65-7.67 (2H, d), 7.76-7.78 (2H, q), 8.77 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.000794μM

Example 6g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87-0.91 (3H, t), 1.18-1.20 (3H, d), 1.41-1.50 (2H, m), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 3.04-3.09 (2H, q), 3.13-3.19 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H, td), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.14-4.18 (1H, d), 4.47 (1H, bs), 6.16-6.19 (1H, t), 6.67 (1H, s), 7.34-7.36 (2H, d), 7.65-7.67 (2H, d0, 7.77-7.78 (2H, q), 8.62 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.00225μM

Example 6h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.20 (3H, d), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 2.65-2.67 (3H, d), 3.13-3.20 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H,

dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.15-4.17 (1H, d), 4.46 (1H, bs), 6.02-6.06 (1H, q), 6.67 (1H, s), 7.35-7.38 (2H, q), 7.65-7.67 (2H, d), 7.77-7.78 (2H, q), 8.71 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.000799μM

Example 6i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21 (3H, d), 1.69-1.72 (2H, q), 1.97-2.00 (2H, q), 3.14-3.21 (1H, td), 3.44-3.50 (1H, td), 3.61-3.64 (1H, dd), 3.74-3.77 (1H, d), 3.95-3.98 (1H, dd), 4.16-1.20 (1H, d), 4.48 (1H, bs), 6.70 (1H, s), 7.44-7.46 (2H, d), 7.64-7.70 (4H, q), 7.72-7.75 (2H, q), 7.78-7.79 (2H, q), 8.87-8.89 (2H, q), 9.03 (1H, s), 9.11 (1H, s).

mTOR Kinase Assay (Echo): 0.00462μM

Example 6j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.20 (3H, d), 1.24 (6H, s), 1.67-1.70 (2H, q), 1.96-1.99 (2H, q), 3.13-3.20 (1H, td), 3.38-3.40 (2H, d), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.15-4.18 (1H, d), 4.46 (1H, bs), 4.94-4.96 (1H, t), 5.97 (1H, s), 6.67 (1H, s), 7.30-7.32 (2H, d), 7.63-7.65 (2H, q), 7.76-7.78 (2H, q), 8.71 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.00593μM

Example 6k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.20 (3H, d), 1.57-1.63 (2H, m), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 3.13-3.20 (3H, m), 3.43-3.50 (3H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.14-4.18 (1H, d), 4.46 (1H, bs), 4.46-4.49 (1H, t), 6.16-6.19 (1H, t), 6.67 (1H, s), 7.34-7.36 (2H, q), 7.65-7.67 (2H, d), 7.76-7.78 (2H, q), 8.68 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.00186μM

Example 6l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.20 (3H, d), 1.68-1.71 (2H, q), 1.96-1.99 (2H, q), 3.13-3.21 (1H, td), 3.44-3.50 (1H, td), 3.60-3.63 (1H, dd), 3.74-3.77 (1H, d), 3.79 (3H, s), 3.95-3.98 (1H, dd), 4.16-4.19 (1H, d), 4.47 (1H, bs), 6.68 (1H, s), 7.39-7.42 (3H, m), 7.68-7.70 (2H, d), 7.77-7.79 (3H, m), 8.37 (1H, s), 8.82 (1H, s), 8.86-8.88 (2H, q).

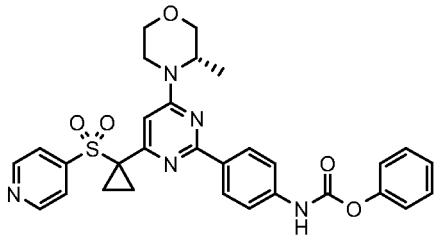
mTOR Kinase Assay (Echo): 0.00119μM

Example 6m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44(2H, m), 0.63-0.67(2H, m), 1.18-1.20(3H, d), 1.68-1.71(2H, q), 1.96-1.99(2H, q), 2.53-2.59(1H, m), 3.13-3.20(1H, td), 3.43-3.63(1H, td), 3.59-3.63(1H, dd), 3.73-3.76(1H, d), 3.94-3.98(1H, dd), 4.15-4.18(1H, d), 4.46(1H, bs), 6.40-6.41(1H, d), 6.67(1H, s), 7.36-7.38(2H, q), 7.65-7.68(2H, q), 7.77-7.78(2H, q), 8.51(1H, s), 8.86-8.87(2H, q).

mTOR Kinase Assay (Echo): 0.000936μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate

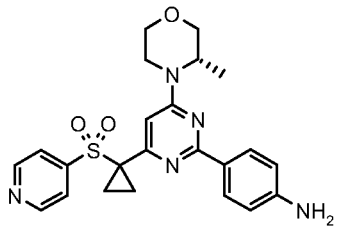


Phenyl chloroformate (0.341 mL, 2.71 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (1.224 g, 2.71 mmol) and sodium bicarbonate (0.342 g, 4.07 mmol) in dioxane (175 mL) at RT under air. The resulting slurry was stirred at RT for 2 hours. Additional portions of phenyl chloroformate (2 x 0.005 mL) were added to the reaction. Water was added to the reaction mixture and the material extracted with DCM. The combined organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 4% methanol in DCM, to give the desired material as a beige solid (1.72 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.28-1.29 (3H, d), 1.60-1.69 (2H, m), 1.97-2.05 (2H, m), 3.22-3.30 (1H, td), 3.52-3.59 (1H, td), 3.71-3.72 (1H, dd), 3.78-3.81 (1H, d), 3.99-4.03 (1H, dd), 4.09-4.13 (1H, d), 4.38-4.39 (1H, bs), 6.72 (1H, s), 7.13-7.15 (2H, d), 7.19-7.21 (1H, t), 7.32-7.36 (2H, t), 7.46-7.48 (2H, d), 7.61-7.63 (2H, q), 7.97-7.99 (2H, d), 8.74-8.75 (2H, q).

LCMS Spectrum: m/z (ES+) (M+H)+=450; HPLC tR=2.66 min.

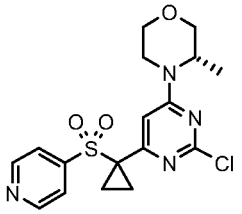
4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline



trans-Dichlorobis(triphenylphosphine)palladium (II) (0.095 g, 0.14 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidine (1.07 g, 2.71 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.89 g, 4.06 mmol) and sodium carbonate (6.77 mL, 13.55 mmol) in 18% DMF in a 7:3:2 mixture of DME:water:ethanol (50 mL) at RT under nitrogen. The resulting solution was stirred at 80°C for 5 hours. The reaction was cooled and diluted with ethyl acetate and water. The reaction mixture was extracted with ethyl acetate, the combined organics dried ($MgSO_4$), filtered and evaporated to afford the desired material (1.224 g).

LCMS Spectrum: m/z (ES+) (M+H)+=452; HPLC tR=2.03 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidine

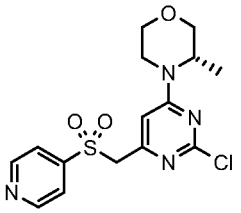


50% v/v Aqueous sodium hydroxide (23 mL, 9.52 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidine (3.51 g, 9.52 mmol), 1,2-dibromoethane (0.820 mL, 9.52 mmol) and tetrabutylammonium bromide (0.307 g, 0.95 mmol) in DCM (100 mL) and the reaction warmed to 30ºC under air. The resulting slurry was stirred at 30°C for 4 hours then allowed to cool, DCM added and the layers separated. The organic layer was washed with water, dried ($MgSO_4$) and filtered. The resulting solution was evaporated on to silica and purified by flash silica chromatography, eluting with 0 to 60% ethyl acetate in DCM, to give the desired material as a yellow solid (1.07 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15-1.16 (3H, d), 1.61-1.65 (2H, m), 1.90-1.93 (2H, m), 3.11-3.19 (1H, td), 3.37-3.44 (1H, td), 3.53-3.57 (1H, dd), 3.68-3.71 (1H, d), 3.89-3.96 (1H, dd), 3.96 (1H, bs), 4.28 (1H, bs), 6.75 (1H, s), 7.74-7.75 (2H, dd), 8.88-8.90 (2H, dd).

LCMS Spectrum: m/z (ES+) (M+H)+=395; HPLC tR=1.65 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidine

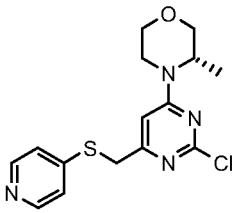


A solution of hydrogen peroxide (1.799 mL, 58.19 mmol) was added dropwise to a stirred solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfanylmethyl)pyrimidine (0.980 g, 2.91 mmol), sodium tungstate dihydrate (0.005 mL, 0.06 mmol) and 2N sulfuric acid (0.075 mL) in dioxane (200 mL) at 55ºC, over a period of 5 minutes under air. The resulting solution was stirred at 55 °C for 3 hours. Water (200mL) was added and the reaction was cooled, the solids filtered, washed with water and dried in the vacuum oven at 50ºC overnight to give the desired material as a white solid (0.580 g). Additional material was obtained by extracting the aqueous layer with DCM. The extracts were dried ($MgSO_4$), filtered, evaporated and chromatographed on silica, eluting with 0 - 3% methanol in DCM, to give a further portion of the desired material (0.144 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.17-1.19(3H, d), 3.14-3.22(1H, td), 3.40-3.47(1H, td), 3.56-3.60(1H, dd), 3.71-3.74(1H, d), 3.90(1H, bs), 3.91-3.95(1H, dd), 4.20(1H, bs), 4.79(2H, s), 6.79(1H, s), 7.77-7.79(2H, q), 8.92-8.93(2H, q).

LCMS Spectrum: m/z (ES+) (M+H)+=369; HPLC tR=1.40 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfanylmethyl)pyrimidine

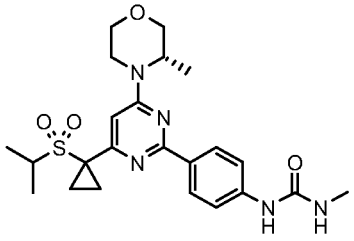


4-Mercaptopyridine (0.752 g, 6.77 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.596 g, 4.51 mmol) in acetonitrile (100 mL) at RT under air. DBU (0.3 mL, 2.01 mmol) was then added and the resulting solution was stirred at RT for 2 minutes. The solvent was removed and DCM was added. The reaction mixture was washed sequentially with water, the organic layer dried ($MgSO_4$), filtered and evaporated. The crude product was chromatographed on silica, eluting with 0 - 2% methanol in DCM. Impure fractions were further chromatographed on silica, eluting with 0 – 4.5% methanol in DCM and combined with the initial pure fractions to give the desired material as a yellow gum (0.980 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.14-1.16(3H, d), 3.11-3.18(1H, td), 3.37-3.44(1H, td), 3.53-3.57(1H, dd), 3.64-3.67(1H, d), 3.86-3.90(2H, dd), 4.01(2H, s), 4.14(1H, bs), 6.43(1H, s), 7.04-7.06(2H, d), 8.29-8.30(2H, d).
LCMS Spectrum: m/z (ES+) (M+H)+=337; HPLC tR=1.62 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier

Example 7: 3-Methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



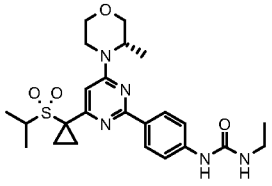
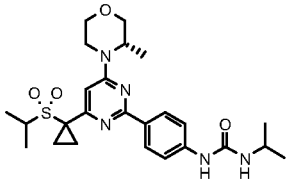
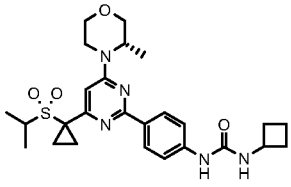
To a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.22 mmol) in DMF (2 mL) was added triethylamine (0.094 mL, 0.67 mmol) followed by methylamine (0.5 mL, 1.1 mmol) and the reaction heated at 50°C for 2 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (71 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.34 (6H, dd), 1.55 - 1.62 (4H, m), 2.66 (3H, d), 3.17 - 3.24 (1H, m), 3.48 (1H, dt), 3.60 - 3.67 (2H, m), 3.76 (1H,

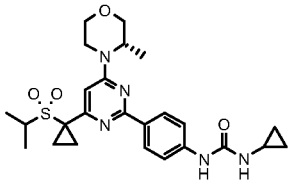
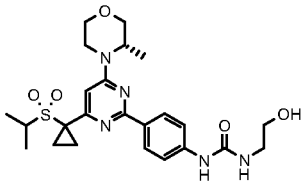
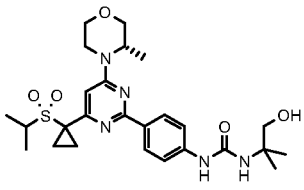
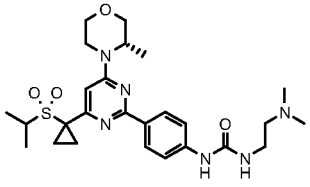
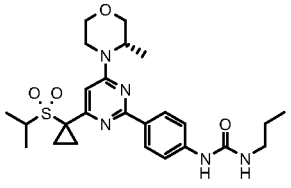
d), 3.98 (1H, dd), 4.19 (1H, d), 4.53 (1H, s), 6.07 (1H, d), 6.79 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.74 (1H, s)

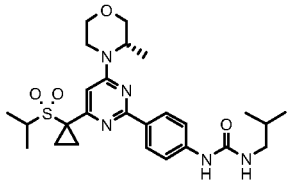
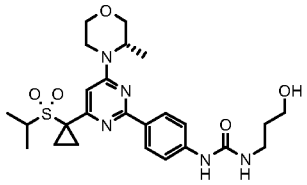
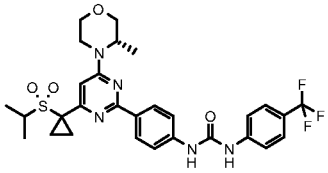
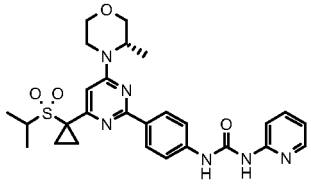
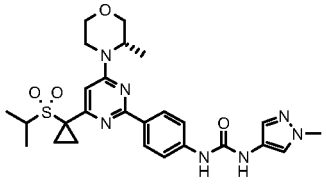
LCMS Spectrum: m/z (ESI+)(M+H)+ = 474; HPLC tR = 1.92 min.

mTOR Kinase Assay (Echo): 0.00315μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
7a		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	488	1.92
7b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	502	2.08
7c		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	514	2.24

Example	Structure	NAME	LCMS MH+	Retention time (min)
7d		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	500	2.34
7e		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	504	2.09
7f		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	532	1.77
7g		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	531	2.06
7h		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-propyl-urea	502	2.00

Example	Structure	NAME	LCMS MH+	Retention time (min)
7i		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	516	2.26
7j		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	518	2.43
7k		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	604	1.81
7l		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	537	2.95
7m		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	540	2.54

Example 7a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.23 (3H, d), 1.34 (6H, dd), 1.52 - 1.61 (4H, m), 3.09 - 3.16 (2H, m), 3.16 - 3.23 (1H, m), 3.49 (1H, dt), 3.62 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, d), 4.19 (1H, d), 4.53 (1H, s), 6.17 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.66 (1H, s).

mTOR Kinase Assay (Echo): 0.00231μM

Example 7b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.23 (3H, d), 1.34 (6H, dd), 1.52 - 1.61 (4H, m), 3.15 - 3.24 (1H, m), 3.49 (1H, dt), 3.60 - 3.67 (2H, m), 3.73 - 3.82 (2H, m), 3.97 (1H, dd), 4.19 (1H, d), 4.53 (1H, s), 6.07 (1H, d), 6.79 (1H, s), 7.48 (2H, d), 8.18 (2H, d), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.0181μM

Example 7c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.52 - 1.66 (6H, m), 1.81 - 1.91 (2H, m), 2.18 - 2.25 (2H, m), 3.20 (1H, dt), 3.48 (1H, dt), 3.60 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.09 - 4.21 (2H, m), 4.53 (1H, s), 6.47 (1H, d), 6.79 (1H, s), 7.48 (2H, d), 8.18 (2H, d), 8.56 (1H, s).

mTOR Kinase Assay (Echo): 0.00646μM

Example 7d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.53 - 1.62 (4H, m), 2.54 - 2.58 (1H, m), 3.17 - 3.24 (1H, m), 3.49 (1H, dt), 3.60 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.20 (1H, d), 4.53 (1H, s), 6.44 (1H, d), 6.80 (1H, s), 7.51 (2H, d), 8.19 (2H, d), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.0038μM

Example 7e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.54 - 1.61 (4H, m), 3.16 - 3.24 (3H, m), 3.44 - 3.52 (3H, m), 3.60 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.19 (1H, d), 4.52 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00212μM

Example 7f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.24 (6H, s), 1.34 (3H, d), 1.35 (3H, d), 1.55 - 1.62 (4H, m), 3.15 - 3.23 (1H, m), 3.39 (2H, d), 3.49 (1H, dt), 3.62 - 3.68 (2H, m), 3.76 (1H, d), 3.97 (1H, d), 4.20 (1H, d), 4.52 (1H, s), 4.95 (1H, t), 6.01 (1H, s), 6.79 (1H, s), 7.46 (2H, d), 8.18 (2H, d), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00915μM

Example 7g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.52 - 1.61 (4H, m), 2.18 (6H, s), 2.34 (2H, t), 3.17 - 3.24 (3H, m), 3.49 (1H, dt), 3.60 - 3.67

(2H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.19 (1H, d), 4.52 (1H, s), 6.16 (1H, t), 6.79 (1H, s), 7.49 (2H, d), 8.18 (2H, d), 8.89 (1H, s).

mTOR Kinase Assay (Echo): 0.211μM

Example 7h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.43 - 1.49 (2H, m), 1.53 - 1.62 (4H, m), 3.07 (2H, q), 3.16 - 3.23 (1H, m), 3.49 (1H, dt), 3.60 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, d), 4.20 (1H, d), 4.54 (1H, s), 6.21 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.0116μM

Example 7i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (6H, d), 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.55 - 1.62 (4H, m), 1.67 - 1.74 (1H, m), 2.94 (2H, t), 3.18 - 3.23 (1H, m), 3.46 - 3.51 (1H, m), 3.60 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.20 (1H, d), 4.51 (1H, s), 6.25 (1H, t), 6.79 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.0182μM

Example 7j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.53 - 1.63 (4H, m), 3.15 - 3.23 (4H, m), 3.45 - 3.51 (4H, m), 3.60 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, d), 4.19 (1H, d), 4.47 (1H, t), 4.53 (1H, s), 6.21 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.71 (1H, s).

mTOR Kinase Assay (Echo): 0.0105μM

Example 7k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.34 (3H, d), 1.36 (3H, d), 1.54 - 1.64 (4H, m), 3.19 - 3.25 (1H, m), 3.50 (1H, t), 3.61 - 3.66 (2H, m), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.55 (1H, s), 6.82 (1H, s), 7.59 (2H, d), 7.64 - 7.70 (4H, m), 8.27 (2H, d), 9.04 (1H, s), 9.14 (1H, s).

mTOR Kinase Assay (Echo): 0.00482μM

Example 7l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.35 (3H, d), 1.37 (3H, d), 1.57 - 1.61 (4H, m), 3.18 - 3.27 (1H, m), 3.50 (1H, dt), 3.63 - 3.70 (2H, m), 3.77 (1H, d), 3.98 (1H, dd), 4.21 (1H, d), 4.55 (1H, s), 6.82 (1H, s), 7.02 - 7.05 (1H, m), 7.55 - 7.58 (1H, m), 7.65 (2H, d), 7.77 (1H, t), 8.27 - 8.31 (3H, m), 9.47 (1H, s), 10.62 (1H, s).

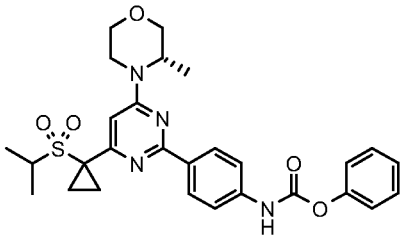
mTOR Kinase Assay (Echo): 0.00913μM

Example 7m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.34 (3H, d), 1.36 (3H, d), 1.53 - 1.63 (4H, m), 3.17 - 3.25 (1H, m), 3.49 (1H, t), 3.61 - 3.68 (2H, m), 3.77 (1H, d), 3.79 (3H, s), 3.97 (1H, d), 4.20 (1H, d), 4.53 (1H, s), 6.81 (1H, s), 7.38 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.22 (2H, d), 8.39 (1H, s), 8.83 (1H, s).

mTOR Kinase Assay (Echo): 0.00504μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate

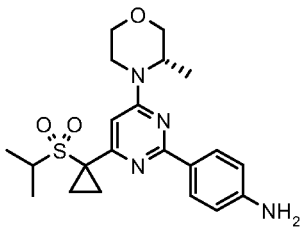


To a solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (1.47 g, 3.53 mmol) in 1,4-dioxane (17.65 mL) was added sodium bicarbonate (0.445 g, 5.29 mmol) and phenyl chloroformate (0.474 mL, 3.77 mmol) and the reaction stirred at RT for 2 hours. The reaction mixture was diluted with DCM (20 mL), and washed with water (20 mL), the organic layer dried ($MgSO_4$), filtered and evaporated. The crude solid was triturated with diethyl ether to give a solid which was collected by filtration and dried under vacuum to give the desired product as a white solid (1.56 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.27 (3H, d), 1.28 (3H, d), 1.49 - 1.55 (4H, m), 3.14 (1H, dt), 3.39 - 3.44 (1H, m), 3.53 - 3.60 (2H, m), 3.70 (1H, d), 3.90 (1H, dd), 4.14 (1H, d), 4.47 (1H, s), 6.77 (1H, s), 7.17 - 7.23 (3H, m), 7.38 (2H, t), 7.57 (2H, d), 8.22 (2H, d), 10.37 (1H, s)

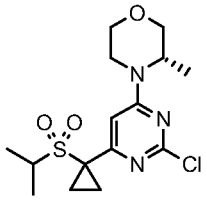
LCMS Spectrum: m/z (ESI+) (M+H)+ = 537; HPLC tR = 2.39 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline



To a solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidine (1.6 g, 4.45 mmol) in DMF (0.24 mL), DME (9.33 mL), water (4.0 mL) and ethanol (2.67 mL) was added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.266 g, 5.78 mmol), sodium carbonate (5 mL, 10.00 mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.156 g, 0.22 mmol) and the suspension heated at 95°C for 2 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate (10 mL) and washed with water (2 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired material as a cream solid (1.47 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.32 (3H, d), 1.34 (3H, d), 1.50 - 1.59 (4H, m), 3.17 (1H, dt), 3.44 - 3.51 (1H, m), 3.59 - 3.66 (2H, m), 3.75 (1H, d), 3.96 (1H, dd), 4.16 (1H, d), 4.49 (1H, d), 5.56 (2H, s), 6.61 (2H, d), 6.69 (1H, s), 8.02 (2H, d)
LCMS Spectrum: m/z (ESI+) (M+H)+ = 417; HPLC tR = 2.09 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidine

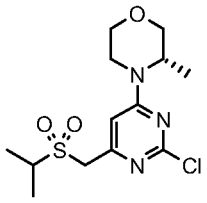


2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidine (2.4 g, 7.19 mmol) was dissolved in DCM (40 mL) and sodium hydroxide concentrate (7.2 mL, 71.89 mmol) was added to the reaction, followed by dibromoethane (0.325 mL, 14.38 mmol). The reaction was stirred at 40°C for 10 hours. The reaction mixture was washed with water (50 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a white solid (1.49 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.27 (6H, d), 1.52 - 1.54 (2H, m), 1.56 - 1.59 (2H, m), 3.21 - 3.24 (1H, m), 3.41 - 3.47 (1H, m), 3.55 - 3.61 (2H, m), 3.72 (1H, d), 3.93 (1H, dd), 4.02 (1H, d), 4.37 (1H, s), 6.94 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ 360, HPLC tR = 1.89 min

2-Chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidine

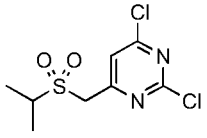


2,4-Dichloro-6-[(isopropylsulfonyl)methyl]pyrimidine (2.65 g, 9.85 mmol) was dissolved in DCM (50 mL) and stirred (under nitrogen) at -5°C. Triethylamine (1.5 mL, 10.84 mmol) was added to give a clear brown solution. (3*S*)-3-Methyl morpholine (997 mg, 9.85 mmol) was dissolved in DCM and added dropwise keeping the reaction below -5°C. The cooling bath was then removed and the reaction mixture stirred at room temperature for 1 hour. The reaction mixture was then washed with water (50 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM to give the desired material as a white solid (2 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (d, 3H), 1.31 (d, 6H), 3.22 (m, 1H), 3.43 (m, 2H), 3.60 (m, 1H), 3.74 (d, 1H), 3.98 (m, 1H), 4.30 (s, 1H), 4.43 (s, 2H), 6.91 (s, 1H)

LCMS Spectrum: m/z (ESI+)(M+H)+ 332, HPLC tR = 1.70 min

2,4-Dichloro-6-[(isopropylsulfonyl)methyl]pyrimidine



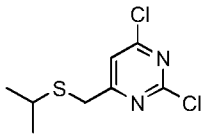
2,4-Dichloro-6-[(isopropylthio)methyl]pyrimidine (6.2 g, 26.16 mmol) was dissolved in DCM (100 mL) and 3,5-dichlorobenzenecarboperoxoic acid (13.5 g, 78.4 mmol) was added portionwise over 10 minutes. The reaction was stirred at room temperature for 4 hours. The reaction mixture was then washed with saturated aqueous sodium bicarbonate (50 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo* to give a cream solid.

Purification by normal phase chromatography, eluting with 0-50% ethyl acetate in iso-hexane gave the desired material as a cream solid (5.3 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (d, 6H), 3.43 (m, 1H), 4.77 (s, 2H), 7.87 (s, 1H)

LCMS Spectrum: m/z $(M-H)^-$ 267, HPLC tR = 1.64 min

2,4-Dichloro-6-[(isopropylthio)methyl]pyrimidine

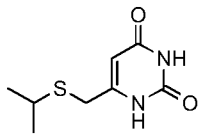


6-[(Isopropylthio)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (8 g, 40 mmol) was added to phosphorus oxychloride (100 mL) and the mixture heated to reflux for 16 hours. The reaction was then cooled to room temperature and the excess phosphorus oxychloride was removed *in vacuo*,. The residue was azeotroped with toluene (2 x 100 mL) and dissolved in DCM. This mixture was then poured slowly onto ice (1 L) and stirred for 20 minutes, then extracted with DCM (3 x 500 mL) The extracts were combined, dried over magnesium sulphate, then concentrated *in vacuo* to give the desired material as a brown oil (6.5 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (d, 6H), 2.96 (m, 1H), 3.85 (s, 2H), 7.82 (s, 1H)

LCMS Spectrum: No mass ion observed, HPLC tR = 2.51 min

6-[(Isopropylthio)methyl]pyrimidine-2,4(1*H*,3*H*)-dione



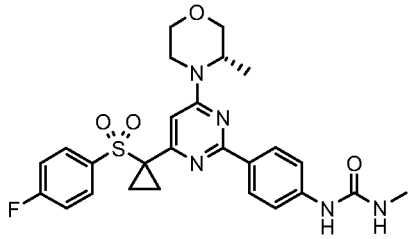
6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (8 g, 50 mmol) was dissolved in acetonitrile (200 mL) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (13 mL, 87.19 mmol) was added and the reaction stirred at room temperature for 15 minutes. Isopropyl mercaptan (8.1 mL, 87.19 mmol) was then added and the reaction stirred at room temperature for a further 2 hours. Solvent removed *in vacuo* and the resulting brown oil was dissolved in DCM and washed

with water. Organic phase dried over magnesium sulphate, filtered and concentrated *in vacuo*. The resulting oil was chromatographed on silica, eluting with 0-10% methanol in DCM to give the desired material as a white solid (8 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (d, 6H), 2.90 (m, 1H), 3.42 (s, 2H), 5.49 (s, 1H), 10.82 (s, 1H), 10.94 (s, 1H)

LCMS Spectrum: m/z $(M-H)^-$ 199, HPLC tR = 0.63 min

Example 8: 1-[4-[4-[1-(4-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea



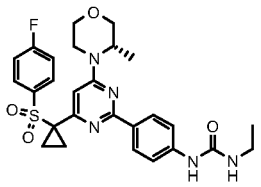
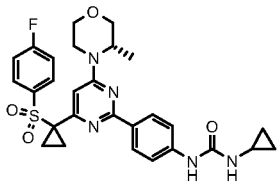
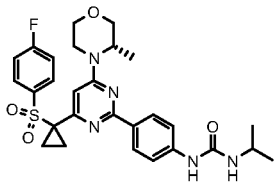
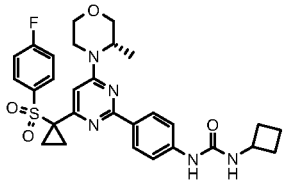
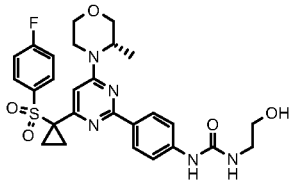
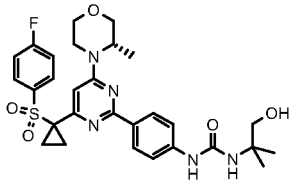
To a solution of phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) in DMF (2 mL) was added triethylamine (0.071 mL, 0.51 mmol) followed by methylamine (0.5 mL, 1.1 mmol) and the reaction heated at 50°C for 2 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (51 mg).

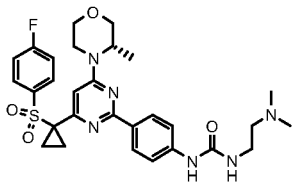
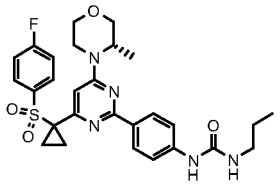
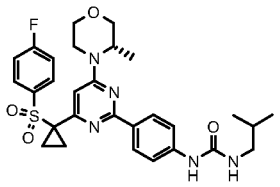
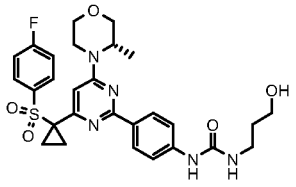
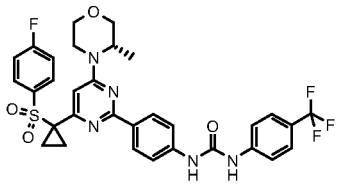
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 - 1.62 (2H, m), 1.88 - 1.90 (2H, m), 2.66 (3H, d), 3.15 (1H, dt), 3.46 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.13 (1H, d), 4.42 (1H, s), 6.03 (1H, d), 6.65 (1H, s), 7.38 - 7.44 (4H, m), 7.79 - 7.86 (4H, m), 8.71 (1H, s)

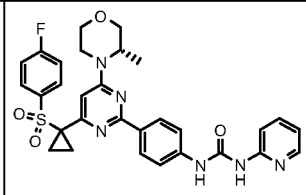
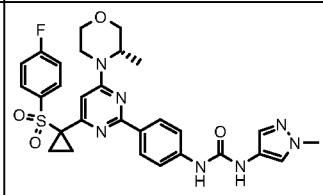
LCMS Spectrum: m/z (ESI+)(M+H)+ = 526; HPLC tR = 2.09 min.

mTOR Kinase Assay (Echo): 0.000576μM

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
8a		1-ethyl-3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	540	2.23
8b		3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	552	2.25
8c		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	554	2.40
8d		3-cyclobutyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	566	2.47
8e		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	556	1.92
8f		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea	584	2.22

Example	Structure	NAME	LCMS MH+	Retention time (min)
8g		3-(2-dimethylaminoethyl)-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	583	2.17
8h		3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea	554	2.40
8i		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	568	2.55
8j		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	570	1.97
8k		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	656	3.01

Example	Structure	NAME	LCMS MH+	Retention time (min)
8l		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	589	2.63
8m		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	592	2.12

Example 8 can also be prepared in an analogous fashion to that described above but using NMP as the solvent and stirring at 75°C for 30 minutes. The material can then be partitioned between ethyl acetate and water and the organic materials purified by chromatography on silica, eluting with 0-3% methanol in ethyl acetate. The material can then be dissolved in DCM and either evapourated rapidly to give the desired material as a foam or left to stand for approximately 6 weeks upon which time the deired material precipitated from solution.

Example 8a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.18 (3H, d), 1.59 - 1.62 (2H, m), 1.88 - 1.90 (2H, m), 3.09 - 3.18 (3H, m), 3.46 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.13 (1H, d), 4.42 (1H, s), 6.12 (1H, t), 6.65 (1H, s), 7.37 - 7.46 (4H, m), 7.79 - 7.86 (4H, m), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.00096μM

Example 8b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.19 (3H, d), 1.58 - 1.63 (2H, m), 1.89 - 1.91 (2H, m), 2.55 - 2.58 (1H, m), 3.15 (1H, t), 3.46 (1H, t), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.14 (1H, d), 4.42 (1H, s), 6.39 (1H, s), 6.65 (1H, s), 7.39 - 7.44 (4H, m), 7.80 - 7.86 (4H, m), 8.51 (1H, s).

mTOR Kinase Assay (Echo): 0.00123μM

Example 8c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.18 (3H, d), 1.58 - 1.62 (2H, m), 1.88 - 1.90 (2H, m), 3.15 (1H, t), 3.46 (1H, t), 3.61 (1H, d), 3.73 - 3.81 (2H, m), 3.96

(1H, d), 4.13 (1H, d), 4.42 (1H, s), 6.02 (1H, d), 6.65 (1H, s), 7.37 (2H, d), 7.42 (2H, t), 7.79 - 7.86 (4H, m), 8.51 (1H, s).

mTOR Kinase Assay (Echo): 0.00185μM

Example 8d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 - 1.66 (4H, m), 1.83 - 1.91 (4H, m), 2.18 - 2.26 (2H, m), 3.12 - 3.19 (1H, m), 3.46 (1H, t), 3.61 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.11 - 4.17 (2H, m), 4.42 (1H, s), 6.42 (1H, d), 6.65 (1H, s), 7.37 (2H, d), 7.42 (2H, t), 7.79 - 7.86 (4H, m), 8.54 (1H, s).

mTOR Kinase Assay (Echo): 0.00134μM

Example 8e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 - 1.62 (2H, m), 1.88 - 1.90 (2H, m), 3.15 - 3.18 (2H, m), 3.40 - 3.48 (2H, m), 3.61 (2H, dd), 3.74 (1H, d), 3.95 (1H, d), 4.05 - 4.16 (2H, m), 4.13 (1H, d), 4.73 (1H, t), 6.22 (1H, t), 6.64 (1H, s), 7.37 - 7.44 (4H, m), 7.79 - 7.86 (4H, m), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.000342μM

Example 8f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.24 (6H, s), 1.57 - 1.63 (2H, m), 1.86 - 1.91 (2H, m), 3.10 - 3.18 (1H, m), 3.38 (2H, d), 3.46 (1H, t), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.14 (1H, d), 4.41 (1H, s), 4.95 (1H, t), 5.97 (1H, s), 6.64 (1H, s), 7.34 (2H, d), 7.42 (2H, t), 7.78 - 7.86 (4H, m), 8.71 (1H, s).

mTOR Kinase Assay (Echo): 0.00882μM

Example 8g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 - 1.62 (2H, m), 1.88 - 1.90 (2H, m), 2.18 (6H, s), 2.33 (2H, t), 3.15 - 3.21 (3H, m), 3.46 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.13 (1H, d), 4.42 (1H, s), 6.13 (1H, t), 6.65 (1H, s), 7.37 - 7.43 (4H, m), 7.79 - 7.86 (4H, m), 8.86 (1H, s).

mTOR Kinase Assay (Echo): 0.0613μM

Example 8h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.18 (3H, d), 1.45 (2H, sextet), 1.59 - 1.62 (2H, m), 1.88 - 1.90 (2H, m), 3.06 (2H, q), 3.12 - 3.16 (1H, m), 3.40 - 3.49 (1H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.96 (1H, dd), 4.13 (1H, d), 4.42 (1H, s), 6.17 (1H, t), 6.64 (1H, s), 7.37 - 7.44 (4H, m), 7.79 - 7.86 (4H, m), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.00176μM

Example 8i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (6H, d), 1.19 (3H, d), 1.59 - 1.62 (2H, m), 1.67 - 1.74 (1H, m), 1.88 - 1.90 (2H, m), 2.94 (2H, t), 3.12 - 3.19 (1H, m), 3.46 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.42 (1H, s), 6.21 (1H, t), 6.65 (1H, s), 7.37 - 7.43 (4H, m), 7.79 - 7.85 (4H, m), 8.62 (1H, s).

mTOR Kinase Assay (Echo): 0.0198μM

Example 8j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.56 - 1.63 (4H, m), 1.88 - 1.90 (2H, m), 3.12 - 3.19 (3H, m), 3.47 (2H, q), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.13 (1H, d), 4.43 (1H, s), 4.47 (2H, t), 6.17 (1H, t), 6.65 (1H, s), 7.37 - 7.45 (4H, m), 7.79 - 7.86 (4H, m), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.000751μM

Example 8k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.60 - 1.63 (2H, m), 1.89 - 1.92 (2H, m), 3.13 - 3.21 (1H, m), 3.47 (1H, dt), 3.62 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.15 (1H, d), 4.43 (1H, s), 6.68 (1H, s), 7.41 - 7.49 (4H, m), 7.63 - 7.69 (4H, m), 7.84 - 7.89 (4H, m), 9.02 (1H, s), 9.10 (1H, s).

mTOR Kinase Assay (Echo): 0.0173μM

Example 8l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.61 - 1.63 (2H, m), 1.89 - 1.92 (2H, m), 3.14 - 3.21 (1H, m), 3.47 (1H, t), 3.62 (1H, d), 3.76 (1H, d), 3.96 (1H, d), 4.16 (1H, d), 4.44 (1H, s), 6.68 (1H, s), 7.02 - 7.05 (1H, m), 7.43 (2H, t), 7.53 (2H, d), 7.57 - 7.62 (1H, m), 7.75 - 7.79 (1H, m), 7.83 - 7.91 (4H, m), 8.30 (1H, d), 9.40 (1H, s), 10.50 (1H, s).

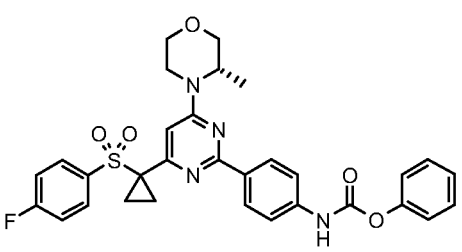
mTOR Kinase Assay (Echo): 0.00813μM

Example 8m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.60 - 1.62 (2H, m), 1.89 - 1.91 (2H, m), 3.12 - 3.20 (1H, m), 3.47 (1H, dt), 3.62 (1H, dd), 3.75 (1H, d), 3.79 (3H, s), 3.96 (1H, dd), 4.14 (1H, d), 4.43 (1H, s), 6.66 (1H, s), 7.38 - 7.45 (5H, m), 7.77 (1H, s), 7.83 - 7.87 (4H, m), 8.35 (1H, s), 8.82 (1H, s).

mTOR Kinase Assay (Echo): 0.00136μM

The preparation of phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

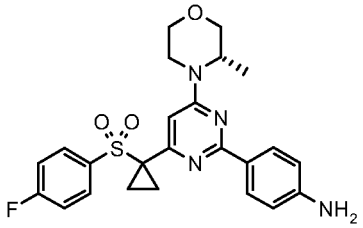


To a solution of 4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.33 g, 2.84 mmol) in 1,4-dioxane (15 mL) was added sodium bicarbonate (0.358 g, 4.26 mmol) and phenyl chloroformate (0.357 mL, 2.84 mmol) and the reaction stirred at RT for 2 hours. The reaction mixture was diluted with DCM (20 mL), and washed with water (20 mL), the organic layer dried ($MgSO_4$), filtered and evaporated. The crude solid was triturated with diethyl ether to give a solid which was collected by filtration and dried under vacuum to give the desired product as a white solid (1.46 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.60 - 1.65 (2H, m), 1.89 - 1.92 (2H, m), 3.18 (1H, dt), 3.47 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.17 (1H, d), 4.45 (1H, s), 6.69 (1H, s), 7.25 (3H, d), 7.40 - 7.47 (4H, m), 7.55 (2H, d), 7.83 - 7.87 (2H, m), 7.92 (2H, d), 10.42 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 589; HPLC tR = 2.92 min.

4-[4-[1-(4-Fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



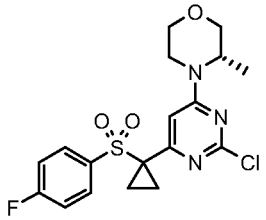
To a solution of 2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.5 g, 3.64 mmol) in DMF (0.48 mL), DME (9.33 mL), water (4.0 mL) and ethanol (2.67 mL) was added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.037 g, 4.73 mmol), sodium carbonate (5 mL, 10.00 mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.128 g, 0.18 mmol) and the suspension heated at 95°C for 2 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate (10 mL) and washed with water (2 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired as a cream solid (1.33 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.57 - 1.59 (2H, m), 1.86 - 1.88 (2H, m), 3.12 (1H, dt), 3.45 (1H, dt), 3.60 (1H, dd), 3.73 (1H, d), 3.95 (1H, dd),

4.10 (1H, d), 4.38 (1H, s), 5.52 (2H, s), 6.49 (2H, d), 6.55 (1H, s), 7.41 (2H, t), 7.64 (2H, d), 7.82 - 7.85 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 469; HPLC tR = 2.47 min.

2-Chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



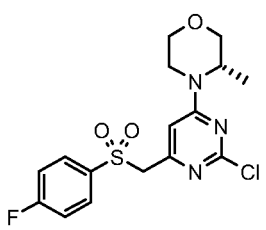
2-Chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.0 g, 7.78 mmol) was dissolved in DCM (40 mL) and sodium hydroxide concentrate (7.8 mL, 77.75 mmol) was added to the reaction, followed by dibromoethane (0.352 mL, 15.55 mmol). The reaction was stirred at 40°C for 16 hours. The reaction mixture was washed with water (50 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated to afford crude product.

The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a white solid (1.50 g,).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.53 - 1.56 (2H, m), 1.82 - 1.85 (2H, m), 3.14 (1H, dt), 3.40 (1H, dt), 3.55 (1H, dd), 3.70 (1H, d), 3.91 (2H, dd), 4.25 (1H, s), 6.70 (1H, s), 7.45 (2H, t), 7.79 - 7.84 (2H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ 412, HPLC tR = 2.14 min

2-Chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



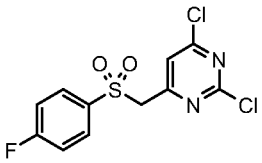
Triethylamine (1.117 ml, 8.01 mmol) was added to 2,4-dichloro-6-[(4-fluorophenyl)sulfonylmethyl]pyrimidine (2.34 g, 7.29 mmol) in DCM (36.4 mL) at 0°C followed by (3*S*)-3-methylmorpholine (0.737 g, 7.29 mmol) in DCM (20 mL) over 15

minutes. The reaction was then stirred at RT for 16 hours. The reaction mixture was washed with water (50 mL), the organic layer dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a beige solid (1.530 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 3.13 - 3.20 (1H, m), 3.27 - 3.28 (1H, m), 3.39 - 3.46 (1H, m), 3.57 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 4.17 (1H, s), 4.65 (2H, s), 6.71 (1H, s), 7.48 (2H, t), 7.83 - 7.87 (2H, m)

LCMS Spectrum: MH+ 386, retention time 1.94 min.

2,4-Dichloro-6-[(4-fluorophenyl)sulfonylmethyl]pyrimidine

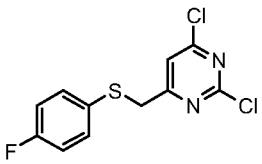


3-Chloroperoxybenzoic acid (3.78 g, 21.89 mmol) was added portionwise to 2,4-dichloro-6-[(4-fluorophenyl)sulfanylmethyl]pyrimidine (2.11 g, 7.30 mmol), in DCM (36.5 mL) and the reaction stirred at RT for 2 hours. The reaction mixture was washed with a saturated aqueous solution ofsodium hydrogen carbonate (50 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated to afford desired product (2.35 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 4.99 (2H, s), 7.48 - 7.52 (2H, m), 7.76 (1H, s), 7.85 - 7.88 (2H, m)

LCMS Spectrum: MH+ 319, retention time 2.01 min.

2,4-Dichloro-6-[(4-fluorophenyl)sulfanylmethyl]pyrimidine



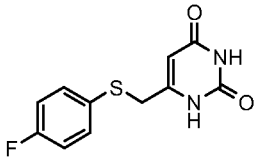
Phosphorus oxychloride (15.2 g, 99.1 mmol) was added to 6-[(4-fluorophenyl)sulfanylmethyl]-1*H*-pyrimidine-2,4-dione (2.5 g, 9.91 mmol), and the resulting solution was stirred at reflux for 7 hours. The reaction was allowed to cool and the phosphorus oxychloride removed under reduced pressure to give a brown oil. This was dissolved in DCM and ice water (50 mL) added followed by solid sodium bicarbonate (until

effervescence stops). The aqueous layer was extracted with DCM (2 x 50 mL) and the organics dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in isohexane, to give the desired material as a yellow gum (2.11 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 4.21 (2H, s), 7.09 - 7.14 (2H, m), 7.34 - 7.38 (2H, m), 7.58 (1H, s)

LCMS Spectrum: M-H+ 287, retention time 2.51 min.

6-[(4-Fluorophenyl)sulfanylmethyl]-1*H*-pyrimidine-2,4-dione

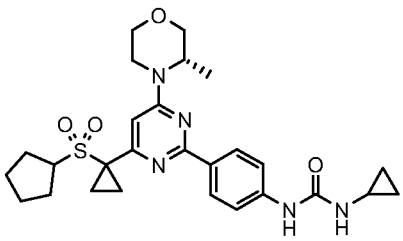


DBU (4.02 mL, 26.91 mmol) was added to 4-fluorobenzenethiol (3.45 g, 26.91 mmol), in DMF (90 mL) at RT. The resulting solution was stirred at 20°C for 15 minutes. 6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (2.88 g, 17.94 mmol) was then added and the reaction stirred for 4 hours. The reaction mixture was concentrated and diluted with DCM (100 mL), and washed with water (100 mL). The aqueous layer was acidified with 2M hydrochloric acid to give a white solid which was filtered and washed with water then dried under vacuum to give desired product (2.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.80 (2H, s), 5.20 (1H, s), 7.18 - 7.23 (2H, m), 7.45 - 7.49 (2H, m), 10.90 (1H, s), 10.93 (1H, s)

LCMS Spectrum: M-H- 251, retention time 0.80 min.

Example 9: 1-[4-[4-(1-Cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropyl-urea



To a solution of phenyl *N*-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (200 mg, 0.36 mmol) and amine

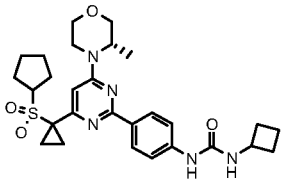
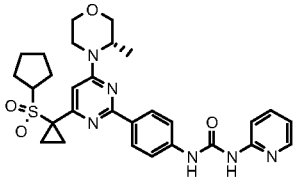
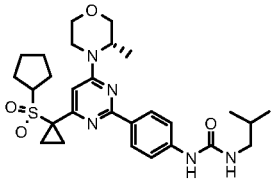
(1.44 mmol) in NMP (2 mL) was added triethylamine (0.198 mL, 1.44 mmol) and mixture heated at 75°C for 6 hours. The reaction was allowed to cool and purified by prep HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a solid (130 mg).

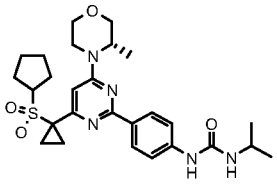
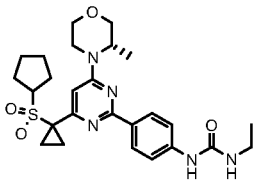
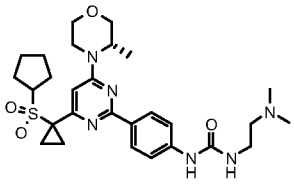
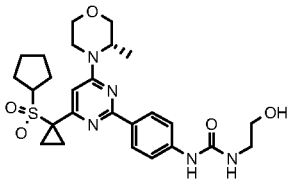
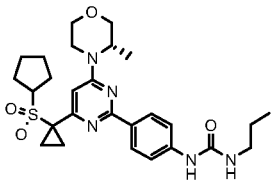
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.23 (3H, d), 1.50 - 1.70 (8H, m), 1.85 - 1.94 (2H, m), 1.99 - 2.07 (2H, m), 3.16 - 3.25 (1H, m), 3.49 (1H, dd), 3.63 (1H, dd), 3.76 (1H, d), 3.89 - 4.00 (2H, m), 4.20 (1H, d), 4.55 (1H, s), 6.46 (1H, s), 6.82 (1H, s), 7.51 (2H, d), 8.20 (2H, d), 8.54 (1H, s)

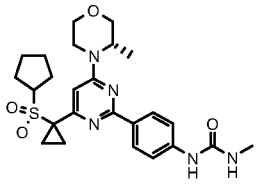
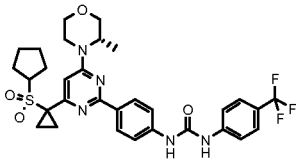
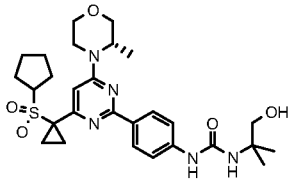
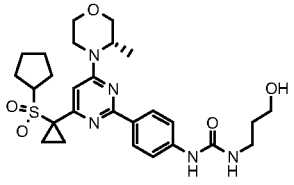
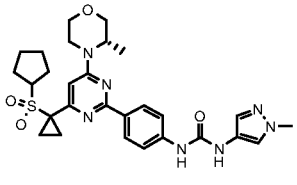
LCMS Spectrum: m/z (ESI+)(M+H)+ = 526; HPLC tR = 2.42 min

mTOR Kinase Assay (Echo): 0.0018μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
9a		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	540	2.67
9b		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	563	2.89
9c		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	542	2.77

Example	Structure	NAME	LCMS MH+	Retention time (min)
9d		3-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethyl-urea	528	2.59
9e		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	514	2.40
9f		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	557	2.33
9g		3-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea	530	2.02
9h		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	528	2.59

Example	Structure	NAME	LCMS MH+	Retention time (min)
9i		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	500	2.25
9j		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea	630	3.25
9k		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	558	2.37
9l		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	544	2.07
9m		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	566	2.26

Example 9a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.51 - 1.70 (10H, m), 1.82 - 1.94 (4H, m), 1.98 - 2.08 (2H, m), 2.17 - 2.25 (2H, m), 3.17 - 3.25 (1H, m), 3.49 (1H, td),

3.63 (1H, dd), 3.76 (1H, d), 3.88 - 4.00 (2H, m), 4.10 - 4.22 (2H, m), 4.55 (1H, s), 6.47 (1H, d), 6.81 (1H, s), 7.48 (2H, d), 8.19 (2H, d), 8.56 (1H, s).

mTOR Kinase Assay (Echo): 0.0129μM

Example 9b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.53 - 1.70 (8H, m), 1.86 - 1.96 (2H, m), 2.00 - 2.09 (2H, m), 3.18 - 3.25 (1H, m), 3.46 - 3.54 (1H, m), 3.65 (1H, dd), 3.77 (1H, d), 3.90 - 4.01 (2H, m), 4.22 (1H, d), 4.57 (1H, s), 6.85 (1H, s), 7.04 (1H, t), 7.56 (1H, d), 7.65 (2H, d), 7.77 (1H, t), 8.26 - 8.32 (5H, m), 9.48 (1H, s), 10.63 (3H, s).

mTOR Kinase Assay (Echo): 0.0215μM

Example 9c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (6H, d), 1.23 (3H, d), 1.51 - 1.75 (8H, m), 1.85 - 1.96 (2H, m), 1.99 - 2.08 (2H, m), 2.94 (2H, t), 3.16 - 3.25 (1H, m), 3.49 (1H, td), 3.63 (1H, dd), 3.76 (1H, d), 3.89 - 4.00 (2H, m), 4.20 (1H, d), 4.55 (1H, s), 6.24 (1H, t), 6.82 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.0483μM

Example 9d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.23 (3H, d), 1.51 - 1.69 (8H, m), 1.85 - 1.94 (2H, m), 1.98 - 2.08 (2H, m), 3.20 (1H, td), 3.49 (1H, td), 3.63 (1H, dd), 3.73 - 3.81 (2H, m), 3.89 - 4.00 (2H, m), 4.19 (1H, d), 4.55 (1H, s), 6.07 (1H, d), 6.83 (1H, s), 7.48 (2H, d), 8.19 (2H, d), 8.54 (1H, s).

mTOR Kinase Assay (Echo): 0.0151μM

Example 9e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.23 (3H, d), 1.49 - 1.71 (8H, m), 1.86 - 1.96 (2H, m), 1.99 - 2.07 (2H, m), 3.12 (2H, q), 3.17 - 3.25 (1H, m), 3.45 - 3.53 (1H, m), 3.61 - 3.66 (1H, m), 3.89 - 3.99 (2H, m), 4.19 (1H, d), 4.56 (1H, s), 6.17 (1H, t), 6.82 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.67 (1H, s).

mTOR Kinase Assay (Echo): 0.00187μM

Example 9f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.50 - 1.70 (8H, m), 1.84 - 1.95 (2H, m), 1.98 - 2.08 (2H, m), 2.20 (6H, s), 2.33 (2H, t), 3.17 - 3.23 (2H, m), 3.49 (1H, td), 3.63 (1H, dd), 3.76 (1H, d), 3.90 - 4.00 (2H, m), 4.20 (1H, d), 4.56 (1H, s), 6.16 (1H, t), 6.82 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.144μM

Example 9g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.50 - 1.71 (8H, m), 1.85 - 1.95 (2H, m), 1.98 - 2.07 (2H, m), 3.14 - 3.24 (3H, m), 3.43 - 3.52 (3H, m), 3.63 (1H, d), 3.76 (1H, d), 3.89 - 4.00 (2H, m), 4.19 (1H, d), 4.55 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.82 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.81 (1H, s).

mTOR Kinase Assay (Echo): 0.00127μM

Example 9h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.23 (3H, d), 1.42 - 1.70 (10H, m), 1.84 - 1.94 (2H, m), 1.98 - 2.08 (2H, m), 3.03 - 3.09 (2H, m), 3.16 - 3.25 (1H, m), 3.50 (1H, d), 3.63 (1H, d), 3.76 (1H, d), 3.90 - 4.00 (2H, m), 4.20 (1H, d), 4.55 (1H, s), 6.21 (1H, t), 6.82 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.66 (1H, s).

mTOR Kinase Assay (Echo): 0.0057μM

Example 9i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.49 - 1.71 (8H, m), 1.85 - 1.95 (2H, m), 1.99 - 2.08 (2H, m), 3.16 - 3.24 (1H, m), 3.49 (1H, td), 3.63 (1H, dd), 3.76 (1H, d), 3.87 - 4.01 (2H, m), 4.20 (1H, d), 4.56 (1H, s), 6.09 (1H, q), 6.82 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.0024μM

Example 9j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.52 - 1.70 (8H, m), 1.87 - 1.96 (2H, m), 1.99 - 2.07 (2H, m), 3.17 - 3.27 (1H, m), 3.46 - 3.54 (1H, m), 3.64 (1H, d), 3.77 (1H, d), 3.89 - 4.01 (2H, m), 4.21 (1H, d), 4.57 (1H, s), 6.85 (1H, s), 7.59 (2H, d), 7.67 (4H, q), 8.27 (2H, d), 9.05 (1H, s), 9.15 (1H, s).

mTOR Kinase Assay (Echo): 0.046μM

Example 9k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 - 1.26 (9H, m), 1.51 - 1.71 (8H, m), 1.86 - 1.93 (2H, m), 1.98 - 2.09 (2H, m), 3.16 - 3.24 (1H, m), 3.39 (2H, d), 3.49 (1H, dd), 3.63 (1H, dd), 3.76 (1H, d), 3.90 - 4.01 (2H, m), 4.20 (1H, d), 4.55 (1H, s), 4.95 (1H, t), 6.02 (1H, s), 6.81 (1H, s), 7.45 (2H, d), 8.18 (2H, d), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.0115μM

Example 9l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.50 - 1.70 (8H, m), 1.85 - 1.95 (2H, m), 1.98 - 2.07 (2H, m), 3.12 - 3.25 (3H, m), 3.23 - 3.33 (2H, m), 3.43 - 3.53 (3H, m), 3.63 (1H, d), 3.77 (1H, d), 3.89 - 4.01 (2H, m), 4.20 (1H, d), 4.48 (1H, t), 4.56 (1H, s), 6.21 (1H, t), 6.81 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.72 (1H, s).

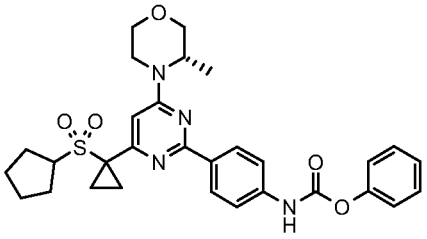
mTOR Kinase Assay (Echo): 0.00395μM

Example 9m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (9H, d), 1.51 - 1.70 (20H, m), 1.86 - 1.95 (6H, m), 1.99 - 2.07 (4H, m), 3.15 - 3.25 (25H, m), 3.50 (1H, d), 3.64 (1H, d), 3.78 (1H, d), 3.90 - 4.01 (2H, m), 4.20 (1H, d), 4.56 (1H, s), 6.86 (1H, s), 7.43 (1H, s), 7.56 (2H, d), 7.81 (1H, s), 8.23 (2H, d), 8.44 (1H, s), 8.87 (1H, s).

mTOR Kinase Assay (Echo): 0.00401μM

The preparation of phenyl *N*-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

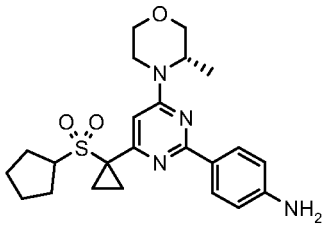


Phenyl chloroformate (1.701 mL, 13.56 mmol) was added to 4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (4 g, 9.04 mmol) and sodium hydrogen carbonate (1.139 g, 13.56 mmol) in dioxane (120 mL) cooled to 5ºC under nitrogen. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (125 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude material which was triturated with diethyl ether and isohexane to give the desired material as a white solid (4.77 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.51 - 1.70 (4H, m), 1.85 - 1.95 (2H, m), 1.98 - 2.08 (2H, m), 3.21 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.90 - 4.00 (2H, m), 4.21 (1H, d), 4.58 (1H, s), 6.88 (1H, s), 7.22 - 7.32 (3H, m), 7.41 - 7.49 (2H, m), 7.64 (2H, d), 8.30 (2H, d), 10.45 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 563; HPLC tR = 3.02 min

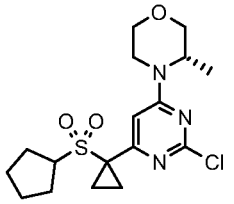
4-[4-(1-Cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Bis(triphenylphosphine)palladium(II) chloride (300 mg, 0.43 mmol) was added to 2-chloro-4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.15 g, 10.75 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.53 g, 16.13 mmol) and sodium carbonate (25 mL, 50.0 mmol) in ethanol (20 mL), DMF (40 mL), water (25 mL) and DME (40 mL) at Rt and the resulting mixture degassed then stirred at 95°C for 18 hours. The reaction mixture was diluted with ethyl acetate (400 mL), and washed with water (2 x 150 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 80% ethyl acetate in isohexane, to give the desired material as a cream solid (4.00 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.46 - 1.72 (7H, m), 1.84 - 1.95 (2H, m), 3.13 - 3.22 (1H, m), 3.47 (1H, td), 3.62 (1H, dd), 3.75 (1H, d), 3.89 - 3.99 (2H, m), 4.15 (1H, d), 4.54 (1H, s), 5.58 (2H, s), 6.61 (2H, d), 6.72 (1H, s), 8.02 (2H, d)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 443; HPLC tR = 2.4 min

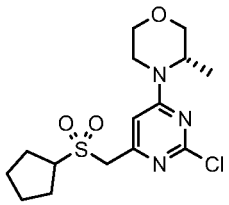
2-Chloro-4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Sodium hydroxide (62.5 mL, 125.04 mmol) was added to 2-chloro-4-(cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.50 g, 12.50 mmol), 1,2-dibromoethane (4.31 mL, 50.02 mmol) and tetrabutylammonium bromide (0.403 g, 1.25 mmol) in toluene (100 mL) at 30°C under nitrogen. The resulting mixture was stirred at 60°C for 3 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 45% ethyl acetate in isohexane, to give the desired material as a colourless gum (4.47 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.47 - 1.68 (8H, m), 1.80 - 1.89 (2H, m), 1.91 - 1.98 (2H, m), 3.21 (1H, dt), 3.44 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.82 (1H, q), 3.93 (1H, dd), 3.98 - 4.06 (1H, m), 4.41 (1H, s), 6.97 (1H, s)

2-Chloro-4-(cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

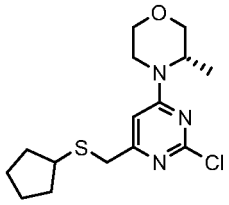


Hydrogen peroxide (19.54 mL, 632 mmol) was added to 2-chloro-4-(cyclopentylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (10.36 g, 31.60 mmol), sodium tungstate dihydrate (0.208 g, 0.63 mmol) (dissolved in minimum quantity of water) and 2M sulphuric acid solution (0.177 mL) in dioxane (100 mL) at 55°C under air. The resulting solution was stirred at 55°C for 2 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water then a 10% aqueous solution of sodium metabisulfite. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 70% ethyl acetate in isohexane, to give the desired material as a colourless gum (9.7 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.64 (4H, m), 1.95 (4H, m), 3.24 (1H, m), 3.45 (1H, td), 3.60 (1H, dd), 3.71 (1H, m), 3.95 (2H, m), 4.35 (1H, s), 4.40 (2H, s), 6.91 (1H, s)

Mass Spectrum: m/z (ESI+)(M+H)+ = 360

2-Chloro-4-(cyclopentylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



DIPEA (9.62 mL, 55.57 mmol) was added to cyclopentanethiol (5.93 mL, 55.57 mmol), in DMF (80 mL) at RT under nitrogen. The resulting solution was stirred at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (13.1g, 37.05 mmol) was added to the reaction and stirred for 2 hours at RT. The reaction mixture was diluted with ethyl acetate (500 mL), and washed with water (2 x 200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by

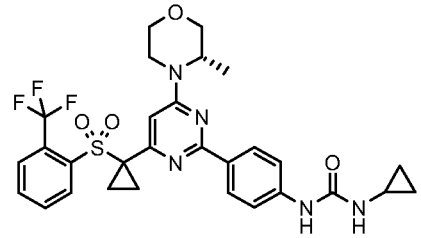
flash silica chromatography, elution gradient 0 to 30% ethyl acetate in isohexane, to give the desired material as a colourless gum (11.13 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.43 (2H, m), 1.53 (2H, m), 1.65 (2H, m), 1.94 (2H, m), 3.16 (2H, m), 3.44 (1H, td), 3.71 (1H, d), 3.95 (2H, m), 4.35 (1H, s), 6.79 (1H, s)

Mass Spectrum: m/z (ESI+)(M+H)+ = 328

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier

Example 10: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea



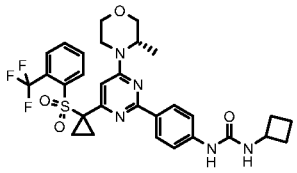
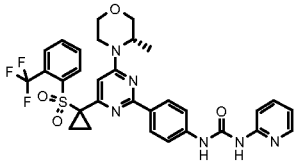
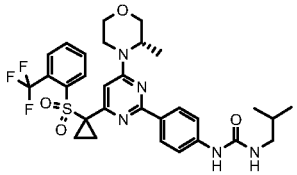
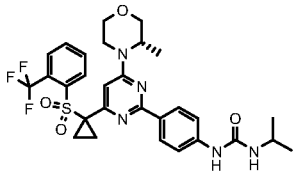
To a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate (200 mg,0.31 mmol) and cyclopropylamine (1.25 mmol) in NMP (2 mL) was added triethylamine (0.175 mL,1.25 mmol). The reaction mixture was heated at 75°C for 6 hours. The reaction mixture was purified by prep HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material (140 mg).

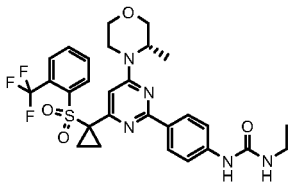
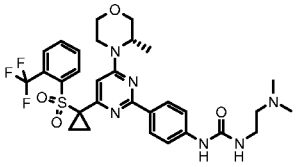
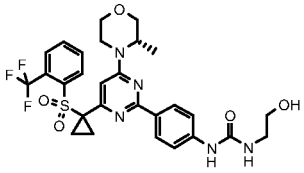
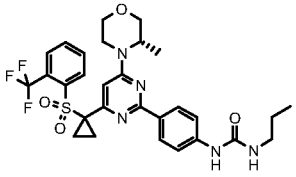
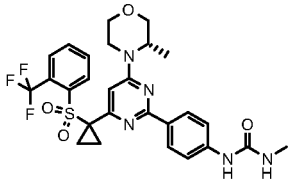
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.14 (3H, d), 1.70 - 1.75 (2H, m), 1.92 - 1.95 (2H, m), 3.11 (1H, td), 3.39 - 3.48 (1H, m), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.43 (1H, s), 6.41 (1H, d), 6.62 (1H, s), 7.37 (2H, d), 7.76 (2H, d), 7.82 - 7.86 (2H, m), 7.91 - 7.95 (1H, m), 8.16 - 8.19 (1H, m), 8.49 (1H, s)

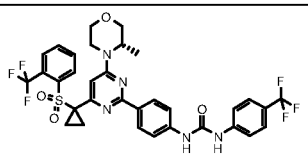
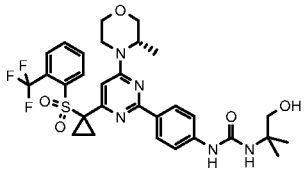
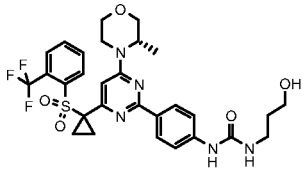
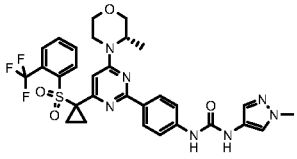
LCMS Spectrum: m/z (ESI+)(M+H)+ = 602; HPLC tR = 2.52 min.

mTOR Kinase Assay (Echo): 0.00448μM

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
10a		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	616	2.73
10b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea		
10c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	618	2.81
10d		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	604	2.66

Example	Structure	NAME	LCMS MH+	Retention time (min)
10e		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	590	2.51
10f		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	633	2.46
10g		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	606	2.16
10h		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-1-propyl-urea	604	2.62
10i		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	576	2.34

Example	Structure	NAME	LCMS MH+	Retention time (min)
10j		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	706	3.22
10k		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	634	2.43
10l		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	620	2.17
10m		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	642	2.35

Example 10a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.56 - 1.75 (4H, m), 1.80 - 1.96 (4H, m), 2.17 - 2.25 (2H, m), 3.11 (1H, td), 3.39 - 3.48 (1H, m), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.04 - 4.18 (2H, m), 4.43 (1H, s), 6.44 (1H, d), 6.61 (1H, s), 7.34 (2H, d), 7.75 (2H, d), 7.82 - 7.86 (2H, m), 7.92 - 7.95 (1H, m), 8.15 - 8.20 (1H, m), 8.52 (1H, s).

mTOR Kinase Assay (Echo): 0.0395μM

Example 10b: mTOR Kinase Assay (Echo): 0.0266μM

Example 10c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (6H, d), 1.14 (3H, d), 1.67 - 1.75 (2H, m), 1.91 - 1.95 (2H, m), 2.94 (2H, t), 3.11 (1H, td), 3.44 (1H, td), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.43 (1H, s), 6.22 (1H, t), 6.61 (1H, s), 7.35 (2H, d), 7.76 (2H, d), 7.81 - 7.87 (2H, m), 7.92 - 7.96 (1H, m), 8.16 - 8.21 (1H, m), 8.60 (1H, s).

mTOR Kinase Assay (Echo): 0.147μM

Example 10d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 - 1.15 (9H, m), 1.68 - 1.77 (2H, m), 1.92 - 1.95 (2H, m), 3.11 (1H, td), 3.44 (1H, td), 3.59 (1H, dd), 3.71 - 3.82 (2H, m), 3.94 (1H, dd), 4.09 (1H, d), 4.42 (1H, s), 6.04 (1H, d), 6.61 (1H, s), 7.34 (2H, d), 7.75 (2H, d), 7.82 - 7.87 (2H, m), 7.91 - 7.95 (1H, m), 8.16 - 8.20 (1H, m), 8.49 (1H, s).

mTOR Kinase Assay (Echo): 0.0432μM

Example 10e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.13 (3H, d), 1.69 - 1.75 (2H, m), 1.91 - 1.95 (2H, m), 3.07 - 3.19 (3H, m), 3.44 (1H, td), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.04 - 4.12 (1H, m), 4.44 (1H, s), 6.14 (1H, t), 6.62 (1H, s), 7.36 (2H, d), 7.75 (2H, d), 7.81 - 7.85 (2H, m), 7.91 - 7.95 (1H, m), 8.16 - 8.20 (1H, m), 8.62 (1H, s).

mTOR Kinase Assay (Echo): 0.00691μM

Example 10f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.69 - 1.74 (2H, m), 1.91 - 1.95 (2H, m), 2.19 (6H, s), 2.33 (2H, t), 3.11 (1H, td), 3.16 - 3.22 (2H, m), 3.44 (1H, td), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.43 (1H, s), 6.15 (1H, t), 6.62 (1H, s), 7.35 (2H, d), 7.75 (2H, d), 7.82 - 7.87 (2H, m), 7.91 - 7.96 (1H, m), 8.16 - 8.20 (1H, m), 8.86 (1H, s).

mTOR Kinase Assay (Echo): 0.174μM

Example 10g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.68 - 1.76 (2H, m), 1.92 - 1.95 (2H, m), 3.08 - 3.20 (3H, m), 3.39 - 3.48 (3H, m), 3.59 (1H, dd), 3.74 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.43 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.62 (1H, s), 7.35 (2H, d), 7.75 (2H, d), 7.82 - 7.85 (2H, m), 7.92 - 7.95 (1H, m), 8.16 - 8.19 (1H, m), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.00156μM

Example 10h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (3H, t), 1.14 (3H, d), 1.45 (2H, q), 1.70 - 1.74 (2H, m), 1.90 - 1.95 (2H, m), 3.03 - 3.15 (3H, m), 3.40 - 3.48 (1H, m), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.41 (1H, s), 6.18 (1H, t), 6.62 (1H, s), 7.36

(2H, d), 7.75 (2H, d), 7.82 - 7.87 (2H, m), 7.92 - 7.95 (1H, m), 8.17 - 8.20 (1H, m), 8.61 (1H, s).

mTOR Kinase Assay (Echo): 0.0268μM

Example 10i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.69 - 1.75 (2H, m), 1.92 - 1.95 (2H, m), 2.66 (3H, d), 3.11 (1H, td), 3.44 (1H, td), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.43 (1H, s), 6.04 (1H, q), 6.61 (1H, s), 7.37 (2H, d), 7.76 (2H, d), 7.82 - 7.85 (2H, m), 7.92 - 7.95 (1H, m), 8.16 - 8.19 (1H, m), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00591μM

Example 10j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.71 - 1.76 (2H, m), 1.91 - 1.96 (2H, m), 3.09 - 3.17 (1H, m), 3.45 (1H, dd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, d), 4.11 (1H, d), 4.44 (1H, s), 6.64 (1H, s), 7.45 (2H, d), 7.63 - 7.70 (4H, m), 7.81 - 7.87 (4H, m), 7.93 - 7.96 (1H, m), 8.17 - 8.21 (1H, m), 9.01 (1H, s), 9.12 (1H, s).

mTOR Kinase Assay (Echo): 0.11μM

Example 10k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.25 (6H, s), 1.69 - 1.75 (2H, m), 1.91 - 1.95 (2H, m), 3.11 (1H, td), 3.37 - 3.48 (3H, m), 3.59 (1H, dd), 3.74 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.42 (1H, s), 4.95 (1H, t), 5.99 (1H, s), 6.62 (1H, s), 7.32 (2H, d), 7.74 (2H, d), 7.82 - 7.87 (2H, m), 7.92 - 7.95 (1H, m), 8.17 - 8.20 (1H, m), 8.69 (1H, s).

mTOR Kinase Assay (Echo): 0.0502μM

Example 10l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.56 - 1.63 (2H, m), 1.69 - 1.74 (2H, m), 1.91 - 1.95 (2H, m), 3.07 - 3.19 (3H, m), 3.40 - 3.50 (3H, m), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.43 (1H, s), 4.47 (1H, t), 6.18 (1H, t), 6.62 (1H, s), 7.36 (2H, d), 7.76 (2H, d), 7.82 - 7.86 (2H, m), 7.91 - 7.96 (1H, m), 8.15 - 8.20 (1H, m), 8.67 (1H, s).

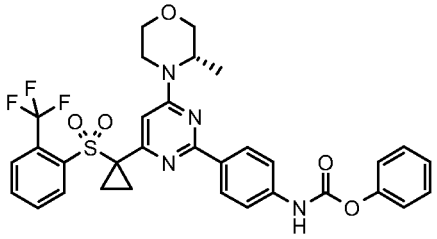
mTOR Kinase Assay (Echo): 0.0183μM

Example 10m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.70 - 1.75 (2H, m), 1.90 - 1.96 (2H, m), 3.12 (1H, td), 3.44 (1H, td), 3.59 (1H, dd), 3.73 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.43 (1H, s), 6.62 (1H, s), 7.37 - 7.44 (3H, m), 7.76 - 7.81 (3H, m), 7.83 - 7.87 (2H, m), 7.92 - 7.95 (1H, m), 8.17 - 8.20 (1H, m), 8.38 (1H, s), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00497μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below.

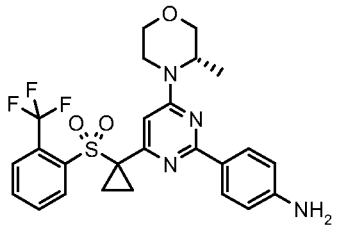
Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (1.669 mL, 13.31 mmol) was added to 4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]aniline (4.6 g, 8.87 mmol) and sodium hydrogen carbonate (1.118 g, 13.31 mmol) in dioxane (20 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 2 hours then the reaction mixture diluted with ethyl acetate (200 mL), and washed with water (125 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was triturated with a mixture of diethyl ether and isohexane to give the desired material (4.55 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.71 - 1.76 (2H, m), 1.92 - 1.96 (2H, m), 3.12 (1H, td), 3.41 - 3.47 (1H, m), 3.59 (1H, d), 3.73 (1H, d), 3.95 (1H, dd), 4.11 (1H, d), 4.45 (1H, s), 6.65 (1H, s), 7.22 - 7.31 (2H, m), 7.43 - 7.52 (3H,

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]aniline



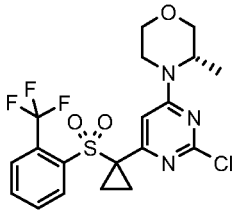
Bis(triphenylphosphine)palladium(II) chloride (300 mg, 0.43 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidine (5 g, 10.83 mmol), 4-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.56 g, 16.24 mmol) and sodium carbonate (20 mL, 40.0 mmol) in a mixture of ethanol (10 mL), DMF (20 mL), water (15 mL) and DME (40 mL) at RT. The resulting mixture was degassed then stirred at 95°C for 18 hours. The reaction was allowed to cool, diluted with ethyl acetate (400 mL), and washed with water (2 x 200 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give the desired material as a cream solid (5.40 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (3H, d), 1.68 - 1.73 (2H, m), 1.90 - 1.93 (2H, m), 3.07 (1H, td), 3.38 - 3.47 (1H, m), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (2H, dd), 4.02 - 4.07 (1H, m), 4.39 (1H, s), 5.50 (2H, s), 6.45 - 6.50 (3H, m), 7.61 (2H, d), 7.81 - 7.85 (2H, m), 7.93 (1H, dd), 8.17 (1H, dd)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 519; HPLC tR = 2.51 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidine

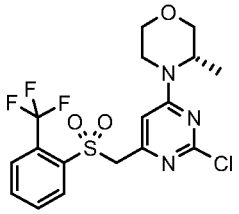


An aqueous solution of sodium hydroxide (30 mL, 247.8 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidine (4.5 g, 10.32 mmol), 1,2-dibromoethane (4.45 mL, 51.62 mmol) and tetrabutylammonium bromide (0.333 g, 1.03 mmol) in toluene (100 mL) at 30°C under nitrogen. The resulting mixture was stirred at 30°C for 3 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired material (4.70 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10 (3H, d), 1.61 - 1.66 (2H, m), 1.86 - 1.91 (2H, m), 3.09 (1H, td), 3.37 (1H, td), 3.52 (1H, dd), 3.68 (1H, d), 3.84 - 3.93 (2H, m), 4.27 (1H, s), 6.69 (1H, s), 7.85 - 7.93 (2H, m), 8.00 (1H, d), 8.07 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 462; HPLC tR = 2.43 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidine

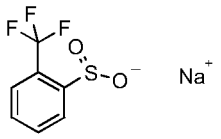


Sodium 2-(trifluoromethyl)benzenesulfinate (10.24 g, 44 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (13 g, 36.77 mmol), in acetonitrile (500 mL) at RT under nitrogen. The resulting mixture was stirred at 80°C for 3 hours. Additional sodium 2-(trifluoromethyl)benzenesulfinate (10.2 g, 44 mmol) was added and reaction heated at 80°C for 1 hour. The reaction mixture allowed to cool and concentrated *in vacuo*. The material was dissolved in ethyl acetate (500 mL), and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in isohexane, to give the desired material as an orange/cream solid (9.48 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 3.17 (1H, td), 3.43 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (2H, m), 4.27 (1H, s), 4.68 (2H, s), 6.79 (1H, s), 7.94 (3H, m), 8.08 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 436; HPLC tR = 2.35 min.

Sodium 2-(trifluoromethyl)benzenesulfinate



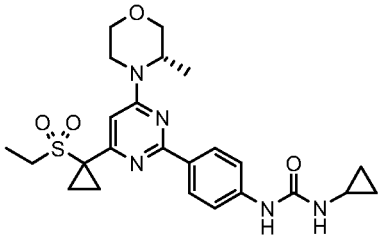
Sodium sulfite (3.92 mL, 81.88 mmol) was dissolved in water and stirred at RT 10 minutes. Sodium bicarbonate (13.74 g, 163.52 mmol) was added and the mixture stirred at 50°C for 1 hour. 2-(Trifluoromethyl)benzene-1-sulfonyl chloride (12.62 mL, 81.76 mmol) was added dropwise to the reaction mixture which was then stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and the residue suspended in methanol (250 mL) and

stirred at RT for 20 minutes. The solid was removed by filtration and the filtrate evaporated to give the desired material (20.00 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.40 (1H, d), 7.51 (1H, d), 7.64 (1H, d), 8.05 (1H, d)

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 11: 3-Cyclopropyl-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



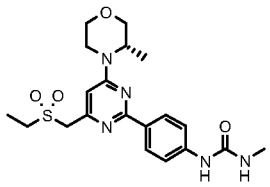
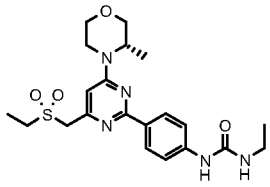
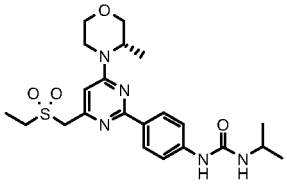
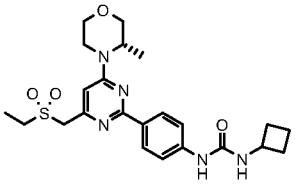
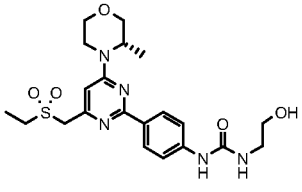
To a solution of phenyl *N*-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.29 mmol) in DMF (2 mL) was added triethylamine (0.120 mL, 0.86 mmol) followed by cyclopropylamine (0.100 mL, 1.44 mmol) and the reaction heated at 50°C for 2 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (90 mg).

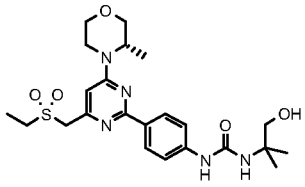
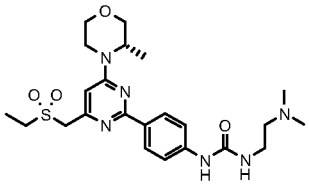
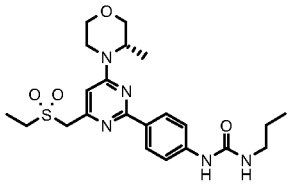
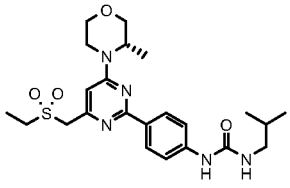
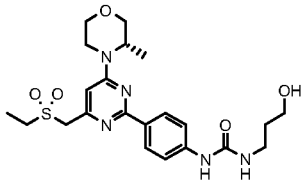
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.23 (3H, d), 1.32 (3H, t), 1.55 (2H, t), 1.62 - 1.65 (2H, m), 2.52 - 2.58 (1H, m), 3.17 - 3.24 (1H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.19 - 4.22 (1H, m), 4.56 (1H, s), 6.44 (1H, d), 6.78 (1H, s), 7.50 - 7.52 (2H, m), 8.18 - 8.20 (2H, m), 8.54 (1H, s).

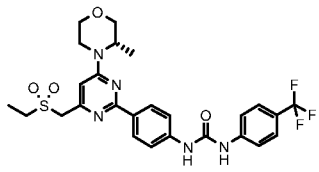
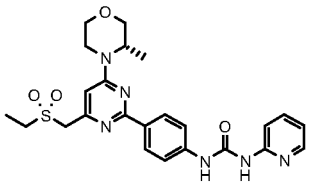
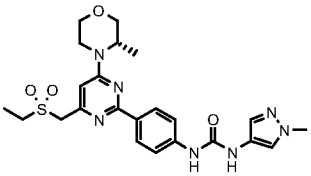
LCMS Spectrum: m/z (ESI+)(M+H)+ = 486; HPLC tR = 1.96 min.

mTOR Kinase Assay (Echo): 0.00165μM

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
11a		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	460	1.79
11b		1-ethyl-3-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	474	1.93
11c		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	488	2.11
11d		3-cyclobutyl-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	500	2.19
11e		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	490	1.63

Example	Structure	NAME	LCMS MH+	Retention time (min)
11f		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea	518	1.92
11g		3-(2-dimethylaminoethyl)-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	517	1.90
11h		3-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea	488	2.11
11i		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	502	2.29
11j		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	504	1.68

Example	Structure	NAME	LCMS MH+	Retention time (min)
11k		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	590	2.80
11l		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	523	2.37
11m		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	526	1.84

Example 11m can also be prepared in an analogous fashion but using DMA as the solvent and stirring at 50°C for 18 hours.

Example 11a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.55 (2H, t), 1.62 - 1.64 (2H, m), 2.67 (3H, t), 3.20 - 3.24 (1H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.19 - 4.22 (1H, m), 4.55 (1H, s), 6.07 (1H, d), 6.77 (1H, s), 7.49 - 7.52 (2H, m), 8.17 - 8.19 (2H, m), 8.74 (1H, s).
mTOR Kinase Assay (Echo): 0.00418μM

Example 11b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.23 (3H, d), 1.32 (3H, t), 1.55 (2H, t), 1.62 - 1.65 (2H, m), 3.09 - 3.16 (2H, m), 3.20 - 3.24 (1H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 (1H, d), 4.56 (1H, s), 6.16 (1H, t), 6.77 (1H, s), 7.48 - 7.52 (2H, m), 8.17 - 8.19 (2H, m), 8.66 (1H, s).
mTOR Kinase Assay (Echo): 0.00333μM

Example 11c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.23 (3H, d), 1.32 (3H, t), 1.55 (2H, t), 1.60 - 1.65 (2H, m), 3.20 - 3.24 (1H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.77 (1H, d), 3.80 (1H, m), 3.95 - 3.99 (1H, m), 4.19 - 4.22 (1H, m), 4.55 (1H, s), 6.07 (1H, d), 6.77 (1H, s), 7.47 - 7.50 (2H, m), 8.17 - 8.19 (2H, m), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.0247μM

Example 11d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.53 - 1.58 (2H, m), 1.62 - 1.64 (2H, m), 1.81 - 1.89 (3H, m), 2.18 - 2.24 (3H, m), 3.20 - 3.24 (1H, m), 3.43 (2H, q), 3.48 - 3.51 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.16 (2H, m), 4.55 (1H, s), 6.46 - 6.48 (1H, m), 6.78 (1H, s), 7.46 - 7.50 (2H, m), 8.18 (2H, d), 8.56 (1H, s).

mTOR Kinase Assay (Echo): 0.00642μM

Example 11e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.55 (2H, t), 1.62 - 1.64 (2H, m), 3.18 (1H, q), 3.20 (2H, d), 3.40 - 3.51 (2H, m), 3.46 (1H, d), 3.42 - 3.52 (2H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 (1H, d), 4.56 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.78 (1H, s), 7.48 - 7.50 (2H, m), 8.19 (2H, d), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00135μM

Example 11f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.24 (6H, s), 1.32 (3H, d), 1.53 - 1.58 (2H, m), 1.62 - 1.64 (2H, m), 3.17 - 3.24 (1H, m), 3.39 (2H, d), 3.45 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.19 - 4.22 (1H, m), 4.54 (1H, s), 4.95 (1H, t), 6.01 (1H, s), 6.77 (1H, s), 7.44 - 7.48 (2H, m), 8.18 (2H, d), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.00337μM

Example 11g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.53 - 1.58 (2H, m), 1.62 - 1.64 (2H, m), 2.18 (6H, s), 2.34 (2H, t), 3.17 - 3.23 (3H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.19 (1H, s), 4.56 (1H, s), 6.16 (1H, t), 6.77 (1H, s), 7.48 - 7.51 (2H, m), 8.17 - 8.19 (2H, m), 8.89 (1H, s).

mTOR Kinase Assay (Echo): 0.313μM

Example 11h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.23 (3H, d), 1.32 (3H, t), 1.41 - 1.50 (2H, m), 1.55 (2H, t), 1.62 - 1.65 (2H, m), 3.04 - 3.09 (2H, m), 3.17 - 3.24 (1H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 (1H, d), 4.55 (1H, s), 6.21 (1H, t), 6.77 (1H, s), 7.48 - 7.51 (2H, m), 8.17 - 8.20 (2H, m), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.00913μM

Example 11i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 (6H, d), 1.23 (3H, d), 1.32 - 1.38 (3H, m), 1.55 (2H, t), 1.62 - 1.65 (2H, m), 1.69 - 1.76 (1H, m), 2.94 (2H, t), 3.17 - 3.24 (1H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 (1H, d), 4.56 (1H, s), 6.25 (1H, t), 6.78 (1H, s), 7.48 - 7.51 (2H, m), 8.18 (1H, t), 8.20 (1H, s), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.0294μM

Example 11j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.55 (2H, q), 1.58 (2H, m), 1.62 - 1.64 (2H, m), 3.15 - 3.19 (3H, m), 3.43 (2H, q), 3.46 - 3.47 (2H, m), 3.50 (1H, d), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 (1H, d), 4.47 (1H, t), 4.55 (1H, s), 6.21 (1H, t), 6.77 (1H, s), 7.48 - 7.51 (2H, m), 8.17 - 8.20 (2H, m), 8.71 (1H, s).

mTOR Kinase Assay (Echo): 0.0122μM

Example 11k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.33 (3H, t), 1.56 (2H, t), 1.63 - 1.66 (2H, m), 3.18 - 3.26 (1H, m), 3.44 (2H, q), 3.46 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.22 (1H, d), 4.57 (1H, s), 6.81 (1H, s), 7.58 - 7.60 (2H, m), 7.64 - 7.70 (4H, m), 8.27 (2H, d), 9.05 (1H, s), 9.14 (1H, s).

mTOR Kinase Assay (Echo): 0.00332μM

Example 11l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.34 (3H, t), 1.55 - 1.59 (2H, m), 1.63 - 1.66 (2H, m), 3.18 - 3.23 (1H, m), 3.45 (2H, q), 3.47 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.20 - 4.24 (1H, m), 4.57 (1H, s), 6.81 (1H, s), 7.02 - 7.05 (1H, m), 7.56 (1H, d), 7.65 (2H, d), 7.75 - 7.77 (1H, m), 8.26 - 8.31 (1H, m), 8.27 - 8.31 (2H, m), 9.45 (1H, d), 10.61 (1H, s).

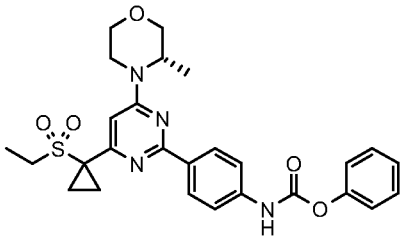
mTOR Kinase Assay (Echo): 0.00356μM

Example 11m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.33 (3H, t), 1.56 (2H, t), 1.63 - 1.65 (2H, m), 3.17 - 3.25 (1H, m), 3.44 (2H, q), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.75 (1H, s), 3.79 (3H, s), 3.96 - 4.00 (1H, m), 4.21 (1H, d), 4.56 (1H, s), 6.79 (1H, s), 7.38 - 7.39 (1H, m), 7.53 - 7.57 (2H, m), 7.76 (1H, s), 8.22 (2H, d), 8.39 (1H, s), 8.84 (1H, s).

mTOR Kinase Assay (Echo): 0.00437μM

The preparation of phenyl *N*-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

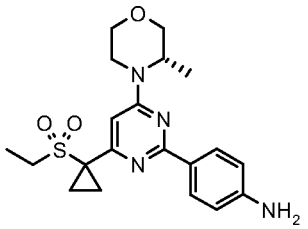


Phenyl chloroformate (0.566 mL, 4.50 mmol) was added dropwise to 4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.81 g, 4.50 mmol) and sodium bicarbonate (0.567 g, 6.75 mmol) in dioxane (30 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in ethyl acetate (200 mL) and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as a white solid (2.36 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.33 (3H, t), 1.55 - 1.59 (2H, m), 1.63 - 1.65 (2H, m), 3.21 - 3.25 (1H, m), 3.43 - 3.48 (2H, m), 3.41 - 3.52 (1H, m), 3.62 - 3.65 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.21 (1H, s), 4.57 (1H, s), 6.82 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.64 (2H, d), 8.27 - 8.30 (2H, m), 10.44 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 523; HPLC tR = 2.83 min.

4-[4-(1-Ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



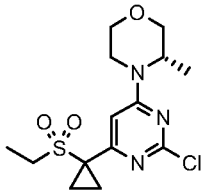
Dichlorobis(triphenylphosphine)palladium(II) (0.317 g, 0.45 mmol) was added to a degassed solution of 2-chloro-4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.56 g, 4.51 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.235 g, 5.64 mmol) and sodium carbonate (11.28 ml, 22.55 mmol) in a mixture of 18% DMF in DME:water:ethanol (7:3:2) (20 mL). The resulting solution was stirred at 85°C for 30 minutes. The reaction mixture was concentrated and partitioned between DCM (100 mL) and

water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 2.5% methanol in DCM, to give the desired material as a brown oil (2.15 g).

NMR Spectrum: ^1H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.31 (3H, t), 1.53 (2H, m), 1.60 - 1.62 (2H, m), 3.17 - 3.21 (1H, m), 3.37 - 3.47 (2H, m), 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.15 - 4.19 (1H, m), 4.51 - 4.53 (1H, m), 5.55 (2H, d), 6.60 - 6.62 (2H, m), 6.67 (1H, s), 8.00 - 8.04 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 403; HPLC tR = 2.14 min.

2-Chloro-4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

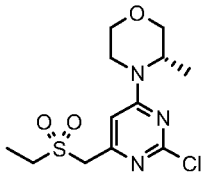


An aqueous sodium hydroxide solution (25.4 mL, 254.1 mmol) was added to tetrabutylammonium bromide (0.328 g, 1.02 mmol), 1,2-dibromoethane (0.876 mL, 10.16 mmol) and 2-chloro-4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.25 g, 10.16 mmol) in DCM (75 mL). The resulting mixture was stirred at 40°C for 4 hours. The reaction mixture was diluted with DCM (50 mL) and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (1.56 g).

NMR Spectrum: ^1H NMR (400.13 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.23 (3H, s), 1.49 - 1.52 (2H, m), 1.55 - 1.62 (2H, m), 3.18 - 3.23 (1H, m), 3.35 (2H, t), 3.41 - 3.46 (1H, m), 3.56 - 3.60 (1H, m), 3.72 (1H, d), 3.91 - 3.95 (1H, m), 4.15 - 4.19 (1H, m), 4.40 (1H, s), 6.93 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 346; HPLC 1.97 tR = min.

2-Chloro-4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



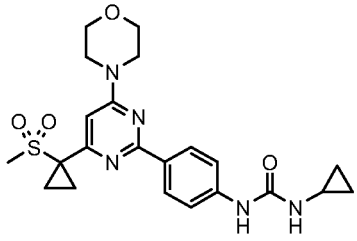
Ethane sulfinic acid sodium salt (3.94 g, 33.94 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (12.0 g, 33.94 mmol) in acetonitrile (250 mL) at RT. The resulting suspension was stirred at 80°C for 16 hours. The reaction mixture was evaporated to dryness and the residue partitioned between DCM (250mL), and water (200mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a yellow solid (5.94 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, m), 1.28 (3H, t), 3.22 (2H, d), 3.32 (1H, s), 3.42 - 3.49 (1H, m), 3.58 - 3.62 (1H, m), 3.73 (1H, d), 3.92 - 3.96 (2H, m), 4.25 - 4.31 (1H, m), 4.43 (2H, s), 6.92 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 320; HPLC tR = 1.46 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 12: 3-Cyclopropyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea



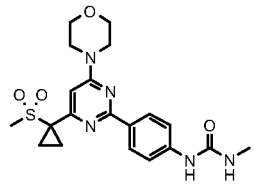
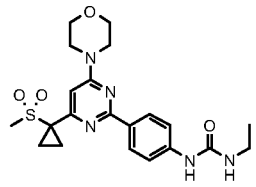
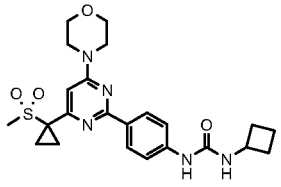
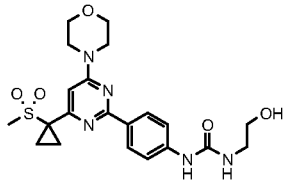
To a solution of phenyl *N*-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate (150 mg, 0.29 mmol) in DMF (2 mL) was added triethylamine (0.127 mL, 0.91 mmol) followed by cyclopropylamine (0.106 mL, 1.52 mmol) and the reaction heated at 50°C for 20 hours. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (80 mg).

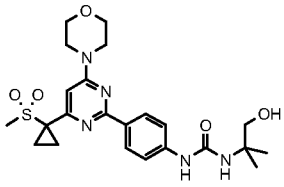
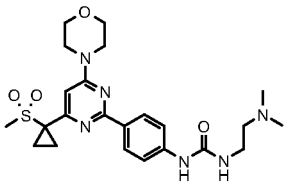
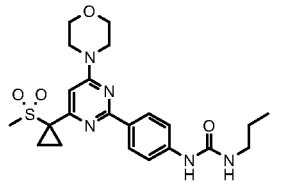
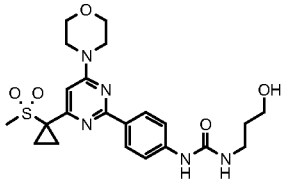
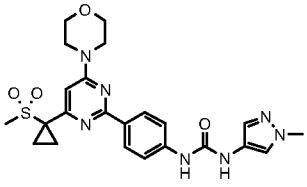
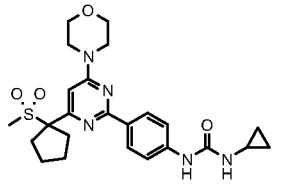
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.64 - 0.66 (2H, m), 1.54 - 1.57 (1H, m), 1.55 (1H, d), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 2.60 (1H, m), 3.30 (3H, s), 3.72 (8H, s), 6.43 (1H, d), 6.81 (1H, s), 7.50 - 7.52 (2H, m), 8.19 - 8.22 (2H, m), 8.55 (1H, s)

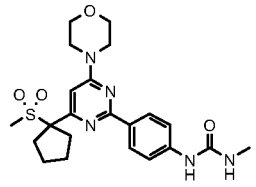
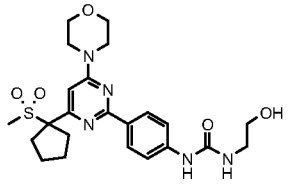
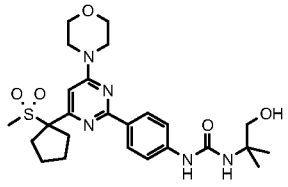
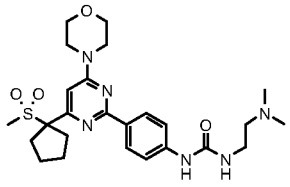
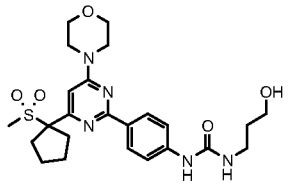
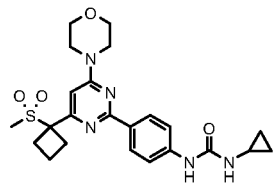
LCMS Spectrum: m/z (ESI+)(M+H)+ = 458; HPLC tR = 1.44 min.

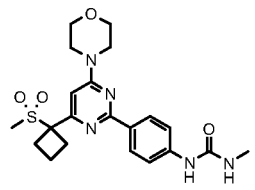
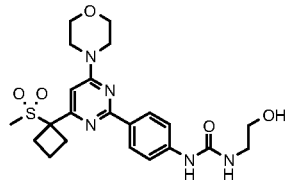
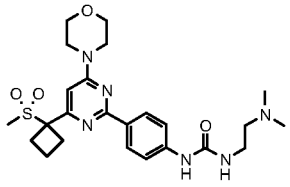
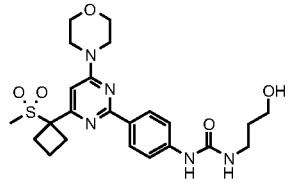
mTOR Kinase Assay (Echo): 0.00421μM

The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate, phenyl *N*-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate and the appropriate amines.

Example	Structure	NAME	LCMS MH+	Retention time (min)
12a		3-methyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	432.5	1.27
12b		3-ethyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	446.5	1.39
12c		3-cyclobutyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	471.5	1.73
12d		3-(2-hydroxyethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	462.5	1.15

Example	Structure	NAME	LCMS MH+	Retention time (min)
12e		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	490.5	1.43
12f		3-(2-dimethylaminoethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	489.5	1.05
12g		1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-propylurea	460.5	1.6
12h		3-(3-hydroxypropyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	476.5	1.18
12i		3-(1-methylpyrazol-4-yl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	498.5	1.38
12j*		3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	486	2.04

Example	Structure	NAME	LCMS MH+	Retention time (min)
12k*		3-methyl-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	460	1.88
12l*		3-(2-hydroxyethyl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	490	1.73
12m*		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	518	2.00
12n*		3-(2-dimethylaminoethyl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	517	1.98
12o*		3-(3-hydroxypropyl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	504	1.77
12p**		3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	472	2.06

Example	Structure	NAME	LCMS MH+	Retention time (min)
12q**		3-methyl-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	446	1.88
12r**		3-(2-hydroxyethyl)-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	476	1.72
12s**		3-(2-dimethylaminoethyl)-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	503	1.92
12t**		3-(3-hydroxypropyl)-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	490	1.77

* Reaction stirred at 55°C for 6 hours

** Reaction stirred at 40°C for 6 hours

The crude material for **Example 12** can also be purified either by chromatography on silica, eluting with 50-80% ethyl acetate in isohexane, or by dissolving the material in ethyl acetate and allowing the desired material to precipitate from solution on stirring.

Example 12a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.53 - 1.57 (1H, m), 1.55 - 1.56 (1H, m), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 2.66 (3H, d), 3.30 (3H, s), 3.72 (8H, s), 6.06 (1H, d), 6.81 (1H, s), 7.49 - 7.52 (2H, m), 8.19 - 8.21 (2H, m), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.00167μM

Example 12b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.54 - 1.57 (1H, m), 1.55 (1H, d), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 3.11 - 3.14 (2H, m), 3.30 (3H, s), 3.72 (8H, s), 6.16 (1H, s), 6.81 (1H, s), 7.49 - 7.51 (2H, m), 8.19 - 8.21 (2H, m), 8.67 (1H, s).

mTOR Kinase Assay (Echo): 0.00271μM

Example 12c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.53 - 1.57 (2H, m), 1.55 (2H, d), 1.59 - 1.67 (2H, m), 1.82 - 1.85 (1H, m), 1.89 (1H, t), 2.18 - 2.25 (2H, m), 3.30 (3H, s), 3.72 (8H, s), 4.14 (1H, d), 6.46 (1H, d), 6.81 (1H, s), 7.47 - 7.49 (2H, m), 8.20 (2H, d), 8.57 (1H, s).

mTOR Kinase Assay (Echo): 0.00152μM

Example 12d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.54 - 1.57 (1H, m), 1.55 - 1.56 (1H, m), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 3.18 (2H, q), 3.30 (3H, s), 3.46 (2H, q), 3.72 (8H, s), 4.73 (1H, t), 6.25 (1H, t), 6.81 (1H, s), 7.48 - 7.50 (2H, m), 8.19 - 8.22 (2H, m), 8.81 (1H, s).

mTOR Kinase Assay (Echo): 0.00155μM

Example 12e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (6H, s), 1.54 - 1.57 (1H, m), 1.55 (1H, d), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 3.30 (3H, s), 3.39 (2H, d), 3.72 (8H, s), 4.95 (1H, t), 6.00 (1H, s), 6.80 (1H, s), 7.44 - 7.47 (2H, m), 8.18 - 8.20 (2H, m), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.00459μM

Example 12f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.54 - 1.57 (1H, m), 1.55 - 1.56 (1H, m), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 2.18 (6H, s), 2.34 (2H, t), 3.20 (2H, t), 3.30 (3H, s), 3.72 (8H, s), 6.16 (1H, t), 6.80 (1H, s), 7.47 - 7.51 (2H, m), 8.20 (2H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.0605μM

Example 12g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.41 - 1.50 (2H, m), 1.54 - 1.57 (1H, m), 1.55 (1H, d), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 3.04 - 3.09 (2H, m), 3.30 (3H, s), 3.72 (8H, s), 6.20 (1H, t), 6.81 (1H, s), 7.48 - 7.51 (2H, m), 8.18 - 8.22 (2H, m), 8.66 (1H, s).

mTOR Kinase Assay (Echo): 0.00273μM

Example 12h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.53 - 1.58 (2H, m), 1.61 (2H, d), 1.65 - 1.68 (2H, m), 3.17 (2H, d), 3.30 (3H, s), 3.45 - 3.48 (2H, m), 3.72 (8H, s), 4.47 (1H, t), 6.20 (1H, s), 6.81 (1H, s), 7.48 - 7.51 (2H, m), 8.19 - 8.21 (2H, m), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.00392μM

Example 12i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.54 - 1.58 (1H, m), 1.56 - 1.56 (1H, m), 1.67 (2H, t), 3.30 (3H, s), 3.72 (8H, s), 3.79 (3H, s), 6.82 (1H, s), 7.38 - 7.38 (1H, m), 7.54 - 7.56 (2H, m), 7.76 (1H, s), 8.23 - 8.25 (2H, m), 8.38 (1H, s), 8.84 (1H, s).

mTOR Kinase Assay (Echo): 0.000771μM

Example 12j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.58 (2H, t), 1.81 (2H, d), 2.39 - 2.47 (2H, m), 2.57 (1H, t), 2.74 (2H, t), 2.91 (3H, s), 3.73 (8H, s), 6.42 (1H, d), 6.84 (1H, s), 7.49 - 7.53 (2H, m), 8.22 - 8.26 (2H, m), 8.54 (1H, s).

mTOR Kinase Assay (Echo): 0.00167μM

Example 12k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.56 - 1.57 (2H, m), 1.80 - 1.82 (2H, m), 2.42 (2H, d), 2.46 (2H, d), 2.67 (3H, t), 2.91 (3H, s), 3.73 (8H, s), 6.06 (1H, d), 6.84 (1H, s), 7.49 - 7.52 (2H, m), 8.22 - 8.25 (2H, m), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.0043μM

Example 12l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.58 (2H, t), 1.81 (2H, d), 2.41 - 2.44 (2H, m), 2.73 (2H, d), 2.91 (3H, s), 3.18 (2H, q), 3.46 (2H, q), 3.73 (8H, s), 4.72 (1H, t), 6.25 (1H, s), 6.84 (1H, s), 7.48 - 7.50 (2H, m), 8.23 - 8.25 (2H, m), 8.81 (1H, s).

mTOR Kinase Assay (Echo): 0.00138μM

Example 12m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (6H, s), 1.58 (2H, t), 1.81 (2H, d), 2.41 - 2.44 (2H, m), 2.71 - 2.75 (2H, m), 2.91 (3H, s), 3.39 (2H, d), 3.73 (8H, s), 4.95 (1H, t), 6.00 (1H, s), 6.84 (1H, s), 7.44 - 7.47 (2H, m), 8.22 - 8.24 (2H, m), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.0101μM

Example 12n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.56 - 1.57 (2H, m), 1.81 (2H, d), 2.18 (6H, s), 2.34 (2H, t), 2.39 - 2.46 (2H, m), 2.73 (2H, q), 2.91 (3H, s), 3.19 (2H, q), 3.73 (8H, s), 6.15 (1H, t), 6.84 (1H, s), 7.48 - 7.50 (2H, m), 8.23 - 8.25 (2H, m), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.238μM

Example 12o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.56 - 1.59 (2H, m), 1.57 - 1.63 (2H, m), 1.81 (2H, d), 2.39 - 2.46 (2H, m), 2.72 - 2.74 (2H, t), 2.91 (3H, s), 3.15 - 3.19 (2H, m), 3.45 - 3.50 (2H, m), 3.73 (8H, s), 4.47 (1H, t), 6.20 (1H, t), 6.84 (1H, s), 7.48 - 7.51 (2H, m), 8.22 - 8.25 (2H, m), 8.71 (1H, s).

mTOR Kinase Assay (Echo): 0.00509μM

Example 12p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.41 - 0.43 (2H, m), 0.63 - 0.66 (2H, m), 1.90 (1H, m), 2.08 (1H, m), 2.33 (1H, t), 2.68 (1H, t), 2.80 - 2.82 (1H,m), 2.87 (3H, s), 2.90 (2H, m), 3.73 (8H, s), 6.43 - 6.44 (1H, m), 6.77 (1H, s), 7.49 - 7.51 (2H, m), 8.21 - 8.24 (2H, m), 8.56 (1H, s).

mTOR Kinase Assay (Echo): 0.0014μM

Example 12q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.99 - 2.06 (1H, m), 2.09 (1H, m), 2.32 - 2.34 (3H, m), 2.87 (3H, s), 2.90 (2H, s), 2.93 (2H, s), 3.73 (8H, s), 6.06 (1H, d), 6.76 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.00162μM

Example 12r: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.89 (1H, t), 2.07 (1H, d), 2.76 - 2.83 (2H, m), 2.87 (3H, s), 2.90 - 2.93 (2H, m), 3.18 (2H, m), 3.46 (2H, m), 3.73 (8H, s), 4.72 (1H, t), 6.25 (1H, t), 6.76 (1H, s), 7.48 - 7.50 (2H, m), 8.21 - 8.23 (2H, m), 8.81 (1H, s).

mTOR Kinase Assay (Echo): 0.000991μM

Example 12s: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.89 (1H, t), 2.07 (1H, t), 2.18 (6H, s), 2.34 (2H, t), 2.80 (2H, d), 2.87 (3H, s), 2.90 (2H, m), 3.19 (2H, t), 3.73 (8H, s), 6.16 (1H, s), 6.76 (1H, s), 7.47 - 7.50 (2H, m), 8.21 - 8.23 (2H, m), 8.90 (1H, s).

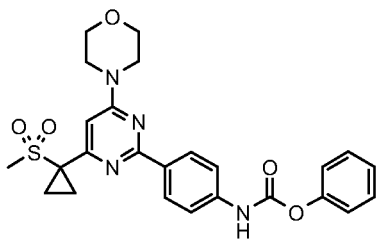
mTOR Kinase Assay (Echo): 0.134μM

Example 12t: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.58 (2H, t), 1.87 - 1.92 (1H, m), 2.06 - 2.10 (1H, m), 2.76 - 2.82 (2H, m), 2.87 (3H, s), 2.90 - 2.93 (2H, m), 3.14 - 3.19 (2H, m), 3.45 - 3.49 (2H, m), 3.73 (8H, s), 4.47 (1H, t), 6.20 (1H, t), 6.76 (1H, s), 7.48 - 7.50 (2H, m), 8.21 - 8.23 (2H, m), 8.71 (1H, s).

mTOR Kinase Assay (Echo): 0.0366μM

The preparation of phenyl *N*-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate



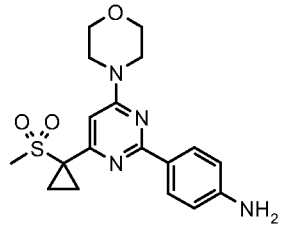
Phenyl chloroformate (0.4 mL, 3.18 mmol) was added dropwise to 4-(4-(1-(methylsulfonyl)cyclopropyl)-6-morpholinopyrimidin-2-yl)aniline (1.19 g, 3.18 mmol) and sodium bicarbonate (0.40 g, 4.77 mmol) in dioxane (30 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and

redissolved in ethyl acetate (100mL) and washed with water (100mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a yellow solid (1.68 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.57 (1H, d), 1.55 - 1.62 (1H, m), 1.68 (1H, d), 1.66 - 1.69 (1H, m), 3.40 (3H, s), 3.73 (8H, s), 6.86 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.63 - 7.65 (2H, m), 8.29 - 8.31 (2H, m), 10.44 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 495; HPLC tR = 2.58 min.

4-[4-(1-Methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline

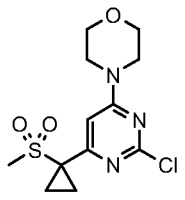


Dichlorobis(triphenylphosphine)palladium(II) (0.636 g, 0.91 mmol) was added to 2-chloro-4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidine (2.88 g, 9.06 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.482 g, 11.33 mmol) and sodium carbonate (22.66 mL, 45.31 mmol) in 18% DMF in 7:3:2 DME:Water:Ethanol (40mL). The resulting solution was stirred at 85°C for 1 hour. The reaction mixture was concentrated, diluted with DCM (200 mL), and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 2.5% methanol in DCM, to give the desired material as a yellow solid (1.19 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.51 - 1.53 (2H, m), 1.65 - 1.66 (2H, m), 3.40 (3H, s), 3.70 (8H, s), 5.56 (2H, d), 6.61 (2H, d), 6.70 (1H, s), 8.04 (2H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 375; HPLC tR = 1.65 min.

2-Chloro-4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidine

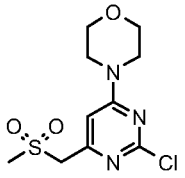


Sodium hydroxide (9.60 mL, 95.97 mmol) was added to 2-chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine (2.80 g, 9.60 mmol), 1,2-dibromoethane (1.654 mL, 19.19 mmol) and tetrabutylammonium bromide (0.619 g, 1.92 mmol) in toluene (120 mL) at RT. The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (200 mL), and washed sequentially with water (200 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 2.5% methanol in DCM, to give the desired material as a yellow solid (2.88 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.49 -1.51 (2H, m), 1.62 - 1.65 (2H, m), 3.19 (3H, s), 3.67 (8H, d), 6.96 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 318; HPLC 1.37 tR = min.

2-Chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine

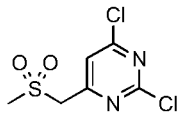


A suspension of 2,4-dichloro-6-(methylsulfonylmethyl)pyrimidine (10.56 g) in DCM (230 mL) was stirred magnetically (under nitrogen) and cooled to -5°C. Triethylamine (6.78 mL) was added followed by the dropwise addition of a solution of morpholine (3.85 mL) in DCM (30 mL) maintaining the reaction temperature below -5°C. The reaction was stirred at room temperature for 1 hour and then the organic mixture washed with water (300 mL). The organic phase was dried (MgSO4), filtered and evaporated to a brown solid which was chromatographed on silica, eluting with 50% ethyl acetate in DCM, to give the desired material (6.81g) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 3.12 (3H, s), 3.63 (4H, s), 3.68 - 3.70 (4H, m), 4.45 (2H, s), 6.96 (1H, s)

Mass Spectrum: MH+ 292.

2,4-Dichloro-6-(methylsulfonylmethyl)pyrimidine

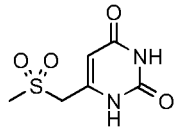


6-(Methylsulfonylmethyl)-1*H*-pyrimidine-2,4-dione (132 g, 0.65 mol) was added to phosphorus oxychloride (1.2 L) and the mixture heated to reflux for 16 hours, then cooled to room temperature. The excess phosphorus oxychloride was removed *in vacuo*, the residue azeotroped with toluene (2 x 500 mL) and dissolved in dichloromethane. This mixture was then poured slowly onto ice (4 L) and stirred for 20 minutes, then extracted with dichloromethane (3 x 1 L) (the insoluble black material was filtered off and discarded) and ethyl acetate (2 x 1 L). The extracts were combined, dried, then evaporated to leave the desired material as a dark brown solid (51 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 3.13 (s, 3H), 4.79 (s, 2H), 7.87 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 239; HPLC 1.21 tR = min.

6-(Methylsulfonylmethyl)-1*H*-pyrimidine-2,4-dione

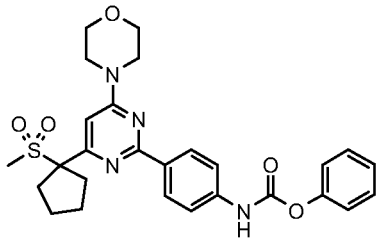


6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (175 g, 1.09 mol) was dissolved in DMF (2 L) and methanesulphinic acid sodium salt (133.5 g, 1.31 mol) was added. The reaction was heated to 125°C for 2 hours then allowed to cool and the suspension filtered and concentrated *in vacuo* to give a yellow solid. The crude material was washed with water, filtered, then triturated with toluene. The solid was filtered then triturated with isohexane to leave the desired compound as a yellow solid (250 g). The material was used without further purification.

6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione is a commercially available material.

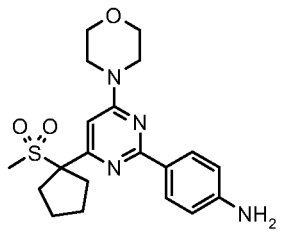
The preparation of phenyl *N*-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.541 mL, 4.30 mmol) was added dropwise to 4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline (1.73 g, 4.30 mmol) and sodium bicarbonate (0.542 g, 6.45 mmol) in dioxane (50 mL) under nitrogen. The resulting suspension was stirred at RT for 1 hour. The reaction mixture was evaporated to dryness and partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a yellow solid (1.7 g). NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.58 (2H, t), 1.82 (2H, d), 2.40 - 2.47 (2H, m), 2.73 - 2.75 (2H, m), 2.91 (3H, s), 3.74 (8H, s), 6.88 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.64 (2H, d), 8.33 - 8.35 (2H, m), 10.43 (1H, s), LCMS Spectrum: m/z (ESI+) (M+H)+ = 523; HPLC tR = 2.90 min.

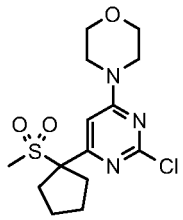
4-[4-(1-Methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline



Dichlorobis(triphenylphosphine)palladium (II) (0.224 g, 0.32 mmol) was added to a solution of 2-chloro-4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidine (2.21 g, 6.39 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.75 g, 7.99 mmol) and aqueous sodium carbonate solution (15.98 mL, 31.95 mmol) in a solvent mixture of 18% DMF in 7:3:2 DME:Water:Ethanol (40 mL). The resulting solution was stirred at 85°C for 1 hour. The reaction mixture was concentrated and diluted with DCM (200 mL) and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford

crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 2.5% methanol in DCM, to give the desired material as a yellow solid (1.73 g).
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.57 (2H, t), 1.80 (2H, d), 2.37 - 2.44 (2H, m), 2.69 - 2.74 (2H, m), 2.90 (3H, s), 3.71 (8H, s), 5.55 (2H, d), 6.59 - 6.63 (2H, m), 6.74 (1H, s), 8.05 - 8.09 (2H, m)
LCMS Spectrum: m/z (ESI+) (M+H)+ = 403; HPLC tR = 2.22 min.

2-Chloro-4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidine

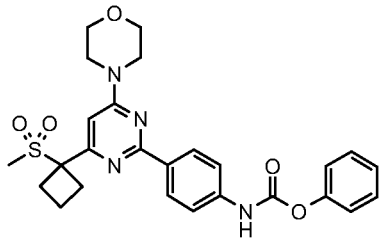


10N Sodium hydroxide solution (8.57 mL, 85.69 mmol) was added to 2-chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine (2.50 g, 8.57 mmol), 1,4-dibromobutane (1.014 mL, 8.57 mmol) and tetrabutylammonium bromide (0.552 g, 1.71 mmol) in toluene (120 mL) at RT. The resulting solution was stirred at 60°C for 4 hours. The reaction mixture was evaporated to dryness and the residue partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (2.215 g).
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.51 - 1.58 (2H, m), 1.76 - 1.80 (2H, m), 2.33 - 2.40 (2H, m), 2.52 - 2.59 (2H, m), 2.89 (3H, s), 3.67 (8H, s), 6.96 (1H, s)
LCMS Spectrum: m/z (ESI+) (M+H)+ = 346; HPLC 2.12 tR = min.

The preparation of 2-chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate

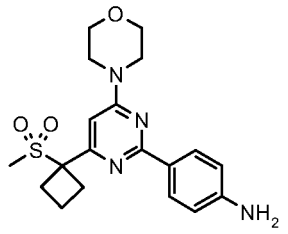


Phenyl chloroformate (0.084 mL, 0.67 mmol) was added dropwise to 4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline (260 mg, 0.67 mmol) and sodium bicarbonate (84 mg, 1.00 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (100 mL) and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a cream solid (380 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.91 (1H, d), 2.06 (1H, t), 2.80 - 2.84 (2H, m), 2.88 (3H, s), 2.93 (2H, d), 3.74 (8H, d), 6.80 (1H, s), 7.24 - 7.26 (2H, m), 7.25 - 7.30 (1H, m), 7.43 - 7.47 (2H, m), 7.63 (2H, d), 8.32 (2H, d), 10.43 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 509; HPLC tR = 2.77 min.

4-[4-(1-Methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline



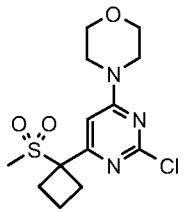
Dichlorobis(triphenylphosphine)palladium(II) (0.167 g, 0.24 mmol) was added to a degassed solution of 2-chloro-4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidine (0.790 g, 2.38 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.652 g, 2.98 mmol) and an aqueous solution of sodium carbonate (5.95 mL, 11.90 mmol) in a solvent mixture of 18% DMF in 7:3:2 DME:Water:Ethanol (40 mL). The resulting solution was stirred at 85°C for 1 hour. The reaction mixture was concentrated, diluted with DCM (200 mL), and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude

product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in isohexane, to give the desired material as a white solid (0.22 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.89 (1H, d), 2.03 - 2.07 (1H, m), 2.74 - 2.81 (2H, m), 2.86 (3H, s), 2.88 - 2.93 (2H, m), 3.71 (8H, s), 5.54 (2H, d), 6.59 - 6.62 (2H, m), 6.66 (1H, s), 8.04 - 8.07 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 389; HPLC tR = 2.05 min.

2-Chloro-4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidine

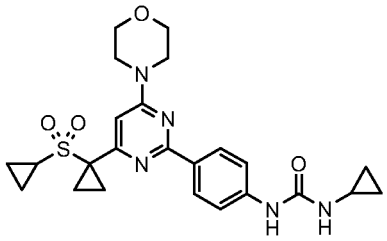


10N Sodium hydroxide solution (9.60 mL, 95.97 mmol) was added to 1,3-dibromopropane (0.979 mL, 9.60 mmol), 2-chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine (2.80 g, 9.60 mmol) and tetrabutylammonium bromide (0.619 g, 1.92 mmol) in toluene (120 mL) at RT. The resulting solution was stirred at 60°C for 18 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (200 mL), and washed sequentially with water (200 mL) and saturated brine solution (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in isohexane, to give the NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.87 - 1.89 (1H, m), 2.01 (1H, d), 2.66 - 2.73 (2H, m), 2.81 - 2.84 (2H, m), 2.86 (3H, s), 3.67 (8H, s), 6.88 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 332; HPLC 1.44 tR = min.

The preparation of 2-chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine was described earlier.

Example 13: 3-Cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea



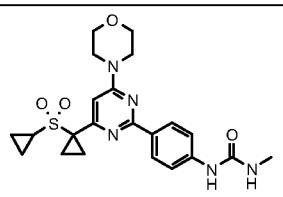
To a solution of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate (100 mg, 0.19 mmol) in DMF (2 mL) was added triethylamine (0.08 mL, 0.58 mmol) followed by cyclopropylamine (55 mg, 0.96 mmol) and the reaction heated at 50°C for 8 hours. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (60 mg).

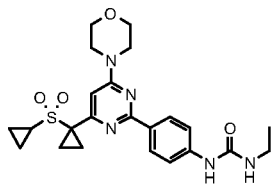
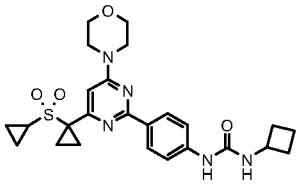
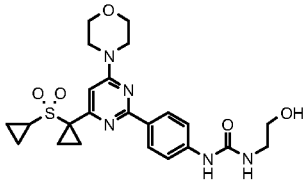
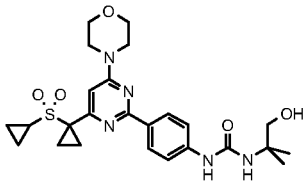
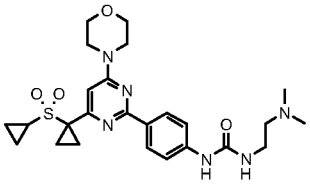
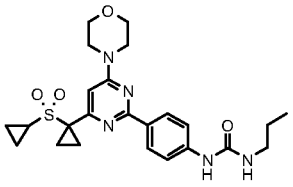
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.41 - 0.43 (2H, m), 0.64 - 0.66 (2H, m), 0.93 - 0.95 (2H, m), 1.02 - 1.05 (2H, m), 1.57 (2H, d), 1.65 (2H, d), 2.56 (1H, m), 3.02 (1H, s), 3.71 (8H, s), 6.42 (1H, s), 6.88 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.53 (1H, s)

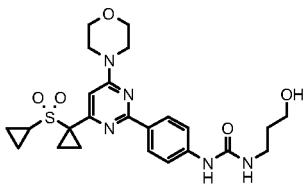
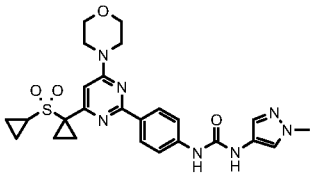
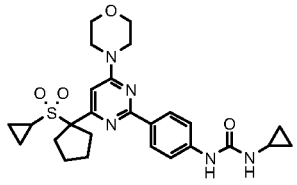
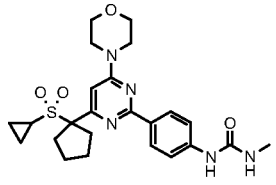
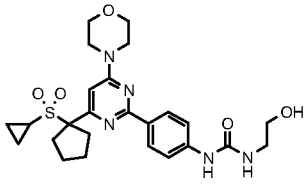
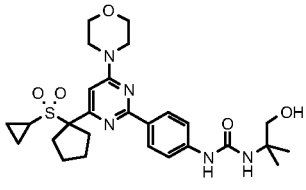
LCMS Spectrum: m/z (ESI+)(M+H)+ = 484; HPLC tR = 1.80 min.

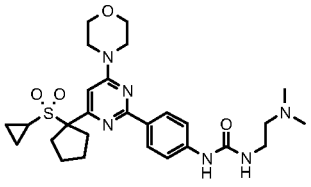
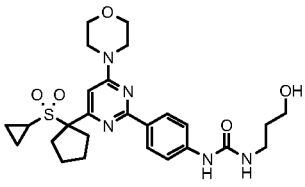
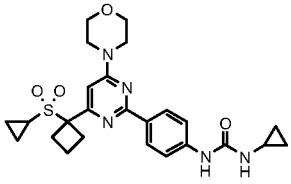
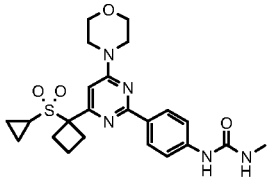
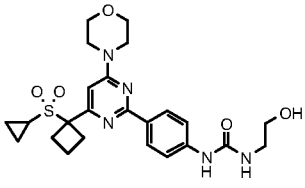
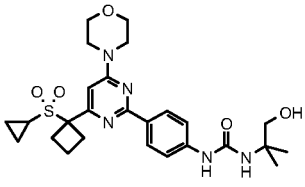
mTOR Kinase Assay (Echo): 0.00357μM

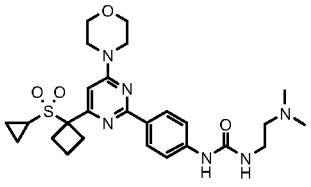
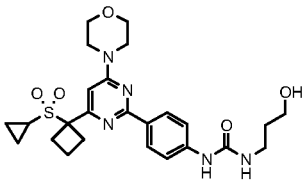
The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate, phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
13a		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea	458.3	1.63

Example	Structure	NAME	LCMS MH+	Retention time (min)
13b		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-ethylurea	472.4	1.78
13c		3-cyclobutyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	498.4	2.04
13d		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	488.4	1.5
13e		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	516.4	1.78
13f		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	515.4	1.71
13g		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-propylurea	486.4	1.96

Example	Structure	NAME	LCMS MH+	Retention time (min)
13h		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	502.4	1.54
13i		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	524.4	1.71
13j*		3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	512	2.30
13k*		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea	486	2.13
13l*		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	516	1.92
13m*		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	544	2.25

Example	Structure	NAME	LCMS MH+	Retention time (min)
13n*		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	543	2.18
13o*		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	530	1.97
13p*		3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	498	2.05
13q*		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea	498	2.05
13r*		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	502	1.72
13s*		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	530	2.01

Example	Structure	NAME	LCMS MH+	Retention time (min)
13t*		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	529	1.98
13u*		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	516	1.76

* Reaction stirred at 40°C for 6 hours

Example 13a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.95 (2H, m), 1.02 - 1.05 (2H, m), 1.55 - 1.58 (2H, m), 1.63 - 1.66 (2H, m), 2.66 (3H, d), 3.02 (1H, s), 3.71 (8H, s), 6.06 (1H, d), 6.88 (1H, s), 7.48 - 7.51 (2H, m), 8.20 - 8.22 (2H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00341μM

Example 13b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.96 (2H, m), 1.02 (2H, m), 1.06 (3H, q), 1.56 - 1.58 (2H, m), 1.62 - 1.66 (2H, m), 3.00 - 3.04 (1H, m), 3.10 - 3.16 (2H, m), 3.71 (8H, s), 6.15 (1H, t), 6.88 (1H, s), 7.47 - 7.51 (2H, m), 8.20 - 8.23 (2H, m), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.0037μM

Example 13c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 1.00 (2H, m), 1.02 - 1.05 (2H, m), 1.56 (2H, d), 1.56 - 1.60 (2H, m), 1.61 - 1.68 (2H, m), 1.82 - 1.88 (2H, m), 2.17 - 2.24 (2H, m), 3.00 - 3.04 (1H, m), 3.71 (8H, s), 4.14 (1H, d), 6.45 (1H, d), 6.88 (1H, s), 7.46 - 7.48 (2H, m), 8.20 - 8.22 (2H, m), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.0024μM

Example 13d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.95 (2H, m), 1.03 - 1.04 (2H, d), 1.55 - 1.58 (2H, m), 1.63 - 1.66 (2H, m), 3.02 (1H, s), 3.18 (2H, d), 3.45 (2H, t), 3.71 (8H, s), 4.73 (1H, s), 6.25 (1H, s), 6.88 (1H, s), 7.47 - 7.49 (2H, m), 8.22 (2H, d), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00351μM

Example 13e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.95 (2H, m), 1.03 - 1.05 (2H, m), 1.24 (6H, s), 1.56 (2H, d), 1.63 -1.65 (2H, d), 3.02 (1H, m), 3.38 - 3.40 (2H, m), 3.71 (8H, s), 4.95 (1H, s), 5.99 (1H, s), 6.88 (1H, s), 7.45 (2H, d), 8.20 (2H, d), 8.73 (1H, s).
mTOR Kinase Assay (Echo): 0.0301μM

Example 13f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.96 (2H, m), 1.03 - 1.05 (2H, m), 1.55 - 1.58 (2H, m), 1.63 - 1.66 (2H, m), 2.18 (6H, s), 2.34 (2H, t), 3.02 (1H, t), 3.19 (2H, q), 3.71 (8H, s), 6.15 (1H, s), 6.88 (1H, s), 7.47 - 7.49 (2H, m), 8.20 - 8.22 (2H, m), 8.88 (1H, s).
mTOR Kinase Assay (Echo): 0.386μM

Example 13g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 (3H, t), 0.93 - 0.96 (2H, m), 1.03 (2H, d), 1.41 - 1.50 (2H, m), 1.56 - 1.58 (2H, t), 1.62 - 1.66 (2H, m), 3.00 - 3.02 (1H, m), 3.06 (2H, s), 3.71 (8H, s), 6.19 (1H, t), 6.88 (1H, s), 7.49 (2H, d), 8.21 (2H, d), 8.64 (1H, s).
mTOR Kinase Assay (Echo): 0.00479μM

Example 13h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.98 (2H, m), 0.98 - 1.07 (2H, m), 1.55 - 1.56 (2H, m), 1.58 (2H, d), 1.61 - 1.66 (2H, m), 2.99 - 3.05 (1H, m), 3.15 - 3.19 (2H, m), 3.45 - 3.50 (2H, m), 3.71 (8H, s), 4.47 (1H, t), 6.19 (1H, t), 6.88 (1H, s), 7.47 - 7.51 (2H, m), 8.20 - 8.23 (2H, m), 8.70 (1H, s).
mTOR Kinase Assay (Echo): 0.0106μM

Example 13i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.94 (2H, t), 1.03 - 1.06 (2H, m), 1.55 - 1.59 (2H, m), 1.64 - 1.67 (2H, m), 3.02 (1H, s), 3.72 (8H, s), 3.79 (3H, s), 6.89 (1H, s), 7.38 (1H, s), 7.54 (2H, d), 7.76 (1H, s), 8.25 (2H, d), 8.38 (1H, s), 8.84 (1H, s).
mTOR Kinase Assay (Echo): 0.00275μM

Example 13j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 0.71 - 0.73 (2H, m), 0.84 - 0.87 (2H, m), 1.55 (2H, t), 1.81 (2H, d), 2.33 (1H, t), 2.43 - 2.45 (2H, m), 2.57 - 2.61 (1H, m), 2.82 (2H, t), 3.72 (8H, s), 6.45 (1H, d), 6.87 (1H, s), 7.50 (2H, d), 8.25 (2H, d), 8.56 (1H, s).
mTOR Kinase Assay (Echo): 0.0178μM

Example 13k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.71 - 0.73 (2H, m), 0.84 - 0.87 (2H, m), 1.55 (2H, t), 1.79 (1H, d), 1.82 (1H, s), 2.43 (2H, t), 2.57 - 2.61 (1H, m), 2.65 (3H, d), 2.82 (2H, d), 3.72 (8H, s), 6.08 (1H, d), 6.86 (1H, s), 7.49 - 7.51 (2H, m), 8.23 - 8.25 (2H, m), 8.77 (1H, s).
mTOR Kinase Assay (Echo): 0.0179μM

Example 13l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.71 - 0.73 (2H, m), 0.83 - 0.88 (2H, m), 1.55 (2H, t), 1.77 - 1.82 (2H, m), 2.43 - 2.48 (2H, m), 2.55 - 2.62 (1H, m), 2.81 (1H, t), 2.84 (1H, s), 3.15 - 3.18 (2H, m), 3.45 (2H, q), 3.72 (8H, s), 4.77 (1H, t), 6.26 (1H, t), 6.86 (1H, s), 7.47 - 7.50 (2H, m), 8.23 - 8.26 (2H, m), 8.83 (1H, s).

mTOR Kinase Assay (Echo): 0.0108μM

Example 13m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.72 - 0.74 (2H, m), 0.85 - 0.88 (2H, m), 1.24 (6H, s), 1.55 (2H, t), 1.79 (2H, d), 2.42 (1H, s), 2.45 (1H, d), 2.59 (1H, s), 2.80 (2H, s), 3.38 (2H, d), 3.72 (8H, s), 4.99 (1H, t), 6.01 (1H, s), 6.86 (1H, s), 7.44 - 7.46 (2H, m), 8.22 - 8.24 (2H, m), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.0532μM

Example 13n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.71 - 0.73 (2H, m), 0.85 - 0.87 (2H, m), 1.55 (2H, t), 1.79 (2H, d), 2.17 (6H, s), 2.33 (2H, t), 2.42 (1H, s), 2.45 (1H, d), 2.59 (1H, s), 2.81 (2H, s), 3.19 (2H, q), 3.72 (8H, s), 6.17 (1H, s), 6.86 (1H, s), 7.47 - 7.49 (2H, m), 8.23 - 8.25 (2H, m), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.997μM

Example 13o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.71 - 0.73 (2H, m), 0.83 - 0.88 (2H, m), 1.53 - 1.62 (4H, m), 1.79 - 1.82 (1H, m), 1.81 (1H, d), 2.44 (2H, d), 2.57 - 2.61 (1H, m), 2.81 (1H, t), 2.84 (1H, s), 3.14 - 3.18 (2H, m), 3.44 - 3.49 (2H, m), 3.72 (8H, s), 4.52 (1H, t), 6.21 (1H, t), 6.86 (1H, s), 7.48 - 7.50 (2H, m), 8.23 - 8.25 (2H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.0287μM

Example 13p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 0.74 - 0.78 (2H, m), 0.85 - 0.87 (2H, m), 1.88 - 1.91 (1H, m), 2.07 (1H, t), 2.50 (1H, s), 2.53 - 2.58 (1H, m), 2.85 - 2.89 (2H, m), 2.94 - 2.99 (2H, m), 3.73 (8H, s), 6.42 (1H, d), 6.77 (1H, s), 7.48 - 7.52 (2H, m), 8.23 - 8.26 (2H, m), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.00202μM

Example 13q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.74 - 0.78 (2H, m), 0.84 - 0.89 (2H, m), 1.88 - 1.91 (1H, m), 2.07 (1H, t), 2.50 (1H, m), 2.66 (3H, d), 2.85 - 2.89 (2H, m), 2.94 - 2.99 (2H, m), 3.72 (8H, s), 6.06 (1H, q), 6.76 (1H, s), 7.48 - 7.51 (2H, m), 8.22 - 8.26 (2H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00192μM

Example 13r: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.76 - 0.78 (2H, m), 0.85 - 0.88 (2H, m), 1.91 (1H, s), 2.07 (1H, t), 2.50 (1H, s), 2.85 - 2.89 (2H, m), 2.94 - 2.97 (2H, m), 3.17 (2H, q),

3.46 (2H, q), 3.72 (8H, s), 4.72 (1H, t), 6.24 (1H, t), 6.76 (1H, s), 7.47 - 7.49 (2H, m), 8.23 - 8.25 (2H, m), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.00198μM

Example 13s: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.76 - 0.79 (2H, m), 0.85 - 0.88 (2H, m), 1.24 (6H, s), 1.91 (1H, s), 2.07 (1H, t), 2.50 (1H, s), 2.85 - 2.89 (2H, m), 2.94 (1H, d), 2.96 - 2.97 (1H, m), 3.39 (2H, d), 3.72 (8H, s), 4.95 (1H, t), 6.00 (1H, s), 6.76 (1H, s), 7.44 - 7.46 (2H, m), 8.22 - 8.24 (2H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00846μM

Example 13t: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.75 - 0.77 (2H, m), 0.85 - 0.88 (2H, m), 1.88 - 1.91 (1H, m), 2.07 (1H, t), 2.18 (6H, s), 2.32 (1H, s), 2.34 (2H, t), 2.86 (1H, d), 2.88 (1H, s), 2.94 (1H, d), 2.96 (1H, s), 3.20 (2H, t), 3.72 (8H, s), 6.15 (1H, s), 6.76 (1H, s), 7.47 - 7.49 (2H, m), 8.23 - 8.25 (2H, m), 8.88 (1H, s).

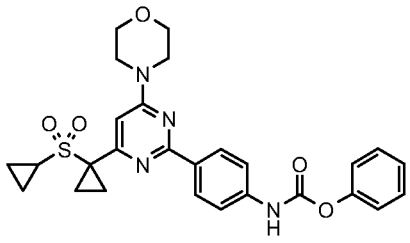
mTOR Kinase Assay (Echo): 0.172μM

Example 13u: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.74 - 0.78 (2H, m), 0.84 - 0.89 (2H, m), 1.57 (1H, d), 1.61 (1H, t), 1.88 - 1.91 (1H, m), 2.06 (1H, d), 2.50 (1H, m), 2.85 - 2.89 (2H, m), 2.94 - 2.99 (2H, m), 3.14 - 3.19 (2H, m), 3.45 - 3.49 (2H, m), 3.72 (8H, s), 4.47 (1H, t), 6.19 (1H, t), 6.76 (1H, s), 7.47 - 7.50 (2H, m), 8.23 - 8.25 (2H, m), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00477μM

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate



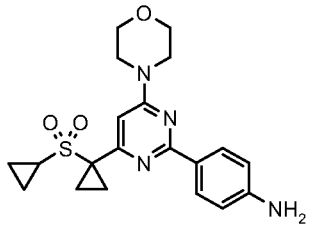
Phenyl chloroformate (0.440 mL, 3.50 mmol) was added dropwise to 4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline (1.40g, 3.50 mmol) and sodium bicarbonate (0.440 g, 5.24 mmol) in dioxane (50 mL) under nitrogen. The

resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (100 mL) and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a yellow solid (1.82 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.95 (2H, m), 1.05 (2H, d), 1.59 (1H, s), 1.60 (1H, t), 1.65 (1H, t), 1.67 (1H, d), 3.01 - 3.05 (1H, m), 3.58 (1H, s), 3.73 (8H, s), 6.94 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.64 (2H, d), 8.31 (2H, d), 10.44 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 521; HPLC tR = 2.68 min.

4-[4-(1-Cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline

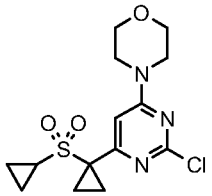


Dichlorobis(triphenylphosphine)palladium(II) (0.376 g, 0.54 mmol) was added to 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidine (1.84 g, 5.35 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.466 g, 6.69 mmol) and sodium carbonate (13.38 mL, 26.76 mmol) in 18% DMF in 7:3:2 DME:Water:Ethanol (40 mL). The resulting solution was stirred at 85°C for 1 hour. The reaction mixture was concentrated and diluted with DCM (200 mL), and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.40 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.97 (2H, m), 0.98 - 1.06 (2H, m), 1.52 - 1.58 (2H, m), 1.59 - 1.64 (2H, m), 2.97 - 3.04 (1H, m), 3.68 (4H, d), 3.71 - 3.71 (4H, m), 5.54 (2H, d), 6.58 - 6.62 (2H, m), 6.79 (1H, s), 8.03 (2H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 401; HPLC tR = 1.62 min.

2-Chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidine

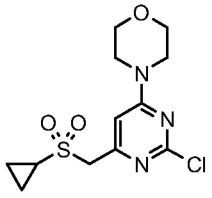


Sodium hydroxide (8.81 mL, 88.11 mmol) was added to 2-chloro-4-(cyclopropylsulfonylmethyl)-6-morpholin-4-ylpyrimidine (2.80 g, 8.81 mmol), 1,2-dibromoethane (1.519 mL, 17.62 mmol) and tetrabutylammonium bromide (0.568 g, 1.76 mmol) in toluene (120 mL) at RT. The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (200 mL), and washed sequentially with water (200 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.84 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 - 0.93 (2H, m), 1.00 - 1.05 (2H, m),), 1.50 (2H, d), 1.62 (2H, d), 2.89 - 2.96 (1H, m), 3.65 (4H, m), 3.66 - 3.67 (4H, m), 7.01 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 344; HPLC 1.48 tR = min.

2-Chloro-4-(cyclopropylsulfonylmethyl)-6-morpholin-4-ylpyrimidine

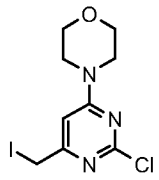


Cyclopropanesulfinic acid sodium salt (5.66 g, 44.17 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine (12.5 g, 36.81 mmol) in acetonitrile (300 mL) at RT. The resulting suspension was stirred at 80 °C for 24 hours. The resulting mixture was evaporated to dryness and the residue was azeotroped with MeCN to afford the desired material (7.12 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.94 - 0.99 (2H, m), 1.01 - 1.07 (2H, m), 2.77 - 2.84 (1H, m), 3.62 (4H, s), 3.67 - 3.69 (4H, s), 4.47 (2H, s), 6.95 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 318; HPLC tR = 1.46 min.

2-Chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine

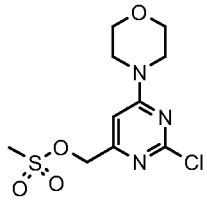


Sodium iodide (27.2 g, 181.31 mmol) was added to (2-chloro-6-morpholin-4-ylpyrimidin-4-yl)methyl methanesulfonate (27.9 g, 90.66 mmol) in acetone (400 mL) at RT under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM (400 mL) and was washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a brown solid (33.9 g).

NMR Spectrum: ^1H NMR (400.13 MHz, DMSO-d_6) δ 3.59 (4H, s), 3.63 - 3.68 (4H, m), 4.29 (2H, s), 6.97 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+339 = ; HPLC tR = 1.87 min.

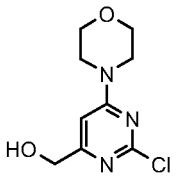
(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)methyl methanesulfonate



Methanesulfonyl chloride (10.57 mL, 136 mmol) was added dropwise to (2-chloro-6-morpholin-4-ylpyrimidin-4-yl)methanol (20.83 g, 90.70 mmol) and DIPEA (23.70 mL, 136 mmol) in DCM (375 mL) at 0°C over a period of 15 minutes, under a nitrogen atmosphere. The resulting solution was stirred at RT for 1 hour. The reaction mixture was diluted with water (100 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated to afford the desired material as a brown oil (27.9 g).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 308; HPLC tR = 1.58 min.

(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)methanol

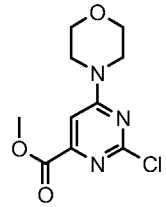


To a suspension of methyl 2-chloro-6-morpholin-4-ylpyrimidine-4-carboxylate (60 g, 232.85 mmol) in THF (1200 mL) at -5°C was added lithium borohydride (2M in THF, 0.122 L, 244.50 mmol) dropwise over 30 minutes. The reaction mixture was warmed to RT and stirred for 1 hour. To this was added water (600 mL), the mixture stirred for 2 hours and then filtered. Further water (600 mL) was added and the solution was extracted three times with ethyl acetate (600 mL). The combined organics were washed with 50% aqueous brine (900 mL), dried ($MgSO_4$) and the solvent was then removed under reduced pressure to give the desired product as a white solid (49.8 g).

NMR Spectrum: ^1H NMR (400.13 MHz, DMSO-d_6) δ 3.59 - 3.68 (8H, m), 4.35 (2H, dd), 5.50 (1H, t), 6.77 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 230; HPLC tR = 1.08 min

Methyl 2-chloro-6-morpholin-4-ylpyrimidine-4-carboxylate



To a solution of 2,6-dichloropyrimidine-4-carboxylate (60 g, 289.84 mmol) in DCM (400 mL) at -5°C was added triethylamine (44.4 mL, 318.82 mmol), washing in with DCM (80 mL). To the resulting solution was added morpholine (26.6 mL, 304.33 mmol) in DCM (120 mL) dropwise over 2 hours, maintaining the temperature below 5°C. The reaction mixture was stirred at 0°C for 2 hours and then warmed to RT. Water (600 mL) was added and the layers were separated. The organic layer was washed twice with water (180 mL) and the combined aqueous fractions extracted twice with DCM (180 mL). The combined organics were washed twice with 75% aqueous brine (180 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to give the crude product. This was purified by

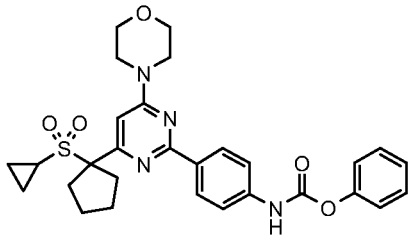
crystallisation from ethyl acetate/isohexane to give the desired product as a white solid (65.4g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.72 - 3.82 (8H, m), 3.99 (3H, s), 7.20 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 258; HPLC tR = 1.38 min

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate

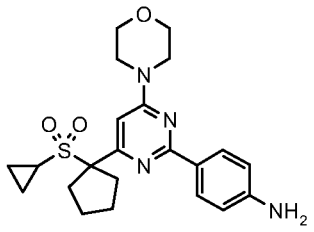


Phenyl chloroformate (0.455 mL, 3.62 mmol) was added dropwise to 4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline (1.55 g, 3.62 mmol) and sodium bicarbonate (0.456 g, 5.43 mmol) in dioxane (50 mL) under nitrogen. The resulting suspension was stirred at RT for 3 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (100 mL) and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as a yellow solid (2.31 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.71 - 0.75 (2H, m), 0.84 - 0.89 (2H, m), 1.56 (2H, t), 1.78 - 1.83 (2H, m), 2.45 (1H, t), 2.57 - 2.63 (2H, m), 2.81 - 2.84 (2H, m), 3.73 (8H, s), 6.90 (1H, s), 7.23 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.63 (2H, d), 8.33 - 8.36 (2H, m), 10.42 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 549; HPLC tR = 3.02 min.

4-[4-(1-Cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline

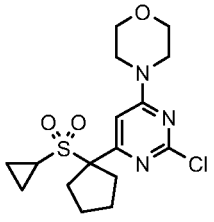


Dichlorobis(triphenylphosphine)palladium(II) (0.170 g, 0.24 mmol) was added to a degassed solution of 2-chloro-4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidine (1.80 g, 4.84 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.326 g, 6.05 mmol) and an aqueous solution of sodium carbonate (12.10 mL, 24.20 mmol) in a solvent mixture of 18% DMF in 7:3:2 DME:Water:Ethanol (40 mL). The resulting solution was stirred at 85°C for 1 hour. The reaction mixture was concentrated, diluted with DCM (100 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 70% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.55 g).

NMR Spectrum: ^1H NMR (400.13 MHz, DMSO-d_6) δ 0.73 - 0.75 (2H, m), 0.83 - 0.88 (2H, m), 1.55 (2H, t), 1.78 (1H, s), 1.81 (1H, t), 2.41 (1H, d), 2.45 - 2.47 (1H, m), 2.54 - 2.58 (1H, m), 2.79 (1H, t), 2.82 (1H, s), 3.70 (8H, d), 5.53 (2H, s), 6.59 - 6.62 (2H, m), 6.77 (1H, s), 8.07 - 8.09 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 429; HPLC tR = 2.36 min.

2-Chloro-4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidine



10N Sodium hydroxide solution (5.70 mL, 56.96 mmol) was added to 2-chloro-4-(cyclopropylsulfonylmethyl)-6-morpholin-4-ylpyrimidine (1.81 g, 5.70 mmol), 1,4-dibromobutane (0.674 mL, 5.70 mmol) and tetrabutylammonium bromide (0.367 g, 1.14 mmol) in toluene (100 mL) at RT. The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (75 mL) and washed

with water (75 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (1.8 g).

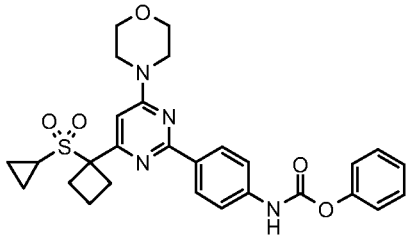
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.71 - 0.75 (2H, m), 0.90 - 0.94 (2H, m), 1.50 - 1.59 (2H, m), 1.77 - 1.80 (2H, m), 2.36 - 2.44 (2H, m), 2.57 - 2.68 (3H, m), 3.67 (8H, s), 6.97 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 372; HPLC tR = 2.26 min.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-morpholin-4-ylpyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate

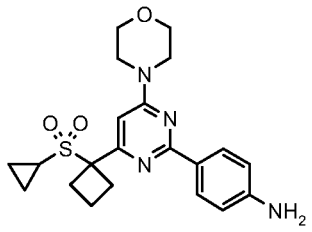


Phenyl chloroformate (0.106 mL, 0.84 mmol) was added dropwise to 4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline (350 mg, 0.84 mmol) and sodium bicarbonate (106 mg, 1.27 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (50 mL) and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as a cream solid (453 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.75 - 0.77 (2H, m), 0.85 - 0.88 (2H, m), 1.90 (1H, d), 2.07 (1H, d), 2.54(1H, m), 2.86 - 2.90 (2H, m), 2.93 - 2.98 (2H, s), 3.73 (8H, s), 6.80 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.63 (2H, d), 8.33 - 8.35 (2H, m), 10.42 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 535; HPLC tR = 2.91 min.

4-[4-(1-Cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline

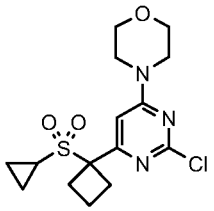


2-Chloro-4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidine (430 mg, 1.20 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (329 mg, 1.50 mmol), dichlorobis(triphenylphosphine)palladium(II) (42.2 mg, 0.06 mmol) and an aqueous solution of sodium carbonate (3.00 mL, 6.01 mmol) were suspended in a solvent mixture of 18% DMF in 7:3:2 DME:Water:Ethanol (8 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 30 minutes in the microwave reactor and cooled to RT. The crude product was purified by ion exchange chromatography using an SCX column, the desired product was eluted from the column using 7M ammonia in methanol. The isolated material was further purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a white solid (350 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.74 - 0.78 (2H, m), 0.83 - 0.88 (2H, m), 1.85 - 1.91 (1H, m), 2.03 - 2.07 (1H, m), 2.44 - 2.48 (1H, m), 2.83 - 2.87 (2H, m), 2.90-2.97 (2H, m), 3.70 - 3.71 (8H, m), 5.52 (2H, d), 6.58 - 6.62 (2H, m), 6.67 (1H, s), 8.06 - 8.09 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 415; HPLC tR = 2.19 min.

2-Chloro-4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidine



10N Sodium hydroxide solution (9.60 mL, 95.97 mmol) was added to 1,3-dibromopropane (0.979 mL, 9.60 mmol), 2-chloro-4-(cyclopropylsulfonylmethyl)-6-morpholin-4-ylpyrimidine (2.80 g, 9.60 mmol) and tetrabutylammonium bromide (0.619 g, 1.92 mmol) in toluene (120

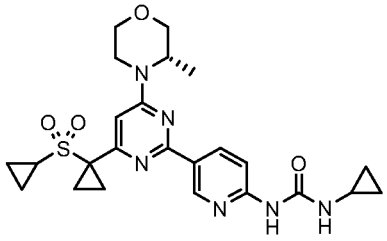
mL) at RT. The resulting solution was stirred at 60°C for 18 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (200 mL), and washed sequentially with water (200 mL) and saturated brine solution (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (0.795 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.73 - 0.77 (2H, m), 0.89 - 0.94 (2H, m), 1.85 - 1.92 (1H, m), 2.04 - 2.08 (1H, m), 2.53 - 2.57 (1H, m), 2.70 - 2.78 (2H, m), 2.85 - 2.93 (2H, m), 3.66 (8H, d), 6.88 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 358; HPLC 1.95 tR = min.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-morpholin-4-ylpyrimidine was described earlier.

Example 14: 3-Cyclopropyl-1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]urea



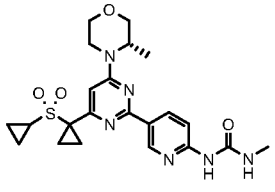
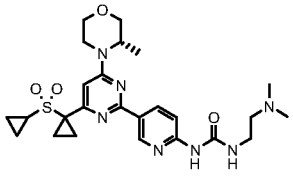
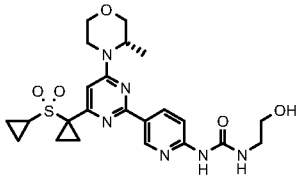
Triethylamine (0.208 mL, 1.5 mmol) was added to a solution of phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate (200 mg, 0.37 mmol) and cyclopropylamine (1.48 mmol) in NMP (2 mL). The reaction was heated at 75°C for 4 hours then purified by prep HPLC, using a mixture of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a solid (40 mg).

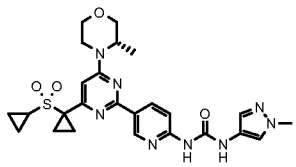
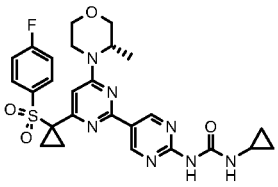
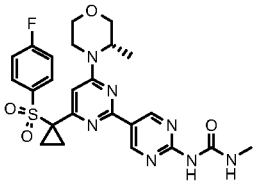
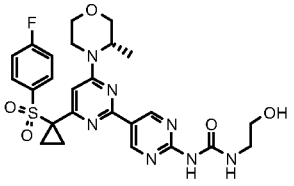
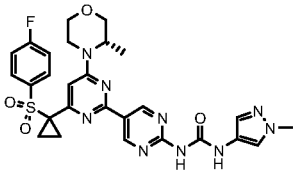
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.44 - 0.50 (2H, m), 0.64 - 0.72 (2H, m), 0.89 - 0.96 (2H, m), 1.00 - 1.06 (2H, m), 1.23 (3H, d), 1.54 - 1.60 (2H, m), 1.59 - 1.68 (2H, m), 2.59 - 2.66 (1H, m), 2.96 - 3.01 (1H, m), 3.16 - 3.25 (1H, m), 3.44 - 3.52 (1H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 (1H, s), 4.54 (1H, s), 6.90 (1H, s), 7.50 (1H, d), 8.18 (1H, s), 8.50 (1H, d), 9.09 (1H, s), 9.37 (1H, s)

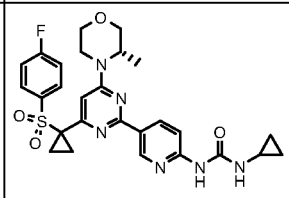
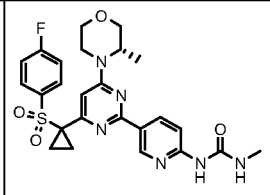
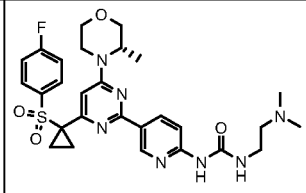
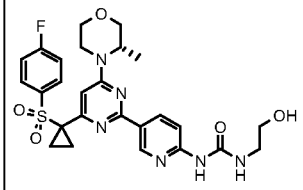
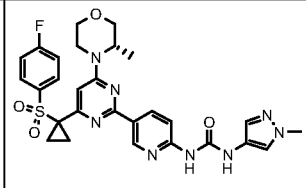
LCMS Spectrum: m/z (ESI+)(M+H)+ = 499; HPLC tR = 2.15 min.

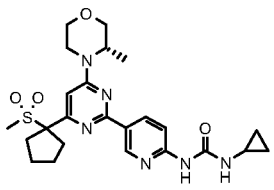
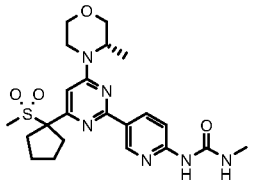
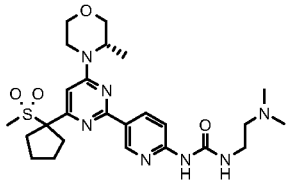
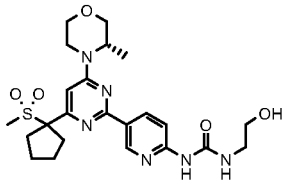
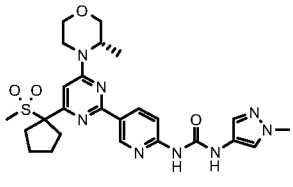
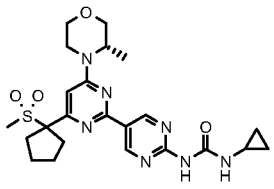
mTOR Kinase Assay (Echo): 0.0465μM

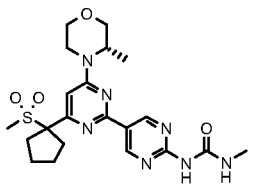
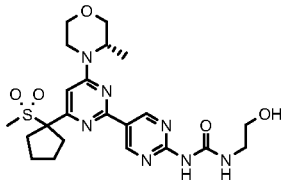
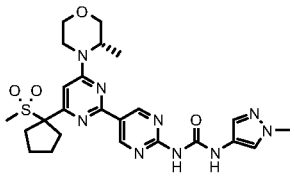
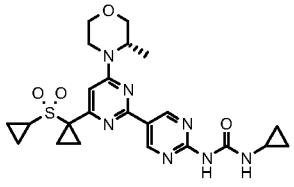
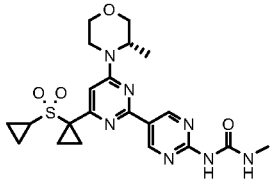
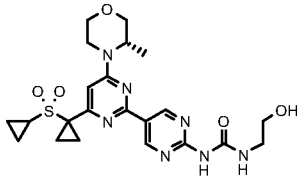
The following compounds were prepared in an analogous fashion from either phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate, phenyl *N*-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]carbamate, phenyl *N*-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate, phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]carbamate, phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]carbamate or phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]carbamate using the appropriate amine.

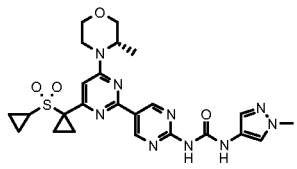
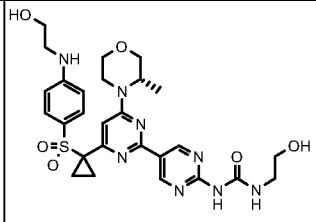
Example	Structure	NAME	LCMS MH+	Retention time (min)
14a		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-methylurea	473	2.03
14b		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(2-dimethylaminoethyl)urea	530	1.97
14c		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(2-hydroxyethyl)urea	503	1.73

Example	Structure	NAME	LCMS MH+	Retention time (min)
14d		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(1-methylpyrazol-4-yl)urea	539	2.01
14e		3-cyclopropyl-1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]urea	554	2.37
14f		1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-methylurea	528	2.16
14g		1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(2-hydroxyethyl)urea	558	1.91
14h		1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(1-methylpyrazol-4-yl)urea	594	2.19

Example	Structure	NAME	LCMS MH+	Retention time (min)
14i		3-cyclopropyl-1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]urea	553	2.26
14j		1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-methylurea	527	2.20
14k		3-(2-dimethylaminoethyl)-1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]urea	584	2.22
14l		1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(2-hydroxyethyl)urea	557	1.92
14m		1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(1-methylpyrazol-4-yl)urea	593	2.13

Example	Structure	NAME	LCMS MH+	Retention time (min)
14n		3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea	501	2.18
14o		3-methyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea	475	2.01
14p		3-(2-dimethylaminoethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea	532	2.01
14q		3-(2-hydroxyethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea	505	1.78
14r		1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]-3-(1-methylpyrazol-4-yl)urea	541	2.01
14s		3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]urea	502	2.15

Example	Structure	NAME	LCMS MH+	Retention time (min)
14t		3-methyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]urea	476	1.99
14u		3-(2-hydroxyethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]urea	506	1.70
14v		1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]-3-(1-methylpyrazol-4-yl)urea	542	1.95
14w		3-cyclopropyl-1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]urea	500	2.0
14x		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-methylurea	474	1.79
14y		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(2-hydroxyethyl)urea	504	1.54

Example	Structure	NAME	LCMS MH+	Retention time (min)
14z		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(1-methylpyrazol-4-yl)urea	540	1.82
14aa*		3-(2-hydroxyethyl)-1-[5-[4-[1-[4-(2-hydroxyethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]urea	599	1.63

* Isolated as a by product from the reaction to generate **14g**

Example 14a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.90 - 0.96 (2H, m), 1.01 - 1.06 (2H, m), 1.24 (3H, d), 1.55 - 1.60 (2H, m), 1.62 - 1.68 (2H, m), 2.78 (3H, s), 3.18 - 3.27 (1H, m), 3.44 - 3.54 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.20 (1H, d), 4.56 (1H, s), 6.91 (1H, s), 7.43 (1H, d), 8.15 (1H, s), 8.49 (1H, d), 9.12 (1H, s), 9.48 (1H, s), 9.49 (1H, s).

mTOR Kinase Assay (Echo): 0.0136μM

Example 14b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.95 (2H, m), 1.00 - 1.05 (2H, m), 1.23 (3H, d), 1.56 - 1.60 (2H, m), 1.63 - 1.66 (2H, m), 2.18 (6H, s), 2.36 (2H, t), 2.98 - 3.04 (1H, m), 3.17 - 3.29 (3H, m), 3.48 (1H, td), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.20 (1H, s), 4.54 (1H, s), 6.90 (1H, s), 7.53 (1H, d), 8.05 (1H, s), 8.49 (1H, d), 9.09 (1H, d), 9.48 (1H, s).

mTOR Kinase Assay (Echo): 1.39μM

Example 14c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.90 - 0.94 (2H, m), 1.01 - 1.05 (2H, m), 1.23 (3H, d), 1.55 - 1.60 (2H, m), 1.63 - 1.67 (2H, m), 2.96 - 3.03 (1H, m), 3.16 - 3.28 (3H, m), 3.43 - 3.52 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.20 (1H, s), 4.54 (1H, s), 4.80 (1H, t), 6.90 (1H, s), 7.47 (1H, d), 8.29 (1H, s), 8.50 (1H, d), 9.10 (1H, s), 9.51 (1H, s).

mTOR Kinase Assay (Echo): 0.0401μM

Example 14d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 - 0.96 (2H, m), 1.00 - 1.05 (2H, m), 1.24 (3H, d), 1.58 - 1.61 (2H, m), 1.64 - 1.70 (2H, m), 2.97 - 3.04 (1H, m), 3.22 (1H, td), 3.43 - 3.55 (1H, m), 3.64 (1H, dd), 3.75 - 3.82 (4H, m), 3.98 (1H, dd), 4.23 (1H, s), 4.55 (1H, s), 6.92 (1H, s), 7.49 (1H, d), 7.87 (1H, s), 8.55 (1H, d), 9.18 (1H, s), 9.73 (1H, s), 10.36 (1H, s).

mTOR Kinase Assay (Echo): 0.0143μM

Example 14e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.53 - 0.55 (2H, m), 0.69 - 0.74 (2H, m), 1.19 (3H, d), 1.60 - 1.63 (2H, m), 1.88 - 1.92 (2H, m), 3.12 - 3.21 (1H, m), 3.44 (1H, d), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.14 - 4.24 (1H, m), 4.40 - 4.54 (1H, m), 6.77 (1H, s), 7.44 (2H, t), 7.85 (2H, dd), 8.88 (2, s), 9.11 (1H, d), 10.11 (1H, s).

mTOR Kinase Assay (Echo): 0.11μM

Example 14f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.59 - 1.65 (2H, m), 1.89 - 1.92 (2H, m), 2.79(3H,d), 3.17 (1H, t), 3.46 - 3.63 (2H, m), 3.74 (1H, d), 3.95 (1H, d), 4.18 (1H, s), 4.46 (1H, s), 6.77 (1H, s), 7.43 (2H, t), 7.85 (2H, dd), 8.94 (2H, s), 10.08 (1H, s).

mTOR Kinase Assay (Echo): 0.189μM

Example 14g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.59 - 1.66 (2H, m), 1.88 - 1.92 (2H, m), 3.18 (1H, d), 3.30 (2H, q), 3.44 (1H, d), 3.49 - 3.54 (2H, m), 3.60 (1H, d), 3.72 - 3.98 (4H, m), 4.18(1H,s), 4.45(1H,s), 6.77 (1H, s), 7.43 (2H, t), 7.79 - 7.89 (2H, m), 8.91(2H,s), 9.13 - 9.20 (1H, m), 10.08 (1H, s).

mTOR Kinase Assay (Echo): 0.0857μM

Example 14h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.61 - 1.65 (2H, m), 1.89 - 1.94 (2H, m), 3.19 (1H, d), 3.41 - 3.50 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.82 (3H, s), 3.96 (1H, d), 4.22 (1H, s), 4.48 (1H, s), 6.78 (1H, s), 7.46 (2H, t), 7.54 (1H, s), 7.86 (2H, dd), 7.90 (1H, s), 8.97 (2H, s), 10.47 (1H, s).

mTOR Kinase Assay (Echo): 0.14μM

Example 14i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.46 - 0.51 (2H, m), 0.65 - 0.70 (2H, m), 1.18 (3H, d), 1.57 - 1.64 (2H, m), 1.86 - 1.92 (2H, m), 2.60 - 2.65 (1H, m), 3.14 - 3.19 (1H, m), 3.45 (1H, dd), 3.60 (1H, dd), 3.74 (1H, d), 3.92 - 3.99 (1H, m), 4.45 (1H, s), 6.73 (1H, s), 7.38 - 7.48 (2H, m), 7.84 (2H, dd), 8.05 - 8.16 (3H, m), 8.62 (1H, s), 9.37 (1H, s).

mTOR Kinase Assay (Echo): 0.0339μM

Example 14j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.57 - 1.64 (2H, m), 1.88 - 1.91 (2H, m), 2.74 (3H, d), 3.11 - 3.21 (1H, m), 3.42 - 3.50 (1H, m), 3.60 (1H, d), 3.74 (1H,

d), 3.93 - 3.98 (1H, m), 4.13 - 4.19 (1H, m), 4.40 - 4.47 (1H, m), 6.71 (1H, s), 7.35 (1H, d), 7.43 (2H, t), 7.84 (2H, dd), 7.98 - 8.07 (2H, m), 8.67 (1H, s), 9.50 (1H, s).

mTOR Kinase Assay (Echo): 0.0129μM

Example 14k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.58 - 1.62 (2H, m), 1.88 - 1.91 (2H, m), 2.19 (6H, s), 2.32 - 2.35 (2H, m), 3.17 (1H, d), 3.24 - 3.29 (2H, m), 3.44 (1H, d), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.13 - 4.21 (1H, m), 4.41 - 4.49 (1H, m), 6.71 (1H, s), 7.39 - 7.46 (3H, m), 7.84 (2H, dd), 7.98 (1H, s), 8.06 (1H, d), 8.65 (1H, s), 9.48 (1H, s).

mTOR Kinase Assay (Echo): 0.275μM

Example 14l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 - 1.65 (2H, m), 1.85 - 1.92 (2H, m), 3.12 - 3.21 (1H, m), 3.22 - 3.27 (2H, m), 3.43 - 3.50 (3H, m), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.17 (1H, s), 4.44 (1H, s), 4.79 (1H, t), 6.71 (1H, s), 7.37 - 7.46 (3H, m), 7.80 - 7.89 (2H, m), 7.84 (3H, dd), 8.04 (1H, d), 8.16 (1H, s), 8.70 (1H, s), 9.49 (1H, s).

mTOR Kinase Assay (Echo): 0.0137μM

Example 14m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.58 - 1.65 (2H, m), 1.88 - 1.92 (2H, m), 3.13 - 3.22 (1H, m), 3.42 - 3.49 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.81 (3H, s), 3.96 (1H, d), 4.14 - 4.24 (1H, m), 4.43 - 4.51 (1H, m), 6.73 (1H, s), 7.42 - 7.50 (3H, m), 7.82 - 7.90 (2H, m), 8.07 - 8.20 (1H, m), 8.71 (1H, s), 9.72 (1H, s), 10.28 (1H, s).

mTOR Kinase Assay (Echo): 0.0143μM

Example 14n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.44 - 0.51 (2H, m), 0.66 - 0.71 (2H, m), 1.22 (3H, d), 1.50 - 1.61 (2H, m), 1.78 - 1.85 (2H, m), 2.40 - 2.47 (2H, m), 2.60 - 2.66 (1H, m), 2.69 - 2.78 (2H, m), 2.90 (3H,s), 3.15 - 3.27 (1H, m), 3.44 - 3.54 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.98 (1H, d), 4.29 (1H, s), 4.58 (1H, s), 6.84 (1H, s), 7.51 (1H, d), 8.20 (1H, s), 8.53 (1H, d), 9.12 (1H, s), 9.37 (1H, s).

mTOR Kinase Assay (Echo): 0.0363μM

Example 14o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.51 - 1.60 (2H, m), 1.75 - 1.86 (2H, m), 2.40 - 2.47 (2H, m), 2.71 - 2.79 (5H, m), 2.90(3H,s), 3.22 (1H, d), 3.48 (1H, d), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.21 - 4.32 (1H, m), 4.58 (1H, s), 6.84 (1H, s), 7.42 (1H, d), 8.18 (1H, s), 8.52 (1H, d), 9.14 (1H, s), 9.52 (1H, s).

mTOR Kinase Assay (Echo): 0.0217μM

Example 14p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.61 (2H, m), 1.78 - 1.84 (2H, m), 2.18 (6H, s), 2.32 - 2.38 (2H, m), 2.38 - 2.47 (2H, m), 2.69 - 2.79 (2H, m), 2.90

(3H,s), 3.14 - 3.29 (3H, m), 3.43 - 3.55 (1H, m), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.26 (1H, s), 4.58 (1H, s), 6.84 (1H, s), 7.54 (1H, d), 8.03 (1H, s), 8.52 (1H, d), 9.12 (1H, s), 9.48 (1H, s).

mTOR Kinase Assay (Echo): 0.537μM

Example 14q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.51 - 1.61 (2H, m), 1.76 - 1.86 (2H, m), 2.37 - 2.46 (2H, m), 2.69 - 2.78 (2H, m), 2.90 (3H, s), 3.17 - 3.29 (3H, m), 3.42 - 3.54 (3H, m), 3.64 (1H, dd), 3.76 (1H, d), 3.92 - 4.01 (1H, m), 4.26 (1H, s), 4.57 (1H, s), 4.80 (1H, t), 6.84 (1H, s), 7.47 (1H, d), 8.31 (1H, s), 8.53 (1H, d), 9.12 (1H, s), 9.50 (1H, s).

mTOR Kinase Assay (Echo): 0.0265μM

Example 14r: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.60 (2H, m), 1.79 - 1.85 (2H, m), 2.39 - 2.47 (2H, m), 2.71 - 2.81 (2H, m), 2.90 (3H, s), 3.17 - 3.26 (1H, m), 3.46 - 3.55 (1H, m), 3.65 (2H, d), 3.78 (4H, d), 3.98 (1H, d), 4.28 (1H, s), 4.59 (1H, s), 6.86 (1H, s), 7.50 (2H, d), 7.87 (1H, s), 8.58 (1H, d), 9.20 (1H, s), 9.73 (1H, s), 10.34 (1H, s).

mTOR Kinase Assay (Echo): 0.0103μM

Example 14s: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.51 - 0.58 (2H, m), 0.67 - 0.76 (2H, m), 1.23 (3H, d), 1.50 - 1.62 (2H, m), 1.76 - 1.88 (2H, m), 2.31 - 2.49 (2H, m), 2.64 - 2.79 (2H, m), 2.90 (3H, s), 3.15 - 3.26 (1H, m), 3.49 (1H, t), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.29 (1H, s), 4.59 (1H, s), 6.88 (1H, s), 9.15 (1H, s), 9.36 (2H, s), 10.13 (1H, s).

mTOR Kinase Assay (Echo): 0.122μM

Example 14t: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.56 (2H,m), 1.77 - 1.87 (2H, m), 2.34 (3H, d), 2.38 - 2.46 (2H, m), 2.68 - 2.76 (2H, m), 2.80 (3H, d), 3.16 - 3.23 (1H, m), 3.46 - 3.51 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.96 (1H, d), 4.22 - 4.35 (1H, m), 4.54 - 4.68 (1H, m), 6.89 (1H, s), 8.97 - 9.07 (1H, m), 9.36 (2H, s), 10.11 (1H, s).

mTOR Kinase Assay (Echo): 0.197μM

Example 14u: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.52 - 1.59 (2H, m), 1.78 - 1.85 (2H, m), 2.38 - 2.52 (4H, m), 2.69 - 2.79 (2H, m), 3.20 (1H, d), 3.32 (3H, s), 3.42 - 3.47 (1H, m), 3.49 - 3.55 (2H, m), 3.61 - 3.67 (1H, m), 3.76 (1H, d), 3.97 (1H, d), 4.30 (1H, s), 4.61 (1H, s), 4.83 (1H, t), 6.89 (1H, s), 9.15 - 9.26 (1H, m), 9.36 (2H, s), 10.11 (1H, s).

mTOR Kinase Assay (Echo): 0.123μM

Example 14v: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.60 (2H, m), 1.79 - 1.86 (2H, m), 2.38 - 2.47 (2H, m), 2.65 - 2.81 (5H, m), 3.11 - 3.27 (1H, m), 3.46 - 3.53 (1H,

m), 3.65 (1H, d), 3.76 (1H, d), 3.81 (3H, s), 3.98 (1H, d), 4.27 - 4.35 (1H, m), 4.57 - 4.65 (1H, m), 6.91 (1H, s), 7.55 (1H, s), 7.92 (1H, s), 9.08 (1H, s), 9.44 (2H, s), 10.49 (1H, s).

mTOR Kinase Assay (Echo): 0.0823μM

Example 14w: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.52 - 0.57 (2H, m), 0.68 - 0.74 (2H, m), 0.91 - 0.95 (2H, m), 0.99 - 1.04 (2H, m), 1.23 (3H, d), 1.56 - 1.61 (2H, m), 1.63 - 1.68 (2H, m), 2.65 - 2.73 (1H, m), 2.95 - 3.03 (1H, m), 3.22 (1H, dd), 3.43 - 3.53 (1H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.23 (1H, s), 4.56 (1H, s), 6.95 (1H, s), 9.15 (1H, s), 9.33 (2H, s), 10.13 (1H, s).

mTOR Kinase Assay (Echo): 0.208μM

Example 14x: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 - 0.96 (2H, m), 1.00 - 1.06 (2H, m), 1.24 (3H, d), 1.56 - 1.61 (2H, m), 1.63 - 1.67 (2H, m), 2.80 (3H, d), 2.98 - 3.05 (1H, m), 3.19 - 3.25 (1H, m), 3.48 (1H, dd), 3.57 - 3.66 (1H, m), 3.70 - 3.80 (1H, m), 3.90 - 4.00 (1H, m), 4.21 (1H, s), 4.56 (1H, s), 6.94 (1H, s), 8.98 (1H, d), 9.33 (2H, s), 10.10 (1H, s).

mTOR Kinase Assay (Echo): 0.63μM

Example 14y: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 - 0.95 (2H, m), 1.00 - 1.05 (2H, m), 1.24 (3H, d), 1.57 - 1.61 (2H, m), 1.64 - 1.69 (2H, m), 2.98 - 3.04 (1H, m), 3.18 - 3.27 (1H, m), 3.29 - 3.34 (2H, m), 3.44 - 3.55 (3H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.23 (1H, s), 4.56 (1H, s), 4.83 (1H, t), 6.95 (1H, s), 9.20 (1H, t), 9.35 (2H, s), 10.11 (1H, s).

mTOR Kinase Assay (Echo): 0.152μM

Example 14z: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.95 (2H, m), 0.98 - 1.07 (2H, m), 1.23 (3H, d), 1.58 - 1.61 (2H, m), 1.62 - 1.68 (2H, m), 2.97 - 3.03 (1H, m), 3.23 (1H, td), 3.49 (1H, td), 3.64 (1H, d), 3.76 - 3.85 (4H, m), 3.98 (1H, dd), 4.24 (1H, s), 4.57 (1H, s), 6.96 (1H, s), 7.56 (1H, s), 7.91 (1H, s), 9.41 (2H, s), 10.49 (1H, s), 11.15 (1H, s).

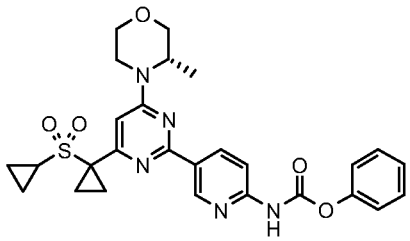
mTOR Kinase Assay (Echo): 0.171μM

Example 14aa: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.53 - 1.61 (2H, m), 1.74 - 1.79 (2H, m), 3.10 - 3.19 (2H, m), 3.28 - 3.36 (4H, m), 3.45 (1H, t), 3.48 - 3.56 (2H, m), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.10 (1H, s), 4.34 (1H, s), 4.75 (1H, t), 4.85 (1H, t), 6.62 (2H, d), 6.65 - 6.70 (2H, m), 7.41 (2H, d), 9.11 (2H, s), 9.20 (1H, t), 10.04 (1H, s).

mTOR Kinase Assay (Echo): 0.0186μM

The preparation of phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate is described below.

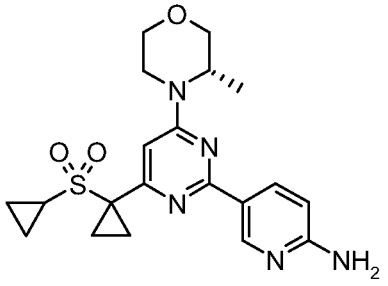
Phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate



Phenyl chloroformate (0.543 mL, 4.33 mmol) was added to a mixture of 5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-amine (1.2 g, 2.89 mmol) and sodium hydrogen carbonate (0.364 g, 4.33 mmol) in dioxane (30 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 1 hour, then at 40°C for 3 hours and again at RT overnight. Additional phenyl chloroformate (1 mL) was added and the mixture heated at 40°C until complete. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was then purified chromatography on silica, eluting with 10 to 80% ethyl acetate in isohexane, to give a mixture of the desired material and material where an additional carbamate group was present (phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-*N*-phenoxycarbonylcarbamate). This material (1 g) was used in the subsequent step without further attempts to purify.

LCMS Spectrum: m/z (ESI+)(M+H)+ = 536; HPLC tR = 2.65 min.

5-[4-(1-Cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-amine



Bis(triphenylphosphine)palladium(II) chloride (118 mg, 0.17 mmol) was added to 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (900 mg, 2.51 mmol), 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (830 mg, 3.77 mmol) and sodium carbonate (5.03 mL, 10.06 mmol) in a mixture of DMF (6 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT . The resulting mixture was stirred at 90°C for 18 hours then the reaction mixture diluted with ethyl acetate (200 mL) and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by chromatography on silica, eluting with 0 to 5% methanol in ethyl acetate. The material was further purified by ion exchange chromatography using an SCX column with the desired material eluted using 7M ammonia in methanol, to give the pure desired material as a white solid (1.2 g).

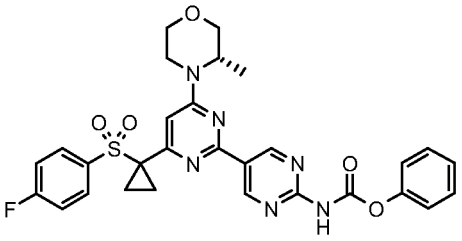
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.95 (2H, m), 1.00 - 1.04 (2H, m), 1.22 (3H, d), 1.53 - 1.59 (2H, m), 1.62 - 1.65 (2H, m), 2.94 - 3.02 (1H, m), 3.19 (1H, td), 3.48 (1H, td), 3.63 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.17 (1H, d), 4.53 (1H, s), 6.39 (2H, s), 6.50 (1H, d), 6.81 (1H, s), 8.23 (1H, d), 8.89 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 416; HPLC tR = 1.81 min.

The preparation of 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]carbamate is described below.

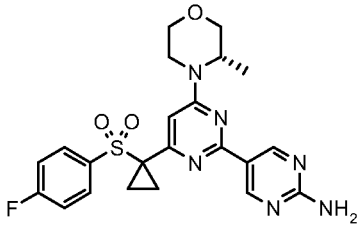
Phenyl *N*-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]carbamate



Phenyl chloroformate (0.306 mL, 2.44 mmol) was added to a mixture of 5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-

yl]pyrimidin-2-amine (765 mg, 1.63 mmol) and sodium hydrogen carbonate (205 mg, 2.44 mmol) in dioxane (10 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT overnight. Additional phenyl chloroformate (0.2 mL) was added and reaction left to stir overnight. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (2 x 100 mL), and a saturated brine solution (50 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford a gum. The crude gum was triturated with diethyl ether to give a solid which was collected by filtration and dried under vacuum to give the desired material as a yellow solid (1.0 g). No further purification was performed at this stage.
LCMS Spectrum: m/z (ESI+)(M+H)+ = 591; HPLC tR = 2.61 min.

5-[4-[1-(4-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-amine

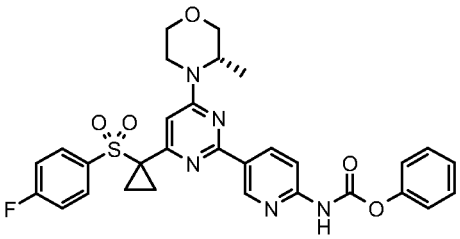


Bis(triphenylphosphine)palladium(II) chloride (0.143 g, 0.20 mmol) was added to 2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.25 g, 3.03 mmol), 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.868 g, 3.95 mmol) and sodium carbonate (3 mL, 6.00 mmol) in a mixture of DMF (3 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT and the atmosphere replaced with nitrogen. The mixture was stirred at 90°C for 5 hours the left to stir at RT overnight. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (2 x 100 mL), and the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with DCM to give a solid which was collected by filtration and dried under vacuum to give the desired material as a beige solid (1.1 g).
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.56 - 1.61 (2H, m), 1.86 - 1.90 (2H, m), 3.15 (1H, td), 3.45 (1H, td), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.14 (1H, d), 4.46 (1H, s), 6.69 (1H, s), 7.13 (2H, s), 7.41 (2H, t), 7.80 - 7.85 (2H, m), 8.65 (2H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 471; HPLC tR = 1.94 min.

The preparation of 2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

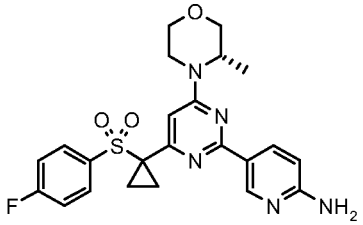
The preparation of phenyl *N*-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate is described below.

Phenyl *N*-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate



Phenyl chloroformate (0.962 mL, 7.67 mmol) was added to a mixture of 5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-amine (900 mg, 1.92 mmol) and sodium hydrogen carbonate (242 mg, 2.88 mmol) in dioxane (50 mL) at 5ºC under nitrogen. The resulting mixture was stirred at RT for 3 days, additional phenyl chloroformate (2 mL) added and the reaction stirred at RT for an additional 16 hours. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (100 mL), and the organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with diethyl ether to give a solid which was collected by filtration and dried under vacuum to give the desired material as a cream solid (900 mg). LCMS Spectrum: m/z (ESI+)(M+H)+ = 591; HPLC tR = 2.63 min.

5-[4-[1-(4-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-amine



Bis(triphenylphosphine)palladium(II) chloride (0.143 g, 0.20 mmol) was added to (2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.25 g, 3.03 mmol), 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.868 g, 3.95 mmol) and sodium carbonate (3 mL, 6.00 mmol) in a mixture of DMF (3 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT under at nitrogen atmosphere. The resulting mixture was stirred at 90°C for 5 hours then at RT for 16 hours. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (2 x 100 mL), and the organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 20 to 80% ethyl acetate in isohexane. The isolated material was further purified by ion exchange chromatography using an SCX column with the desired material eluted from the column using 7M ammonia in methanol. The desired material was isolated as as a white solid (0.94 g).

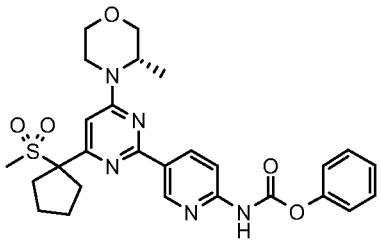
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.57 - 1.61 (2H, m), 1.86 - 1.89 (2H, m), 3.09 - 3.17 (1H, m), 3.41 - 3.49 (1H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.96 (1H, d), 4.11 (1H, d), 4.43 (1H, s), 6.35 - 6.41 (3H, m), 6.63 (1H, s), 7.38 - 7.45 (2H, m), 7.78 - 7.85 (3H, m), 8.51 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 470; HPLC tR = 2.06 min.

The preparation of 2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]carbamate is described below.

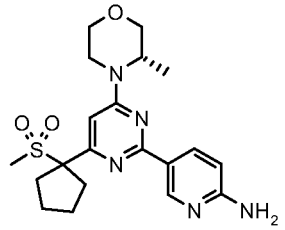
Phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]carbamate



Phenyl chloroformate (1.23 mL, 9.82 mmol) was added to 5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-amine (1.025 g, 2.45 mmol) and sodium hydrogen carbonate (0.309 g, 3.68 mmol) in dioxane (50 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 3 days then additional phenyl chloroformate (2 mL) added and the reaction left to stir at 35°C for 3 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (2 x 100 mL), and the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude liquid was triturated with diethyl ether to give a solid which was collected by filtration and dried under vacuum to give the desired material as a cream solid (1.2 g).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 538; HPLC tR = 2.89 min.

5-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-amine



Bis(triphenylphosphine)palladium(II) chloride (0.261 g, 0.37 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidine (2 g, 5.56 mmol), 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.835 g, 8.34 mmol) and aqueous sodium carbonate solution (11.12 mL, 22.23 mmol) in a mixture of DMF (6 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT under an atmosphere of nitrogen. The resulting mixture was stirred at 90°C for 18 hours. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (2 x 100 mL) and the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 10 to 100% ethyl acetate in isohexane. The isolated material was dissolved in methanol, the solid removed and the filtrate purified by ion exchange chromatography using an SCX column with the desired product eluted from the column using 7M ammonia in methanol. The desired material was isolated as a white solid (2.2 g).

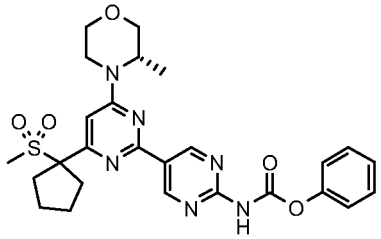
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.54 - 1.60 (2H, m), 1.78 - 1.85 (2H, m), 2.37 - 2.46 (2H, m), 2.65 - 2.78 (2H, m), 2.90 (3H, s), 3.18 (1H, dd), 3.49 (1H, td), 3.64 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.22 (1H, d), 4.56 (1H, s), 6.39 (2H, s), 6.50 (1H, d), 6.75 (1H, s), 8.25 (1H, d), 8.92 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 418; HPLC tR = 2.05 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidine was described earlier.

The preparation of phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]carbamate is described below.

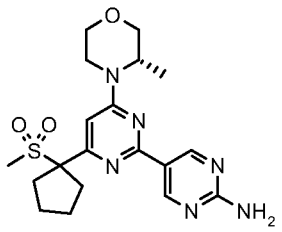
Phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]carbamate



Phenyl chloroformate (0.315 mL, 2.51 mmol) was added to 5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-amine (700 mg, 1.67 mmol), sodium hydrogen carbonate (211 mg, 2.51 mmol) in dioxane (20 mL) at 5ºC under nitrogen. The resulting mixture was stirred at RT for 48 hours.The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was triturated with diethyl ether to give the desired material as a yellow solid (790 mg).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 539; HPLC tR = 2.52 min.

5-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-amine



Bis(triphenylphosphine)palladium(II) chloride (0.261 g, 0.37 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidine (2 g, 5.56 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyrimidin-2-ylamine (1.843 g, 8.34 mmol) and aqueous sodium carbonate solution (11.12 mL, 22.23 mmol) in a mixture of DMF (6 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT. The resulting mixture was stirred at 90°C for 18 hours under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 3% methanol in ethyl acetate. The isolated material was triturated with a mixture of diethyl ether and isohexane and filtered to give the desired material as a cream solid (2.0 g).

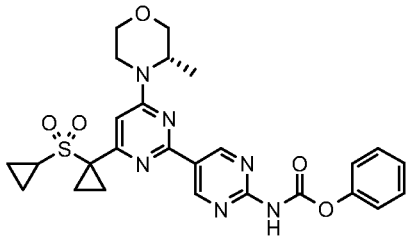
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.53 - 1.60 (2H, m), 1.76 - 1.83 (2H, m), 2.37 - 2.47 (2H, m), 2.64 - 2.76 (2H, m), 2.91 (3H, s), 3.15 - 3.23 (1H, m), 3.49 (1H, td), 3.63 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.24 (1H, d), 4.59 (1H, s), 6.82 (1H, s), 7.14 (2H, s), 9.09 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 419; HPLC tR = 1.83 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidine was described earlier.

The preparation of phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]carbamate is described below.

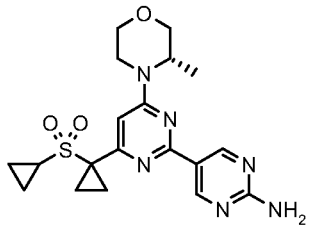
Phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]carbamate



Phenyl chloroformate (0.976 mL, 7.78 mmol) was added dropwise to 5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-amine (2.16 g, 5.19 mmol), sodium hydrogen carbonate (0.654 g, 7.78 mmol) in dioxane (30 mL) cooled to 10°C under nitrogen. The resulting mixture was stirred at RT for 48 hours. The reaction mixture was diluted with ethyl acetate (150 mL), and washed with water (150 mL followed by 125 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was purified by trituration with diethyl ether to give the desired material as a yellow solid (2.5 g).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 537; HPLC tR = 2.33 min.

5-[4-(1-Cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-amine



Bis(triphenylphosphine)palladium(II) chloride (0.381 g, 0.54 mmol) was added to 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.9 g, 8.10 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyrimidin-2-ylamine (2.69 g, 12.16 mmol) and aqueous sodium carbonate solution (4 mL, 8.00 mmol) in a mixture of DMF (18 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT .The resulting mixture was stirred at 90°C for 18 hours under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was

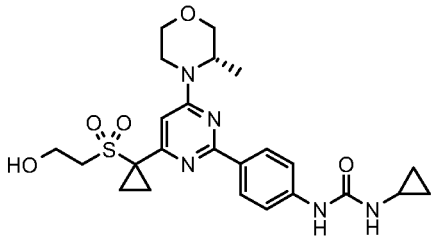
purified by flash silica chromatography, elution gradient 0 to 7% methanol in ethyl acetate. The isolated material was further purified by ion exchange chromatography using an SCX column, eluting with methanol followed by 7M ammonia in methanol, to give the desired material as a white solid (2.16 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.90 - 0.94 (2H, m), 0.99 - 1.04 (2H, m), 1.22 (3H, d), 1.54 - 1.58 (2H, m), 1.60 - 1.65 (2H, m), 2.95 - 3.02 (1H, m), 3.16 - 3.23 (1H, m), 3.47 (1H, td), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.18 (1H, s), 4.50 (1H, s), 6.85 (1H, s), 7.16 (2H, s), 9.05 (2H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 417; HPLC tR = 1.70 min.

The preparation of 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 15: 3-Cyclopropyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



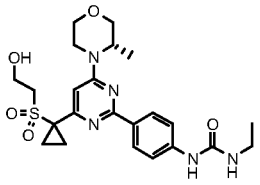
Bis (triphenylphosphine)palladium (II) chloride (6.84 mg, 0.00975 mmol) was added to 2-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane (0.101 g, 0.19 mmol), 1-cyclopropyl-3-(4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (0.088 g, 0.29 mmol) and sodium carbonate (0.487 mL, 0.97 mmol) in a solvent mixture (18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol) at RT under nitrogen. The resulting suspension was stirred at 80°C for 17 hours. The solvent was removed and the residue partitioned between DCM and water. The organic layer was dried ($MgSO_4$), filtered and tetrabutylammonium fluoride (0.975 mL, 0.97 mmol) added to the filtrate and stirred for 2 hours. The mixture was washed with water, the organic layer concentrated *in vacuo* and purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (0.057 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.41-0.44 (2H, m), 0.63-0.68 (2H, m), 1.23-1.25 (3H, d), 1.53-1.56 (2H, m), 1.65-1.66 (2H, m), 2.55-2.59 (1H, m), 3.17-3.25 (1H, td), 3.56-3.52 (1H, td), 3.62-3.66 (3H, m), 3.75-3.78 (1H, d), 3.88-3.89 (2H, m), 3.96-4.00 (1H, dd), 4.20-4.23 (1H, d), 4.56 (1H, bs), 5.03 (1H, bs), 6.45-6.46 (1H, d), 6.78 (1H, s), 7.50-7.52 (2H, d), 8.20-8.22 (2H, d), 8.56 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+ = 502; HPLC tR = 1.86min.

mTOR Kinase Assay (Echo): 0.00154μM

The compound below was prepared in an analogous fashion using the appropriate boronate.

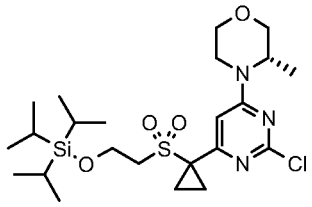
Example	Structure	NAME	LCMS MH+	Retention time (min)
15a		3-ethyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	490	1.82

Example 15a: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.05-1.09 (3H, t), 1.23-1.24 (3H, d), 1.53-1.56 (2H, m), 1.64-1.67 (2H, m), 3.10-3.17 (2H, m), 3.17-3.25 (1H, td), 3.45-3.52 (1H, td), 3.62-3.66 (3H, m), 3.75-3.78 (1H, d), 3.87-3.91 (2H, t), 3.96-3.99 (1H, dd), 4.19-4.22 (1H, d), 4.55 (1H, bs), 5.03 (1H, bs), 6.17-6.20 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, q), 8.19-8.21 (2H, q), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.000591μM

The preparation of 2-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane is described below.

2-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane

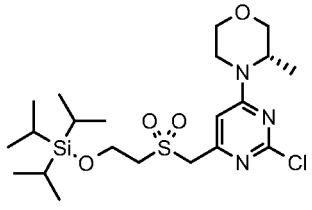


A 50% v/v aqueous sodium hydroxide solution (35 mL, 5.20 mmol) was added to 2-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethoxy-tri(propan-2-yl)silane (2.56 g, 5.20 mmol), 1,2-bibromoethane (1.345 mL, 15.61 mmol) and tetrabutylammonium bromide (0.168 g, 0.52 mmol) in toluene (100 mL) at RT. The resulting slurry was stirred at 60°C for 3 hours then the reaction mixture diluted with water and extracted sequentially with toluene and DCM. The organic layers were combined, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 10% ethyl acetate in DCM, to give the desired material as a colourless oil which solidified on standing (0.304 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.01-1.11 (21H, m), 1.30-1.32 (3H, d), 1.47-1.50 (2H, q), 1.77-1.80 (2H, q), 3.24-3.31 (1H, td), 3.40-3.44 (2H, t), 3.48-3.55 (1H, td), 3.64-3.68 (1H, td), 3.75-3.78 (1H, d), 3.97-4.01 (2H, m), 4.10-4.14 (2H, t), 4.32 (1H, bs), 6.86 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+=518; HPLC tR=3.86min.

2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethoxy-tri(propan-2-yl)silane



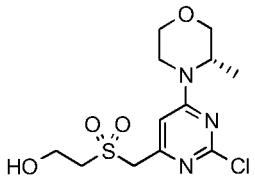
2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethanol (4.21 g, 12.53 mmol) was added to triisopropylsilyl chloride (3.22 mL, 15.03 mmol) and imidazole (2.046 g, 30.06 mmol) in DMF at RT. The resulting solution was stirred at RT overnight under a nitrogen atmosphere. The DMF was removed *in vacuo* and ethyl acetate added. The solids were removed by filtration and the filtrate concentrated *in vacuo* and purified by flash silica chromatography, eluting with 0 to 4% methanol in DCM. The isolated material was

again purified by chromatography on silica, eluting with 0 - 10% ethyl acetate in DCM, to give the desired material to as a clear gum (4.15 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.03-1.15 (21H, m), 1.27-1.29 (3H, d), 3.20-3.28 (1H, td), 3.37-3.40 (2H, m), 3.45-3.52 (1H, td), 3.61-3.65 (1H, dd), 3.71-3.74 (1H, d), 3.93-4.04 (2H, m), 4.15-4.18 (2H, t), 4.28 (3H, s), 6.50 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+ = 492; HPLC tR = 3.72min.

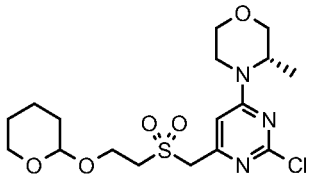
2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethanol



A solution of hydrogen peroxide (30%aqueous solution, 0.225 mL, 7.29 mmol) was added to a stirred solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-(oxan-2-yloxy)ethylsulfonylmethyl]pyrimidine (0.141 g, 0.36 mmol), sodium tungstate dihydrate (2.4 mg, 0.0073 mmol) in water (0.2 mL) and 2N sulfuric acid (0.011 mL) in 1,4-dioxane (1.4 mL) and methanol (1.4 mL) and the reaction stirred at 55°C for 4 hours. Water (50 mL) was added and the reaction cooled. 10% Sodium metabisulfite aqueous solution was added and the mixture extracted with DCM. The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the desired material as a opaque oil (0.198 g).

LCMS Spectrum: m/z (ES+) (M+H)+=336; HPLC tR=1.18 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-(oxan-2-yloxy)ethylsulfonylmethyl]pyrimidine



DIPEA (0.211 g, 1.63 mmol) was added dropwise to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.231 g, 0.65 mmol) and 2-(tetrahydro-2H-pyran-2-yloxy)ethanethiol (0.133 g, 0.82 mmol) in acetonitrile at RT. The resulting solution was stirred at RT for 1 hour. The solvent was removed and the residue partitioned between DCM

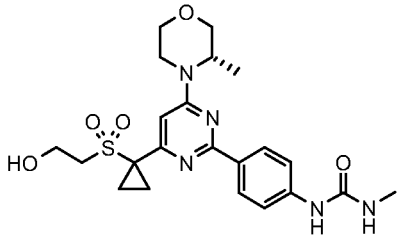
and water. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 2% methanol in DCM, to give the desired material as a colourless oil (0.141 g).

NMR Spectrum: ^{1}H NMR (400MHz, CDCl3) δ 1.24-1.26 (3H, d), 1.40-1.55 (4H, m), 1.60-1.67 (1H, m), 1.69-1.77 (1H, m), 2.68-2.71 (2H, t), 3.17-3.24 (1H, td), 3.41-3.47 (2H, m), 3.50-3.58 (1H, m), 3.59 (2H, s), 3.62-3.63 (1H, d), 3.69-3.72 (1H, d), 3.76-3.86 (2H, m), 3.91-3.95 (1H, dd), 3.97 (1H, bs), 4.25 (1H, bs), 4.52-4.54 (1H, t), 6.44 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+=386; HPLC tR=2.11 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier

Example 16: 1-[4-[4-[1-(2-Hydroxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea



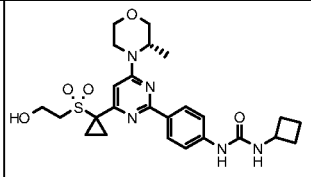
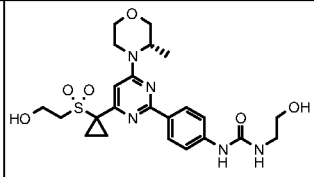
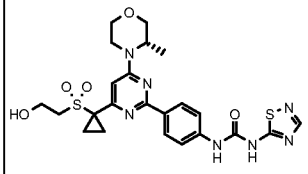
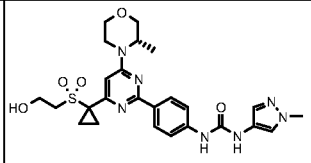
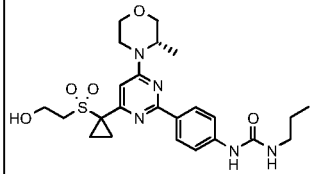
Methylamine (0.542 mL, 1.08 mmol) was added to (S)-phenyl 4- (4- (1- (2-hydroxyethylsulfonyl)cyclopropyl)-6- (3-methylmorpholino)pyrimidin-2-yl)phenylcarbamate (0.117 g, 0.22 mmol) and triethylamine (0.091 mL, 0.65 mmol) in DMF (3 mL) and the solution stirred at RT for 5 minutes. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (0.08 g).

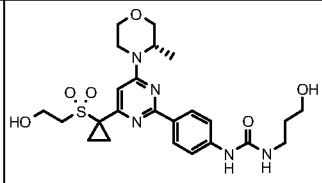
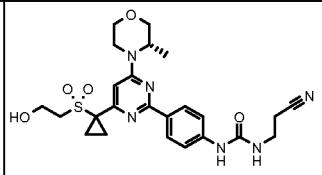
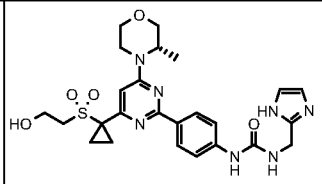
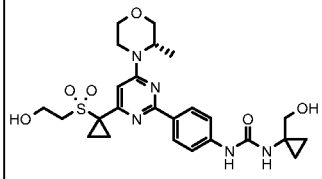
NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.22-1.24 (3H, d), 1.53-1.56 (2H, m), 1.64-1.66 (2H, m), 2.66-2.67 (3H, d), 3.16-3.24 (1H, td), 3.45-3.51 (1H, td), 3.61-3.67 (3H, m), 3.75-3.78 (1H, d), 3.86-3.91 (2H, q), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.56 (1H, bs), 5.06-5.09 (1H, t), 6.08-6.11 (1H, q), 6.77 (1H, s), 7.50-7.52 (2H, d), 8.18-8.21 (2H, d), 8.79 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+=476; HPLC tR=1.69 min.

mTOR Kinase Assay (Echo): 0.00142μM

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
16a		3-cyclobutyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	516	2.11
16b		3-(2-hydroxyethyl)-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	506	1.59
16c		1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	546	1.24
16d		1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	542	1.79
16e		3-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea	504	1.99

Example	Structure	NAME	LCMS MH+	Retention time (min)
16f		1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	520	1.61
16g		3-(2-cyanoethyl)-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	515	1.77
16h		1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	542	1.64
16i		1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea	532	1.66

Example 16a: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.24(3H, d), 1.53-1.69(7H, m), 1.82-1.92(2H, m), 2.18-2.25(2H, m), 3.17-3.24(1H, td), 3.45-3.52(1H, td), 3.63-3.66(3H, m), 3.75-3.78(1H, d), 3.86-3.91(2H, m), 3.96-3.99(1H, dd), 4.20-4.22(1H, d), 4.56(1H, bs), 5.01-5.04(1H, t), 6.46-6.48(1H, d), 6.78(1H, s), 7.47-7.49(2H, d), 8.19-8.21(2H, d), 8.57(1H, s). mTOR Kinase Assay (Echo): 0.0101μM

Example 16b: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.24(3H, d), 1.53-1.56(2H, m), 1.64-1.67(2H, m), 3.16-3.24(3H, m), 3.45-3.52(3H, m), 3.62-3.66(3H, m), 3.75-3.78(1H, d), 3.87-3.91(2H, q), 3.96-3.99(1H, dd), 4.19-4.23(1H, d), 4.56(1H, bs), 4.72-4.75(1H, t), 5.01-5.04(1H, t), 6.25-6.27(1H, t), 6.77(1H, s), 7.48-7.51(2H, d), 8.20-8.22(2H, d), 8.81(1H, s).

mTOR Kinase Assay (Echo): 0.00577μM

Example 16c: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24-1.26(3H, d), 1.55-1.58(2H, m), 1.66-1.68(2H, m), 3.19-3.26(1H, td), 3.47-3.53(1H, td), 3.63-3.67(3H, m), 3.77-3.79(1H, d), 3.88-3.93(2H, m), 3.97-4.01(1H, dd), 4.22-4.24(1H, d), 4.58(1H, bs), 5.02-5.05(1H, t), 6.83(1H, s), 7.62-7.65(2H, d), 8.31-8.33(2H, d), 8.38(1H, s), 9.43(1H, s), 11.37(1H, bs).

mTOR Kinase Assay (Echo): 0.0016μM

Example 16d: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.25(3H, d), 1.54-1.57(2H, m), 1.65-1.67(2H, m), 3.17-3.25(1H, td), 3.46-3.53(1H, td), 3.62-3.67(3H, m), 3.76-3.79(1H, d), 3.79(3H, s), 3.87-3.92(2H, m), 3.97-4.00(1H, dd), 4.20-4.23(1H, d), 4.56(1H, bs), 5.02-5.05(1H, t), 6.79(1H, s), 7.39-7.40(1H, s), 7.54-7.56(2H, d), 7.76(1H, s), 8.23-8.25(2H, d), 8.39(1H, s), 8.84(1H, s).

mTOR Kinase Assay (Echo): 0.00364μM

Example 16e: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87-0.91 (3H, t), 1.23-1.25 (3H, d), 1.42-1.51 (2H, m), 1.53-1.56 (2H, m), 1.64-1.67 (2H, m), 3.05-3.09 (2H, q), 3.17-3.25 (1H, td), 3.46-3.52 (1H, td), 3.62-3.66 (3H, m), 3.75-3.78 (1H, d), 3.87-3.91 (2H, q), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.56 (1H, bs), 5.01-5.04 (1H, t), 6.19-6.22 (1H, t), 6.78 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.65 (1H, s)

Example 16f: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.53-1.57 (2H, m), 1.59-1.62 (2H, t), 1.64-1.67 (2H, m), 3.15-3.24 (3H, m), 3.46-3.50 (3H, m), 3.63-3.66 (3H, m), 3.75-3.78 (1H, d), 3.87-3.91 (2H, q), 3.96-3.99 (1H, dd), 4.19-4.23 (1H, d), 4.47-4.49 (1H, t), 4.55 (1H, bs), 5.01-5.04 (1H, t), 6.20-6.23 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.72 (1H, s).

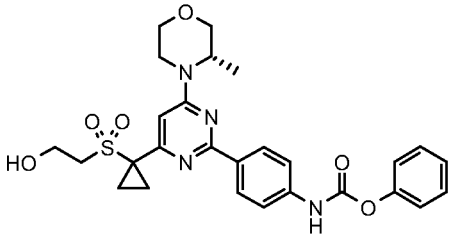
Example 16g: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.54-1.56 (2H, m), 1.65-1.67 (2H, m), 2.69-2.72 (2H, t), 3.17-3.25 (1H, td), 3.35-3.40 (2H, q), 3.46-3.52 (1H, td), 3.62-3.66 (3H, m), 3.75-3.78 (1H, d), 3.87-3.91 (2H, q), 3.96-4.00 (1H, dd), 4.20-4.23 (1H, d), 4.56 (1H, bs), 5.01-5.04 (1H, t), 6.52-6.55 (1H, t), 6.78 (1H, s), 7.51-7.53 (2H, d), 8.21-8.23 (2H, d), 8.93 (1H, s).

Example 16h: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.54-1.56 (2H, m), 1.64-1.67 (2H, m), 3.17-3.25 (1H, td), 3.46-3.52 (1H, td), 3.62-3.66 (3H, m), 3.75-3.78 (1H, d), 3.87-3.91 (2H, q), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.32-4.34 (2H, d), 4.56 (1H, bs), 5.01-5.04 (1H, t), 6.62-6.64 (1H, t), 6.78 (1H, s), 6.93-6.96 (2H, bs), 7.51-7.53 (2H, d), 8.21-8.23 (2H, d), 8.94 (1H, s), 11.84 (1H, s).

Example 16i: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.64-0.67 (2H, m), 0.70-0.73 (2H, m), 1.23-1.24 (3H, d), 1.53-1.56 (2H, m), 1.64-1.67 (2H, m), 3.17-3.25 (1H, td), 3.44-3.52 (3H, m), 3.62-3.66 (3H, m), 3.75-3.78 (1H, d), 3.87-3.91 (2H, q), 3.96-4.00 (1H, dd), 4.19-4.23 (1H, d), 4.55 (1H, bs), 4.84 (1H, bs), 5.01-5.04 (1H, t), 6.58 (1H, s), 6.78 (1H, s), 7.47-7.49 (2H, d), 8.20-8.22 (2H, d), 8.68 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

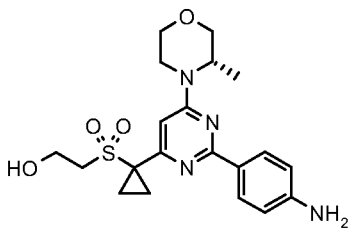
Phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.043 mL, 0.34 mmol) was added to 2-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethanol (0.144 g, 0.34 mmol) and sodium bicarbonate (0.043 g, 0.52 mmol) in dioxane (20 mL) and the resulting slurry stirred at RT overnight. The reaction mixture was partitioned between DCM and water. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica chromatography, eluting with 0 to 40% ethyl acetate in DCM, to give the desired material as a beige solid (0.117 g).

LCMS Spectrum: m/z (ES+) (M+H)+=539; HPLC tR=2.50 min.

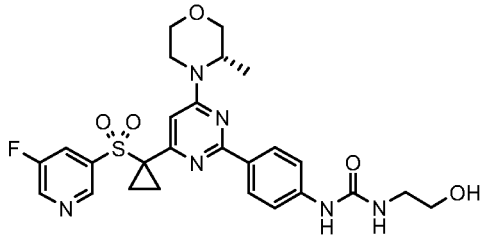
2-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethanol



Bis(triphenylphosphine)palladium (II) chloride (0.012 g, 0.02 mmol) was added to 2-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethoxy-tri(propan-2-yl)silane (0.178 g, 0.34 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.113 g, 0.52 mmol) and an aqueous solution of sodium carbonate (0.859 mL, 1.72 mmol) in a mixture of solvents (18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol). The resulting solution was stirred at 80°C for 4 hours, the solvent removed and the residue partitioned between DCM and water. The organic layer was separated and tetrabutylammonium fluoride (1.718 mL, 1.72 mmol) added. The reaction was allowed to stir for several hours and then additional tetrabutylammonium fluoride (2 mL) was added and the reaction allowed to stir for 2 days. The mixture was washed with a saturated aqueous solution of ammonium chloride, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the desired material which was used without further purification.

LCMS Spectrum: m/z (ES+) (M+H)+ = 419; HPLC tR = 1.83 min.

Example 17: 1-[4-[4-[1-(5-Fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea



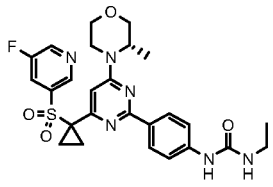
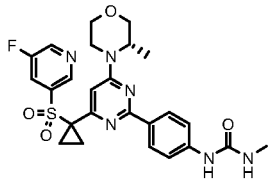
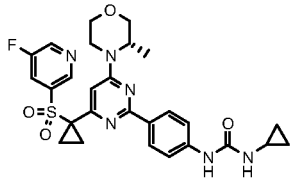
To a solution of phenyl *N*-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (140 mg, 0.24 mmol) in DMF (2 mL) was added triethylamine (0.099 mL, 0.71 mmol) followed by ethanolamine (72mg, 1.19 mmol) and the reaction heated at 50°C for 2 hours. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (55 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.64 - 1.67 (2H, m), 1.99 - 2.02 (2H, m), 3.15 - 3.20 (3H, m), 3.44 - 3.49 (2H, m), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.18 (1H, d), 4.50 (1H, s), 4.73 (1H, t), 6.29 (1H, t), 6.70 (1H, s), 7.38 (2H, d), 7.74 (2H, d), 8.18 - 8.21 (1H, m), 8.81 (2H, d), 8.95 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 557; HPLC tR = 1.82 min.

mTOR Kinase Assay (Echo): 0.00116μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
17a		3-ethyl-1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	541	1.78
17b		1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	527	1.99
17c		3-cyclopropyl-1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	553	2.13

Example 17a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.20 (3H, d), 1.64 - 1.67 (2H, m), 1.99 - 2.02 (2H, m), 3.09 - 3.21 (3H, m), 3.47 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.18 (1H, d), 4.50 (1H, s), 6.19 (1H, t), 6.70 (1H, s), 7.38 (2H, d), 7.74 (2H, d), 8.18 - 8.19 (1H, m), 8.20 - 8.21 (1H, m), 8.68 (1H, s), 8.81 (1H, s), 8.95 (1H, d).

mTOR Kinase Assay (Echo): 0.000942μM

Example 17b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.64 - 1.67 (2H, m), 1.99 - 2.02 (2H, m), 2.66 (3H, d), 3.14 - 3.21 (1H, m), 3.47 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.18 (1H, d), 4.50 (1H, s), 6.09 - 6.12 (1H, m), 6.70 (1H, s), 7.39 (2H, d), 7.74 (2H, d), 8.18 - 8.22 (1H, m), 8.79 (2H, d), 8.94 (1H, d).

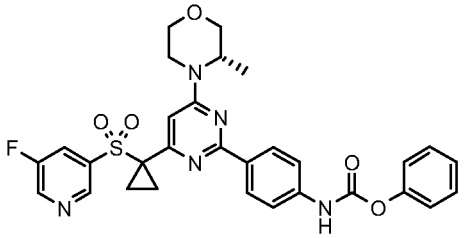
mTOR Kinase Assay (Echo): 0.000584μM

Example 17c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.41 - 0.44 (2H, m), 0.60 - 0.67 (2H, m), 1.20 (3H, d), 1.65 - 1.66 (2H, m), 1.99 - 2.02 (2H, m), 3.15 - 3.21 (2H, m), 3.42 - 3.49 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.18 (1H, d), 4.50 (1H, s), 6.60 (1H, s), 6.70 (1H, s), 7.40 (2H, d), 7.74 (2H, d), 8.18 - 8.22 (1H, m), 8.69 (1H, s), 8.81 (1H, s), 8.95 (1H, d).

mTOR Kinase Assay (Echo): 0.00179μM

The preparation of phenyl *N*-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

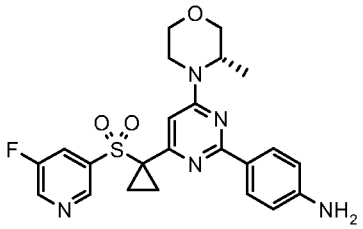


To a solution of 4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (220 mg, 0.47 mmol) in 1,4-dioxane (5 mL) was added sodium bicarbonate (59 mg, 0.70 mmol) and phenyl chloroformate (0.059 mL, 0.47 mmol) and the reaction stirred at RT for 2 hours. The reaction mixture was diluted with DCM (10 mL), and washed with water (10 mL), the organic layer dried ($MgSO_4$), filtered and evaporated. The crude solid was triturated with diethyl ether to give a solid which was collected by filtration and dried under vacuum to give the desired product as a white solid (280 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.65 - 1.69 (2H, m), 2.00 - 2.03 (2H, m), 3.15 - 3.22 (1H, m), 3.44 - 3.52 (1H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.21 (1H, d), 4.51 (1H, s), 6.75 (1H, s), 7.24 - 7.27 (3H, m), 7.45 (2H, t), 7.53 (2H, d), 7.85 (2H, d), 8.20 - 8.23 (1H, m), 8.81 (1H, s), 8.94 (1H, d), 10.40 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 590; HPLC tR = 2.96 min.

4-[4-[1-(5-Fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

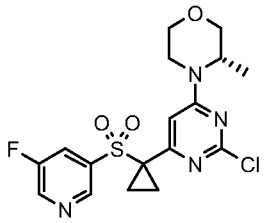


To a solution of 2-chloro-4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (700 mg, 1.70 mmol) in DMF (0.48 mL), DME (9.33 mL), water (4.0 mL) and ethanol (2.67 mL) was added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (483mg, 2.2 mmol), sodium carbonate (2.5 mL, 5.09 mmol) and dichlorobis(triphenylphosphine)palladium(II) (59.5 mg, 0.08 mmol) and the suspension heated at 95°C for 2 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate (10 mL) and washed with water (2 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired material as a cream solid (160 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.61 - 1.65 (2H, m), 1.96 - 2.00 (2H, m), 3.11 - 3.18 (1H, m), 3.42 - 3.49 (1H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.14 (1H, d), 4.46 (1H, s), 5.53 (2H, s), 6.49 (2H, d), 6.60 (1H, s), 7.57 (2H, d), 8.16 - 8.20 (1H, m), 8.80 - 8.80 (1H, m), 8.93 (1H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 470; HPLC tR = 2.30 min.

2-Chloro-4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



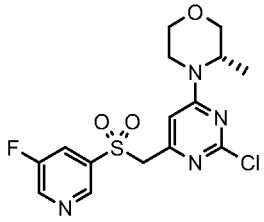
2-Chloro-4-[(5-fluoropyridin-3-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (950 mg, 2.40 mmol) was dissolved in toluene (15 mL) and 10N sodium hydroxide solution (2.45 mL, 24.5 mmol) added, followed by 1,2-dibromoethane (0.42 mL,

4.91 mmol). The reaction was stirred at 60°C for 3 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (200 mL), and washed sequentially with water (200 mL) and saturated brine solution (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired product as a white solid (700 mg,).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.61 - 1.63 (2H, m), 1.94 - 1.97 (2H, m), 3.16 (1H, dt), 3.40 (1H, dt), 3.55 (1H, dd), 3.70 (1H, d), 3.91 (1H, dd), 4.00 (1H, s), 4.33 (1H, s), 6.78 (1H, s), 8.21 (1H, dt), 8.79 (1H, t), 8.96 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 413, HPLC tR = 2.14 min

2-Chloro-4-[(5-fluoropyridin-3-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

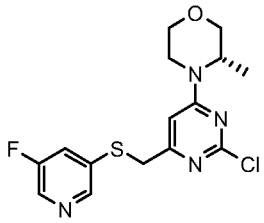


3-Chloroperoxybenzoic acid (2.107 g, 9.16 mmol) was added portion-wise to 2-chloro-4-[(5-fluoropyridin-3-yl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.3 g, 3.66 mmol), in DCM (18.32 mL) and the reaction stirred at RT for 2 hours. The reaction mixture was washed with a saturated aqueous solution of sodium hydrogen carbonate (50 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a white solid (0.940 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 3.16 - 3.23 (1H, m), 3.44 (1H, dt), 3.59 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 3.97 (1H, s), 4.22 (1H, s), 4.84 (2H, s), 6.84 (1H, s), 8.21 (1H, dt), 8.80 (1H, t), 8.99 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 387, HPLC tR = 1.86 min

2-Chloro-4-[(5-fluoropyridin-3-yl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

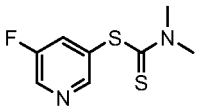


Potassium hydroxide (1.235 g, 22.01 mmol) was added to (5-fluoropyridin-3-yl) dimethylaminomethanedithioate (1.19 g, 5.50 mmol) in ethanol (27.5 mL) at RT. The resulting solution was heated at 65°C for 4 hours The reaction was cooled and 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.72 g, 7.70 mmol) added. The reaction mixture was then stirred at RT for 4 hours. Water (50 mL) was added and the reaction mixture extracted with DCM (2 x 100 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated to give crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a white waxy solid (1.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 3.11 - 3.18 (1H, m), 3.37 - 3.44 (1H, m), 3.56 (1H, dd), 3.70 (1H, d), 3.91 (1H, dd), 3.95 (1H, s), 4.21 (3H, $mult$), 6.81 (1H, s), 7.89 (1H, dt), 8.40 - 8.42 (2H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ 355, HPLC tR = 2.12 min

(5-Fluoropyridin-3-yl) dimethylaminomethanedithioate



3-Bromo-5-fluoropyridine (2.26g, 12.84 mmol) was added portion-wise to isopropylmagnesium chloride - lithium chloride complex (14% in THF, 13.32 mL, 12.84 mmol) at 0ºC over a period of 2 minutes under a nitrogen atmosphere. The resulting solution was warmed to RT over a period of 2 hours then cooled to 0°C and tetramethylthiuram disulfide (3.09 g, 12.84 mmol) in DCM (12.84 mL) added. The reaction was warmed to RT and stirred for 3 hours. The reaction was poured into a saturated aqueous solution of ammonium chloroid (50 mL) and the aqueous layer extracted with DCM (2 x 100mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude

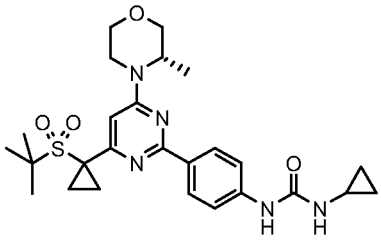
product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a cream waxy solid (1.69 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.48 (3H, s), 3.52 (3H, s), 7.89 (1H, ddd), 8.41 (1H, t), 8.71 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 217, HPLC tR = 1.80 min

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 18: 1-[4-[4-(1-tert-Butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea



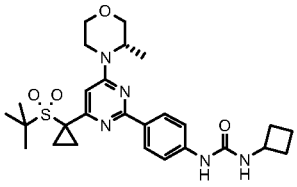
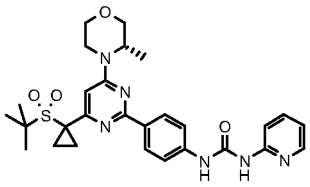
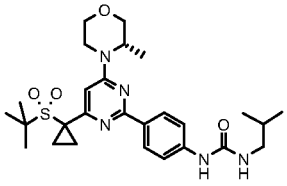
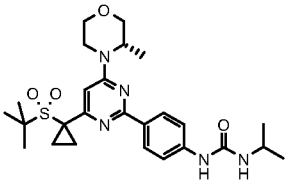
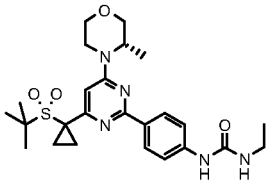
Cyclopropylamine (57 mg, 1.0 mmol) was added to phenyl *N*-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.22 mmol) and triethylamine (0.20 mL, 1.4 mmol) in DMF (1 mL). The reaction mixture was allowed to stand at RT for 4 days. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to afford the desired material as a colourless solid (63 mg).

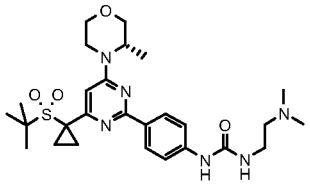
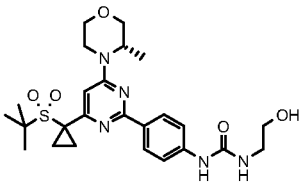
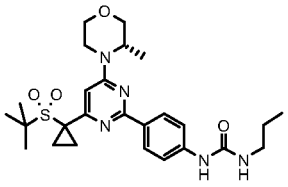
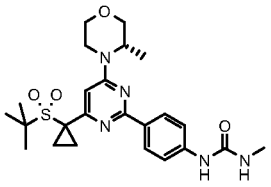
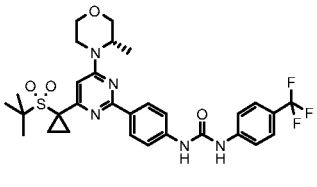
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 1.21 –1.27 (12H, m), 1.47 - 1.53 (1H, m), 1.62 - 1.69 (3H, m), 2.54 – 2.60 (1H, m), 3.15 – 3.24 (1H, m), 3.46 – 4.54 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.95 - 4.02 (1H, d), 4.18 (1H, d), 4.43 (1H, br, s), 6.44 (1H, d), 6.97 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.56 (1H, s).

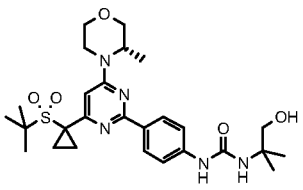
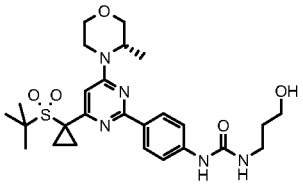
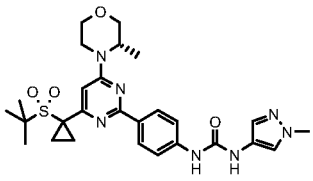
LCMS Spectrum: m/z (ESI+)(M+H)+ = 514; HPLC tR = 2.39 min.

mTOR Kinase Assay (Echo): 0.00135μM

The following compounds were made in an analogous fashion from phenyl *N*-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamateand the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
18a		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutylurea	528	2.62
18b		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea	551	2.83
18c		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	530	2.72
18d		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea	516	2.54
18e		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea	502	2.38

Example	Structure	NAME	LCMS MH+	Retention time (min)
18f		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	545	2.33
18g		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	518	1.98
18h		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propylurea	516	2.56
18i		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	488	2.2
18j		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	618	3.29

Example	Structure	NAME	LCMS MH+	Retention time (min)
18k		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	546	2.32
18l		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	532	2.05
18m		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	554	2.22

Example 18a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.21 – 1.27 (12H, m), 1.47 – 1.53 (1H, m), 1.59 - 1.68 (3H, m), 1.81 – 1.91 (2H, m), 2.17 – 2.26 (2H, m), 3.15 – 3.23 (1H, m), 3.45 – 3.54 (1H, m), 3.62 – 3.68 (1H, m), 3.77 (1H, d), 3.95 – 4.02 (1H, m), 4.10 - 4.24 (2H, m), 4.42 (1H, br, s), 6.47 (1H, d), 6.97 (1H, s), 7.48 (2H, d), 8.22 (2H, d), 8.57 (1H, s).

mTOR Kinase Assay (Echo): 0.00967μM

Example 18b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.25 (12H, m), 1.49 - 1.54 (1H, m), 1.63 - 1.73 (3H, m), 3.16 - 3.25 (1H, m), 3.48 - 3.54 (1H, m), 3.64 - 3.68 (1H, m), 3.78 (1H, d), 3.98 - 4.01 (1H, m), 4.20 (1H, d), 4.43 (1H, br, s), 7.00 (1H, s), 7.03 - 7.06 (1H, m), 7.58 (1H, d), 7.65 (2H, d), 7.78 (1H, t), 8.29 – 8.34 (3H, m), 9.45 (1H, s), 10.57 (1H, s).

mTOR Kinase Assay (Echo): 0.0147μM

Example 18c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.90 (6H, d), 1.22 - 1.25 (12H, m), 1.47 - 1.53 (1H, m), 1.62 - 1.75 (4H, m), 2.95 (2H, t), 3.16 - 3.23 (1H, m), 3.47 - 3.53 (1H, m), 3.63

- 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.18 (1H, d), 4.42 (1H, br, s), 6.25 (1H, t), 6.97 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.66 (1H, s).

mTOR Kinase Assay (Echo): 0.032μM

Example 18d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.12 (6H, d), 1.21 - 1.26 (12H, m), 1.45 – 1.53 (1H, m), 1.62 - 1.71 (3H, m), 3.13 - 3.25 (1H, m), 3.44 - 3.53 (1H, m), 3.62 - 3.67 (1H, m), 3.73 - 3.82 (2H, m), 3.95 - 4.02 (1H, m), 4.18 (1H, d), 4.42 (1H, br, s), 6.07 (1H, d), 6.97 (1H, s), 7.48 (2H, d), 8.23 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.0151μM

Example 18e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.23 (3H, d), 1.25 (9H, s), 1.44 – 1.53 (1H, m), 1.60 – 1.71 (3H, m), 3.08 – 3.25 (3H, m), 3.49 (1H, t), 3.65 (1H, d), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.18 (1H, d), 4.43 (1H, br, s), 6.17 (1H, t), 6.97 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.000654μM

Example 18f: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 - 1.28 (12H, m), 1.47 - 1.54 (1H, m), 1.62 - 1.69 (3H, m), 2.19 (6H, s), 2.34 (2H, t), 3.14 - 3.24 (3H, m), 3.45 - 3.53 (1H, m), 3.62 - 3.67 (1H, m), 3.77 (1H, d), 3.95 - 4.00 (1H, m), 4.18 (1H, d), 4.42 (1H, br, s), 6.17 (1H, t), 6.97 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.91 (1H, s).

mTOR Kinase Assay (Echo): 0.12μM

Example 18g: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.22 - 1.25 (12H, m), 1.48 - 1.52 (1H, m), 1.62 - 1.69 (3H, m), 3.16 - 3.23 (3H, m), 3.45 - 3.53 (3H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.97 - 4.00 (1H, m), 4.18 (1H, d), 4.43 (1H, br, s), 4.74 (1H, t), 6.26 (1H, t), 6.97 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.82 (1H, s).

mTOR Kinase Assay (Echo): 0.00123μM

Example 18h: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.90 (3H, t), 1.19 – 1.28 (12H, m), 1.42 – 1.54 (3H, m), 1.61 - 1.69 (3H, m), 3.07 (2H, q), 3.13 - 3.23 (1H, m), 3.45 - 3.53 (1H, m), 3.61 - 3.68 (1H, m), 3.77 (1H, d), 3.94 – 4.01 (1H, m), 4.18 (1H, d), 4.42 (1H, br, s), 6.21 (1H, t), 6.97 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.67 (1H, s).

mTOR Kinase Assay (Echo): 0.00664μM

Example 18i: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.25 (9H, s), 1.45 – 1.55 (1H, m), 1.60 – 1.69 (3H, m), 2.67 (3H, d), 3.14 - 3.23 (1H, m), 3.50 (1H, t), 3.65 (1H, d), 3.77 (1H, d), 3.94 - 3.99 (1H, m), 4.18 (1H, d), 4.43 (1H, br, s), 6.08 (1H, d), 6.97 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.00555μM

Example 18j: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.35 (9H, s), 1.50 – 1.71 (2H, m), 1.81 - 1.91 (2H, m), 3.23 - 3.33 (1H, m), 3.53 - 3.62 (1H, m), 3.68 - 3.74 (1H, m), 3.81 (1H, d), 3.98 - 4.05 (1H, m), 4.17 (1H, d), 4.42 (1H, br, s), 7.03 (1H, s), 7.23 (1H, s), 7.28 (1H, s), 7.48 (2H, d), 7.52 - 7.55 (4H, m), 8.38 (2H, d).

mTOR Kinase Assay (Echo): 0.0303μM

Example 18k: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 – 1.27 (18H, m), 1.48 - 1.52 (1H, m), 1.62 - 1.69 (3H, m), 3.14 - 3.23 (1H, m), 3.40 (2H, d), 3.45 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.18 (1H, d), 4.41 (1H, br, s), 4.96 (1H, t), 6.01 (1H, s), 6.97 (1H, s), 7.46 (2H, d), 8.22 (2H, d), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.0113μM

Example 18l: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.22 - 1.25 (12H, m), 1.48 - 1.52 (1H, m), 1.57 - 1.68 (5H, m), 3.15 - 3.23 (3H, m), 3.43 – 3.54 (3H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.18 (1H, d), 4.43 (1H, br, s), 4.49 (1H, t), 6.21 (1H, t), 6.97 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.73 (1H, s).

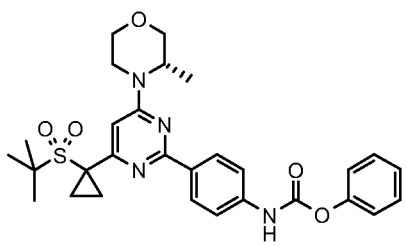
mTOR Kinase Assay (Echo): 0.0102μM

Example 18m: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.21 – 1.29 (12H, m), 1.48 – 1.55 (1H, m), 1.61 – 1.71 (3H, m), 3.16 - 3.25 (1H, m), 3.49 (1H, t), 3.66 (1H, d), 3.74 – 3.83 (4H, m), 3.99 (1H, d), 4.19 (1H, d), 4.43 (1H, br, s), 6.99 (1H, s), 7.39 (1H, s), 7.55 (2H, d), 7.77 (1H, s), 8.27 (2H, d), 8.39 (1H, s), 8.85 (1H, s).

mTOR Kinase Assay (Echo): 0.00315μM

The preparation of phenyl *N*-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

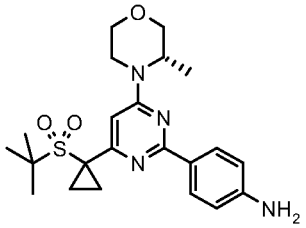


Phenyl chloroformate (0.809 mL, 6.44 mmol) was added to 4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (2.52g, 5.85 mmol) and sodium hydrogen carbonate (0.738 g, 8.78 mmol) in dioxane (45 mL) at RT. The mixture was stirred at RT for 2 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% – 100% ethyl acetate in isohexane, to give the desired material as a near colourless solid (2.99 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.31 - 1.34 (12H, m), 1.48 - 4.58 (1H, m), 1.62 - 1.70 (1H, m), 1.80 - 1.89 (2H, m), 3.31 (1H, dt), 3.60 (1H, dt), 3.75 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.20 (1H, d), 4.45 (1H, br), 7.06 - 7.11 (2H, m), 7.19 - 7.28 (3H, m), 7.41 (2H, t), 7.54 (2H, d), 8.40 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 551; HPLC tR = 3.06 min.

4-[4-(1-tert-Butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

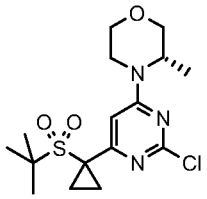


Dichlorobis(triphenylphosphine)-palladium(II) (0.185 g, 0.26 mmol) was added to 4-(1-tert-butylsulfonylcyclopropyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.97 g, 5.27 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.501 g, 6.85 mmol) and 2M aqueous sodium carbonate (9.48 mL, 18.97 mmol) in DMF (11 mL), DME (11 mL), ethanol (11 mL) and water (27.5 mL) at RT under nitrogen. The reaction was purged with nitrogen for 15 minutes and the resulting mixture was stirred at 80°C for 16 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 25% - 100% ethyl acetate in isohexane, to give the desired material as a yellow solid (2.24 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.32 (9H, s), 1.44 - 1.55 (1H, m), 1.60 - 1.68 (1H, m), 1.77 - 1.86 (2H, m), 3.28 (1H, dt), 3.59 (1H, dt), 3.74 (1H, dd), 3.81 (1H, d), 3.90 (2H, s), 4.03 (1H, dd), 4.18 (1H, d), 4.44 (1H, br), 6.71 (2H, d), 6.99 (1H, s), 8.24 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 431; HPLC tR = 2.43 min.

4-(1-tert-Butylsulfonylcyclopropyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

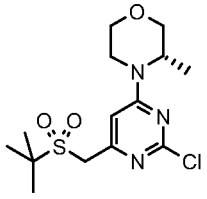


1,2-Dibromoethane (0.349 mL, 15.40 mmol) was added to 4-(tert-butylsulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.68 g, 7.7 mmol) in toluene (40 mL) followed by tetrabutylammonium bromide (0.248 g, 0.77 mmol) and sodium hydroxide concentrate (7.70 mL, 77 mmol). The reaction mixture was vigorously stirred and heated at 60°C for 1 hour. The reaction mixture was cooled and diluted with ethyl acetate and washed with water. The organic solution was concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 0 to 50% ethyl acetate in DCM, to give the desired material as a colourless solid (1.97 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.20 - 1.35 (12H, m), 1.46 - 1.50 (1H, m), 1.52 - 1.61 (1H, m), 1.77 - 1.86 (2H, m), 3.26 (1H, dt), 3.54 (1H, dt), 3.68 (1H, dd), 3.78 (1H, d), 3.98 - 4.08 (2H, m), 4.29 (1H, br, s), 7.14 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 374; HPLC tR = 2.34 min.

4-(tert-Butylsulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



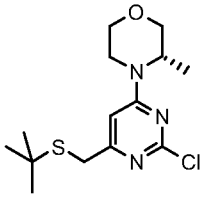
A solution of hydrogen peroxide (35% aqueous solution, 9.48 mL, 107.30 mmol) was added dropwise to a stirred solution of 4-(tert-butylsulfanylmethyl)-2-chloro-6-[(3*S*)-3-

methylmorpholin-4-yl]pyrimidine (9.82 g, 31.1 mmol), sodium tungstate dihydrate (0.205 g, 0.62 mmol) and sulfuric acid (0.6 mL, 1M, 0.6 mmol) in dioxane (80 mL). The mixture was heated at 55°C for 1 hour then diluted with water and cooled. A solution of sodium metabisulfite (10% w/v) was added to destroy remaining peroxide. The solution was extracted with DCM, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the desired material as a near colourless gum (9.34 g).

NMR Spectrum: ^1H NMR (399.9 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.44 (9H, s), 3.29 (1H, dt), 3.54 (1H, dt), 3.69 (1H, dd), 3.78 (1H, d), 3.97 - 4.13 (2H, m), 4.21 (2H, s), 4.30 (1H, br, s), 6.71 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 348; HPLC tR = 1.82 min.

4-(tert-Butylsulfanylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



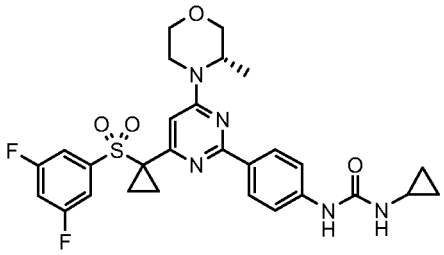
DIPEA (8.61 mL, 49.78 mmol) was added to 2-methyl-2-propanethiol (4.21 mL, 37.33 mmol), in DMF (55 mL) at RT under nitrogen. The resulting solution was stirred at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (11.00 g, 31.11 mmol) was added to the reaction mixture in one portion. The mixture was stirred for 4 hours at RT then at 60°C for 1.5 hours before being partitioned between ethyl acetate and water. The organic layer was washed with additional water and then dried ($MgSO_4$), filtered and evaporated to give the desired material as a yellow gum (10.02 g). The material was used without further purification.

NMR Spectrum: ^1H NMR (399.9 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.34 (9H, s), 3.27 (1H, dt), 3.54 (1H, dt), 3.66 - 3.71 (3H, m), 3.78 (1H, d), 3.97 - 4.07 (2H, m), 4.31 (1H, br, s), 6.56 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 316, 318; HPLC tR = 2.61 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 19: 3-Cyclopropyl-1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



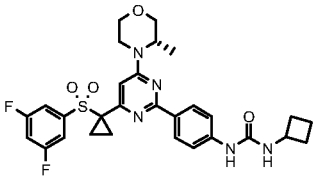
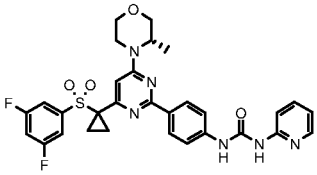
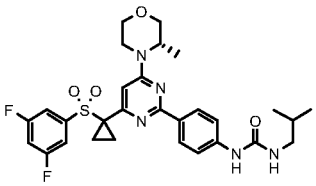
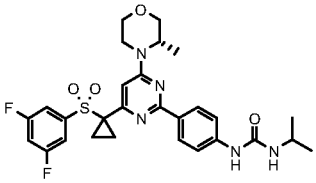
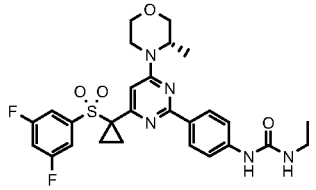
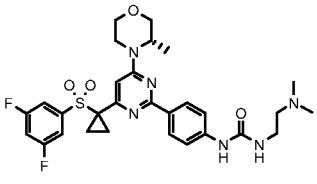
Phenyl *N*-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.22 mmol) was added to a mixture of cyclopropylamine (59 mg, 1.03 mmol) and triethylamine (0.2 mL, 1.49 mmol) in DMF (1 mL) at RT. The reaction mixture was allowed to stand at RT for 65 hours. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a colourless solid (55 mg).

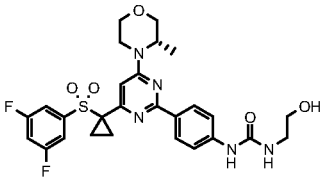
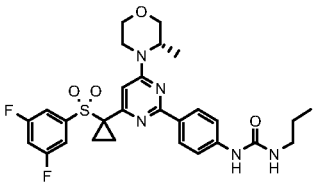
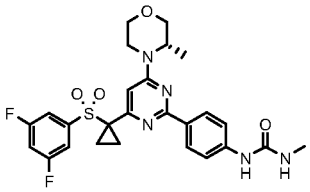
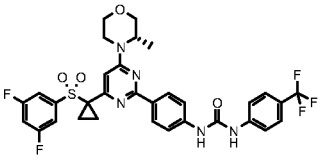
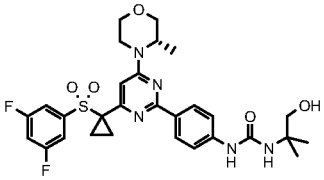
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.41 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 1.20 (3H, d), 1.62 -1.69 (2H, m), 1.96 - 2.00 (2H, m), 2.53 - 2.59 (1H, m), 3.13 - 3.23 (1H, m), 3.42 - 3.50 (1H, m), 3.59 - 3.63 (1H, m), 3.75 (1H, d), 3.94 - 4.00 (1H, m), 4.18 (1H, d), 4.48 (1H, br, s), 6.42 (1H, d), 6.67 (1H, s), 7.42 (2H, d), 7.54 - 7.59 (2H, m), 7.70 - 7.76 (1H, m), 7.82 (2H, d), 8.53 (1H, s)

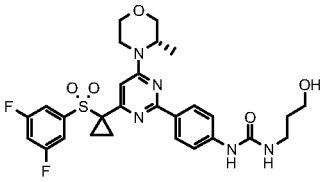
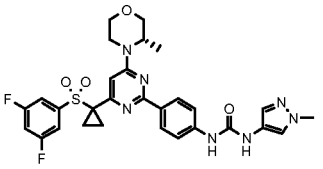
LCMS Spectrum: m/z (ESI+)(M+H)+ = 572; HPLC tR = 2.72 min.

mTOR Kinase Assay (Echo): 0.00131μM

The following compounds were made in an analogous fashion from phenyl *N*-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
19a		3-cyclobutyl-1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	584	2.86
19b		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea	607	3.03
19c		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	586	2.94
19d		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea	572	2.79
19e		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea	558	2.53
19f		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	601	2.5

Example	Structure	NAME	LCMS MH+	Retention time (min)
19g		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	574	2.17
19h		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propylurea	572	2.72
19i		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	544	2.37
19j		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	674	3.27
19k		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	602	2.48

Example	Structure	NAME	LCMS MH+	Retention time (min)
19l		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	588	2.23
19m		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	610	2.39

Example 19a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.58 - 1.70 (4H, m), 1.80 - 1.90 (2H, m), 1.95 - 2.02 (2H, m), 2.16 - 2.25 (2H, m), 3.10 - 3.20 (1H, m), 3.40 - 3.48 (1H, m), 3.58 - 3.62 (1H, m), 3.75 (1H, d), 3.92 - 3.98 (1H, m), 4.10 - 4.20 (2H, m), 4.48 (1H, br, s), 6.45 (1H, d), 6.67 (1H, s), 7.39 (2H, d), 7.55 - 7.57 (2H, m), 7.71 - 7.75 (1H, m), 7.82 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.00425μM

Example 19b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.62 - 1.71 (2H, m), 1.96 - 2.03 (2H, m), 3.13 - 3.23 (1H, m), 3.42 - 3.51 (1H, m), 3.60 - 3.65 (1H, m), 3.76 (1H, d), 3.93 - 3.99 (1H, m), 4.19 (1H, d), 4.50 (1H, br, s), 6.71 (1H, s), 7.03 - 7.06 (1H, m), 7.51 - 7.59 (5H, m), 7.70 - 7.80 (2H, m), 7.92 (2H, d), 8.31 (1H, d), 9.44 (1H, s), 10.55 (1H, s).

mTOR Kinase Assay (Echo): 0.00119μM

Example 19c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.89 (3H, s), 0.90 (3H, s), 1.20 (3H, d), 1.63 - 1.75 (3H, m), 1.94 - 2.00 (2H, m), 2.95 (2H, t), 3.11 - 3.21 (1H, m), 3.41 - 3.50 (1H, m), 3.57 - 3.63 (1H, m), 3.75 (1H, d), 3.92 - 3.98 (1H, m), 4.17 (1H, d), 4.48 (1H, br, s), 6.23 (1H, t), 6.67 (1H, s), 7.40 (2H, d), 7.52 - 7.59 (2H, m), 7.68 - 7.76 (1H, m), 7.83 (2H, d), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.0214μM

Example 19d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.11 (3H, s), 1.13 (3H, s), 1.20 (3H, d), 1.62 - 1.69 (2H, m), 1.95 - 2.00 (2H, m), 3.11 - 3.20 (1H, m), 3.42 - 3.50 (1H, m), 3.57 - 3.63

(1H, m), 3.72 - 3.82 (2H, m), 3.92 - 3.98 (1H, m), 4.17 (1H, d), 4.48 (1H, br, s), 6.05 (1H, d), 6.67 (1H, s), 7.39 (2H, d), 7.52 - 7.59 (2H, m), 7.69 - 7.76 (1H, m), 7.82 (2H, d), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.00318μM

Example 19e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.20 (3H, d), 1.63 - 1.68 (2H, m), 1.95 - 2.00 (2H, m), 3.09 - 3.22 (3H, m), 3.37 (1H, d), 3.42 - 3.49 (1H, m), 3.58 - 3.63 (1H, m), 3.75 (1H, d), 3.93 - 3.98 (1H, m), 4.17 (1H, d), 4.49 (1H, br, s), 6.15 (1H, t), 6.67 (1H, s), 7.40 (2H, d), 7.54 - 7.57 (2H, m), 7.69 - 7.76 (1H, m), 7.82 (2H, d), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.00135μM

Example 19f: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.63 - 1.70 (2H, m), 1.95 - 2.00 (2H, m), 2.19 (6H, s), 2.34 (2H, t), 3.11 - 3.23 (3H, m), 3.41 - 3.50 (1H, m), 3.58 - 3.63 (1H, m), 3.75 (1H, d), 3.92 - 3.98 (1H, m), 4.17 (1H, d), 4.49 (1H, br, s), 6.16 (1H, t), 6.67 (1H, s), 7.40 (2H, d), 7.51 - 7.58 (2H, m), 7.68 - 7.76 (1H, m), 7.83 (2H, d), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.0804μM

Example 19g: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.66 (2H, s), 1.92 - 2.01 (2H, m), 3.11 - 3.20 (3H, m), 3.40 - 3.51 (3H, m), 3.57 - 3.64 (1H, m), 3.75 (1H, d), 3.92 - 3.99 (1H, m), 4.17 (1H, d), 4.48 (1H, br, s), 4.74 (1H, t), 6.24 (1H, t), 6.67 (1H, s), 7.40 (2H, d), 7.50 - 7.59 (2H, m), 7.68 - 7.74 (1H, t), 7.83 (2H, d), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.000274μM

Example 19h: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.20 (3H, d), 1.41 - 1.51 (2H, m), 1.66 (2H, s), 1.94 - 2.00 (2H, m), 3.07 (2H, q), 3.12 - 3.17 (1H, m), 3.42 - 3.49 (1H, m), 3.58 - 3.64 (1H, m), 3.75 (1H, d), 3.92 - 3.98 (1H, m), 4.17 (1H, d), 4.48 (1H, br, s), 6.20 (1H, t), 6.67 (1H, s), 7.40 (2H, d), 7.52 - 7.61 (2H, m), 7.68 - 7.76 (1H, m), 7.82 (2H, d), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.00246μM

Example 19i: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.61 - 1.70 (2H, m), 1.94 - 2.01 (2H, m), 2.67 (3H, d), 3.10 - 3.20 (1H, m), 3.40 - 3.49 (1H, m), 3.58 - 3.63 (1H, m), 3.75 (1H, d), 3.92 - 3.98 (1H, m), 4.17 (1H, d), 4.48 (1H, br, s), 6.02 - 6.08 (1H, m), 6.67 (1H, s), 7.41 (2H, d), 7.53 - 7.58 (2H, m), 7.68 - 7.75 (1H, m), 7.82 (2H, d), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00152μM

Example 91j: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.67 (2H, s), 1.94 - 2.03 (2H, m), 3.13 - 3.22 (1H, m), 3.42 - 3.50 (1H, m), 3.59 - 3.64 (1H, m), 3.76 (1H, d), 3.93 - 3.98

(1H, m), 4.19 (1H, d), 4.49 (1H, br, s), 6.70 (1H, s), 7.50 (2H, d), 7.54 - 7.61 (2H, m), 7.62 - 7.78 (5H, m), 7.91 (2H, d), 9.04 (1H, s), 9.12 (1H, s).

mTOR Kinase Assay (Echo): 0.0199μM

Example 19k: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.23 (6H, s), 1.62 – 1.68 (2H, m), 1.94 – 1.98 (2H, m), 3.13 - 3.20 (1H, m), 3.38 (2H, d), 3.42 - 3.50 (1H, m), 3.58 - 3.64 (1H, m), 3.75 (1H, d), 3.93 - 3.98 (1H, m), 4.17 (1H, d), 4.48 (1H, br, s), 4.94 (1H, t), 5.97 (1H, s), 7.35 (2H, d), 7.52 - 7.58 (2H, m), 7.69 - 7.77 (1H, m), 7.81 (2H, d), 8.71 (1H, s).

mTOR Kinase Assay (Echo): 0.00415μM

Example 19l: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.55 – 1.70 (4H, m), 1.95 - 2.01 (2H, m), 3.13 - 3.21 (3H, m), 3.42 - 3.50 (3H, m), 3.58 - 3.65 (1H, m), 3.75 (1H, d), 3.93 - 3.99 (1H, m), 4.18 (1H, d), 4.43 – 4.52 (2H, m), 6.19 (1H, t), 6.67 (1H, s), 7.39 (2H, d), 7.52 - 7.61 (2H, m), 7.69 - 7.78 (1H, m), 7.83 (2H, d), 8.69 (1H, s).

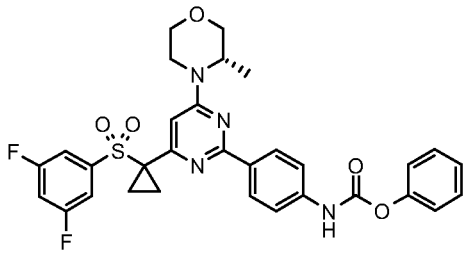
mTOR Kinase Assay (Echo): 0.00152μM

Example 19m: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.60 – 1.69 (2H, m), 1.94 - 2.01 (2H, m), 3.13 - 3.21 (1H, m), 3.42 - 3.50 (3H, m), 3.58 - 3.64 (1H, m), 3.73 – 3.81 (4H, m), 3.93 - 3.98 (1H, m), 4.18 (1H, d), 4.49 (1H, br, s), 6.67 (1H, s), 7.37 (1H, s), 7.43 (2H, d), 7.51 - 7.60 (2H, m), 7.68 - 7.78 (2H, m), 7.76 (2H, d), 8.35 (1H, s), 8.81 (1H, s).

mTOR Kinase Assay (Echo): 0.000944μM

The preparation of phenyl *N*-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamateis described below.

Phenyl *N*-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



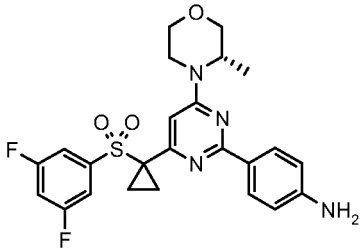
Phenyl chloroformate (0.764 mL, 6.08 mmol) was added to 4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (2.69 g, 5.53 mmol) and sodium hydrogen carbonate (0.697 g, 8.29 mmol) in dioxane (40 mL)

at RT. The resulting slurry was stirred at RT for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 25% - 80% ethyl acetate in isohexane, to give the desired material as a yellow dry film (3.07 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.61 - 1.66 (1H, m), 1.68 - 1.73 (1H, m), 1.94 - 2.05 (2H, m), 3.30 (1H, dt), 3.61 (1H, dt), 3.75 (1H, dd), 3.84 (1H, d), 4.05 (1H, dd), 4.16 (1H, d), 4.43 (1H, br, s), 6.79 (1H, s), 6.94 - 7.03 (2H, m), 7.18 - 7.28 (3H, m), 7.30 - 7.35 (2H, m), 7.37 - 7.47 (4H, m), 8.10 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 607; HPLC tR = 3.12 min.

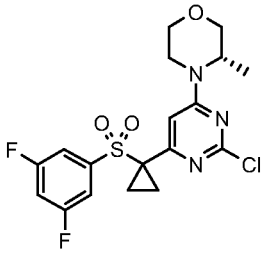
4-[4-[1-(3,5-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



A stream of nitrogen was passed through a mixture of 2-chloro-4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.5 g, 5.82 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.656 g, 7.56 mmol) and 2M aqueous sodium carbonate (10.47 mL, 20.94 mmol) in DMF (11 mL), DME (11 mL), ethanol (11 mL) and water (27.5 mL) at RT for 15 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (0.204 g, 0.29 mmol) was added in one portion and the reaction mixture stirred at 80°C under nitrogen for 1 hour. The reaction mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 25% - 60% ethyl acetate in isohexane, to give the desired material as a near colourless solid (2.76 g).

NMR Spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.62 - 1.66 (1H, m), 1.70 - 1.74 (1H, m), 1.93 - 2.03 (2H, m), 3.28 (1H, dt), 3.59 (1H, dt), 3.72 - 3.74 (1H, dd), 3.79 - 3.89 (3H, m), 4.03 (1H, dd), 4.10 - 4.18 (1H, m), 4.37 - 4.45 (1H, m), 6.61 - 6.65 (2H, m), 6.73 (1H, s), 6.98 (1H, tt), 7.31 - 7.36 (2H, m), 7.93 - 7.96 (2H, m) LCMS Spectrum: m/z (ESI+)(M+H)+ = 487; HPLC tR = 2.86 min.

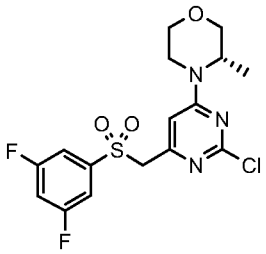
2-Chloro-4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



1,2-Dibromoethane (1.0 mL, 11.6 mmol) was added to 2-chloro-4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.68 g, 9.11 mmol) in toluene (55 mL) followed by tetrabutylammonium bromide (0.294 g, 0.91 mmol) and sodium hydroxide concentrate (9.00 mL, 90 mmol). The reaction mixture was stirred at RT overnight. The mixture was then heated to 80ºC and vigorous stirring continued for 3 hours. A further quantity of 1,2-dibromoethane (1 mL, 11.6 mmol) was added and heating was continued for a further 2 hours. The reaction mixture was diluted with ethyl acetate and washed with water. The organic solution was concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10 to 40% ethyl acetate in isohexane, to give the desired material as a colourless solid (3.0 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.56 - 1.60 (1H, m), 1.63 - 1.68 (1H, m), 1.92 - 2.01 (2H, m), 3.28 (1H, dt), 3.55 (1H, dt), 3.70 (1H, dd), 3.80 (1H, d), 4.00 - 4.09 (2H, m), 4.28 (1H, br, s), 6.87 (1H, s), 7.07 (1H, tt), 7.24 - 7.29 (2H, m)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 430, 432; HPLC tR = 2.55 min.

2-Chloro-4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



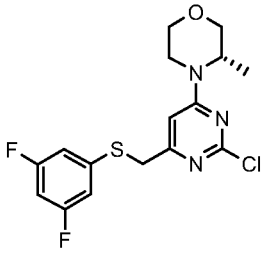
A solution of sodium tungstate dihydrate (199 mg, 0.60 mmol) in water (2 mL) was added to a stirred solution of 2-chloro-4-[(3,5-difluorophenyl)sulfanylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (11.23 g, 30.2 mmol) and sulfuric acid (0.302 mL, 2M,

0.60 mmol) in dioxane (40 mL). Hydrogen peroxide (3.22 mL, 104.19 mmol) was added and the mixture was stirred at RT overnight. A precipitate was collected by filtration and dried *in vacuo*, to give the desired material as a near colourless solid (3.61 g). The filtrate was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 5% - 20% ethyl acetate in DCM, to give the desired material as a near colourless solid (7.66 g).

NMR Spectrum: ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, s), 3.31 (1H, dt), 3.56 (1H, dt), 3.71 (1H, dd), 3.80 (1H, d), 3.98 - 4.10 (2H, m), 4.31 (2H, s), 6.55 (1H, s), 7.12 (1H, tt), 7.30 - 7.36 (2H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 404, 406; HPLC tR = 2.32 min.

2-Chloro-4-[(3,5-difluorophenyl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



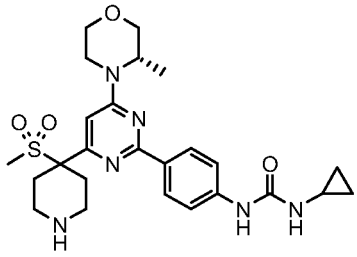
DIPEA (8.07 mL, 46.67 mmol) was added to 3,5-difluorobenzenethiol (5.00 g, 34.22 mmol), in DMF (55 mL) at RT under nitrogen. The resulting solution was stirred at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (11.00 g, 31.11 mmol) was added to the reaction mixture in one portion. The mixture was stirred for 4 hours at RT. The reaction mixture was heated in a water bath at 60°C for 1.5 hours before being partitioned between ethyl acetate and water. The organic solution was washed with further water then was dried ($MgSO_4$), filtered and evaporated to give the desired material as a gum (12.24 g).

NMR Spectrum: ^1H NMR (399.9 MHz, $CDCl_3$) δ 1.27 (3H, d), 3.24 (1H, dt), 3.52 (1H, dt), 3.66 (1H, dd), 3.76 (1H, d), 3.96 - 4.04 (4H, m), 4.21 (1H, br, s), 6.41 (1H, s), 6.59 - 6.66 (1H, m), 6.80 - 6.86 (2H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 372, 374; HPLC tR = 2.66 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 20: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea



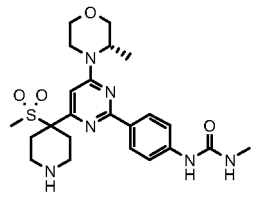
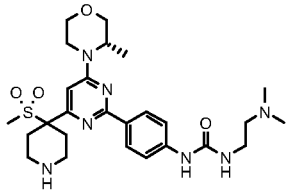
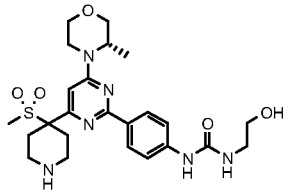
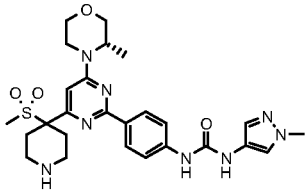
Cyclopropylamine (0.055 mL, 0.76 mmol) was added to tert-butyl 4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate (115 mg, 0.17 mmol) and triethylamine (0.153 mL, 1.10 mmol) in DMF (1 mL) at RT and the reaction was allowed to stand overnight at RT. The mixture was partitioned between ethyl acetate and water. The organic layer was washed twice with water then concentrated under reduced pressure. The residue was dissolved in DCM (1 mL) and treated with TFA (2 mL). The resulting solution was stirred for 30 minutes at RT before being concentrated under reduced pressure. The sample was dissolved in DMF (1.5 mL) and purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a colourless solid (26.7 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.38 - 0.44 (2H, m), 0.61 - 0.68 (2H, m), 1.24 (3H, d), 1.97 - 2.10 (2H, m), 2.30 - 2.45 (2H, m), 2.57 (1H, obscured by DMSO signal), 2.73 - 2.86 (5H, m), 2.90 - 3.00 (2H, m), 3.15 - 3.25 (1H, m), 3.47 - 3.55 (1H, m), 3.63 - 3.69 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.29 (1H, d), 4.56 (1H, br, s), 6.45 (1H, s), 6.79 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.57 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 515; HPLC tR = 1.50 min.

mTOR Kinase Assay (Echo): 0.0128μM

The following compounds were made in an analogous fashion from tert-butyl 4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
20a		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea	489.5	1.34
20b		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea	546.5	1.44
20c		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea	519.5	1.24
20d		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	555.5	1.41

Example 20a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.97 - 2.09 (2H, m), 2.30 - 2.45 (2H, m), 2.67 (3H, d), 2.70 - 2.85 (5H, m), 2.90 - 3.02 (2H, m), 3.15 - 3.25 (1H, m), 3.45 - 3.55 (1H, m), 3.67 (1H, d), 3.77 (1H, d), 3.99 (1H, d), 4.28 (1H, d), 4.56 (1H, br, s), 6.05 – 6.12 (1H, m), 6.79 (1H, s), 7.51 (2H, d), 8.22 (2H, d), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.0163μM

Example 20b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.98 - 2.09 (2H, m), 2.19 (6H, s), 2.30 – 2.47 (4H, m), 2.72 – 2.83 (5H, m), 2.92 – 3.02 (2H, m), 3.16 – 3.27 (3H, m, obscured by water signal), 3.45 - 3.57 (1H, m), 3.63 - 3.69 (1H, m), 3.77 (1H, d), 3.95 - 4.00 (1H, m), 4.28 (1H, d), 4.57 (1H, br, s), 6.17 (1H, t), 6.79 (1H, s), 7.49 (2H, d), 8.22 (2H, d), 8.91 (1H, s).

mTOR Kinase Assay (Echo): 0.874μM

Example 20c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.97 – 2.10 (2H, m), 2.32 – 2.46 (2H, m), 2.74 – 2.83 (5H, m), 2.92 – 3.02 (2H, m), 3.14 - 3.26 (3H, m), 3.41 - 3.55 (4H, m), 3.63 - 3.69 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.28 (1H, d), 4.57 (1H, br, s), 4.74 (1H, t), 6.25 (1H, t), 6.79 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.82 (1H, s).

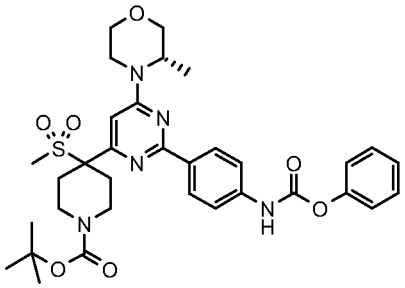
mTOR Kinase Assay (Echo): 0.00559μM

Example 20d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.24 (3H, d), 2.00 – 2.09 (2H, m), 2.32 – 2.47 (2H, m), 2.75 - 2.84 (5H, m), 2.92 – 3.02 (1H, m), 3.17 - 3.26 (1H, m), 3.47 - 3.55 (1H, m), 3.64 - 3.70 (1H, m), 3.75 – 3.82 (4H, m), 3.95 - 4.03 (1H, m), 4.29 (1H, d), 4.57 (1H, br, s), 6.80 (1H, s), 7.38 (1H, d), 7.55 (2H, d), 7.77 (1H, s), 8.26 (2H, d), 8.44 (1H, s), 8.89 (1H, s).

mTOR Kinase Assay (Echo): 0.0133μM

The preparation of tert-butyl 4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate is described below.

tert-Butyl 4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate

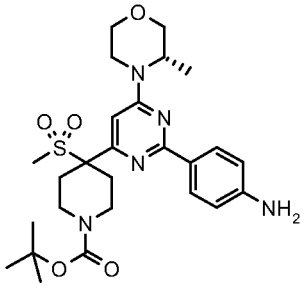


Phenyl chloroformate (0.150 mL, 1.20 mmol) was added to tert-butyl 4-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate (530 mg, 1.00 mmol) and sodium hydrogen carbonate (126 mg, 1.50 mmol) in dioxane (7 mL) at RT. The resulting slurry was stirred at RT for 3 hours. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% - 60% ethyl acetate in DCM, to give a colourless gum which was subsequently triturated with diethyl ether to give the desired material as a colourless solid (576 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.36 (3H, d), 1.44 (9H, s), 2.29 - 2.41 (2H, m), 2.72 (3H, s), 2.73 - 2.85 (4H, m), 3.33 (1H, dt), 3.61 (1H, dt), 3.76 (1H, dd), 3.84 (1H, d), 4.06 (1H, dd), 4.10 - 4.32 (3H, m), 4.46 (1H, br, s), 6.65 (1H, s), 7.12 (1H, br, s), 7.17 - 7.28 (3H, m), 7.36 - 7.44 (2H, m), 7.54 (2H, d), 8.35 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 652; HPLC tR = 3.11 min.

tert-Butyl 4-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate

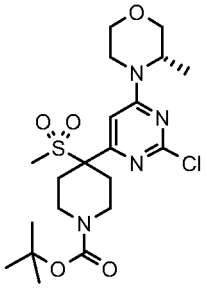


A stream of nitrogen was passed through tert-butyl 4-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate (500 mg, 1.05 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (300 mg, 1.37 mmol) and 2M aqueous sodium carbonate (1.895 mL, 3.79 mmol) in DMF (2 mL), DME (2 mL), ethanol (2 mL) and water (5 mL) at RT for 15 minutes. The reaction mixture was treated with dichlorobis(triphenylphosphine)-palladium(II) (36.9 mg, 0.05 mmol) and the mixture was stirred at 80°C for 30 minutes. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% - 50% ethyl acetate in DCM. The isolated material was triturated with diethyl ether to give the desired material as a pale orange solid (544 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.44 (9H, s), 2.30 - 2.36 (2H, m), 2.71 (3H, s), 2.69 - 2.85 (4H, m), 3.30 (1H, dt), 3.60 (1H, dt), 3.74 (1H, dd), 3.83 (1H, d), 3.93 (2H, s), 4.04 (1H, dd), 4.09 - 4.29 (3H, m), 4.45 (1H, br, s), 6.58 (1H, s), 6.71 (2H, d), 8.18 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 532; HPLC tR = 2.52 min.

tert-Butyl 4-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate

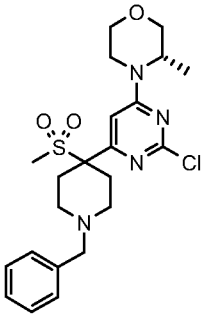


1-Chloroethyl chloroformate (0.315 mL, 2.92 mmol) was added to a solution of 4-(1-benzyl-4-methylsulfonylpiperidin-4-yl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (679 mg, 1.46 mmol) in DCM (10 mL). The solution was heated at reflux for 3 hours. The mixture was cooled, diluted with methanol (10 mL) and allowed to stand overnight. The mixture was treated with di-tert-butyl dicarbonate (0.738 mL, 3.21 mmol) and DIPEA (0.505 mL, 2.92 mmol) and this solution was stirred at RT for 1.5 hours. The solution was partitioned between DCM and water and the organic phase concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% - 30% ethyl acetate in DCM , to give the desired material as a colourless dry film (519 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.45 (9H, s), 2.23 - 2.34 (2H, m), 2.59 - 2.78 (7H, m), 3.30 (1H, dt), 3.55 (1H, dt), 3.70 (1H, dd), 3.80 (1H, d), 3.98 - 4.40 (5H, m), 6.61 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 475, 477; HPLC tR = 2.53 min.

4-(1-Benzyl-4-methylsulfonylpiperidin-4-yl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



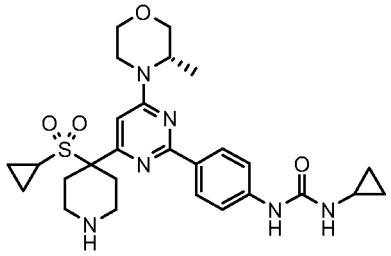
A solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (750 mg, 2.45 mmol) in NMP (8 mL) was treated with sodium hydride (324 mg, 8.10 mmol). The mixture was stirred at RT for 10 minutes before being treated with tetrabutylammonium bromide (979 mg, 3.04 mmol) and *N*-benzyl-2-chloro-*N*-(2-chloroethyl)ethanamine hydrochloride (692 mg, 2.58 mmol). The reaction mixture was stirred for 5 minutes, warmed to 50°C for 1 hour then warmed to 80°C for 2.5 hours. The mixture was allowed to cool and stirred for 65 hours at RT. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution and then extracted with ethyl acetate. The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% - 50% ethyl acetate in DCM, to give the desired material as a colourless solid (710 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.89 - 1.99 (2H, m), 2.40 - 2.50 (2H, m), 2.57 - 2.64 (2H, m), 2.75 (3H, s), 2.87 - 2.95 (2H, m), 3.29 (1H, dt), 3.41 (2H, s), 3.55 (1H, dt), 3.69 (1H, dd), 3.79 (1H, d), 3.95 - 4.08 (2H, m), 4.29 (1H, br, s), 6.59 (1H, s), 7.21 - 7.32 (5H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 465, 467; HPLC tR = 2.59 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine was described earlier.

Example 21: 3-Cyclopropyl-1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



Cyclopropylamine (0.055 mL, 0.76 mmol) was added to tert-butyl 4-cyclopropylsulfonyl-4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]piperidine-1-carboxylate (120 mg, 0.18 mmol) and triethylamine (0.16 mL, 1.15 mmol) in DMF (1 mL) at RT and the reaction was allowed to stand for overnight at RT. The mixture was partitioned between ethyl acetate and water. The organic layer was washed twice with

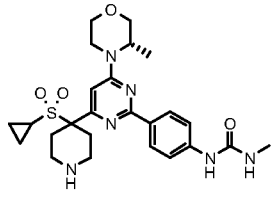
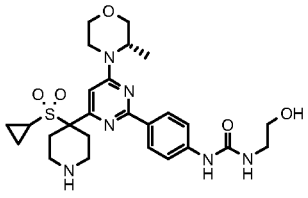
water then concentrated under reduced pressure. The residue was dissolved in DCM (1 mL) and treated with TFA (2 mL). The resulting solution was stirred for 30 minutes at RT before being concentrated under reduced pressure. The sample was dissolved in DMF (1.5 mL). The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% conc. ammonia) and acetonitrile as eluents, to give the desired material as a colourless solid (53 mg).

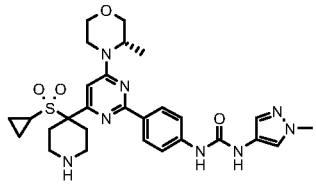
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.38 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 0.70 - 0.74 (2H, m), 0.83 - 0.87 (2H, m), 1.23 (3H, d), 1.98 - 2.12 (2H, m), 2.32 - 2.60 (4H, m), 2.82 – 2.98 (4H, m), 3.15 - 3.24 (1H, m), 3.47 - 3.56 (1H, m), 3.64 - 3.69 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.26 (1H, d), 4.50 – 4.60 (1H, m), 6.44 (1H, s), 6.81 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.54 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 541; HPLC tR = 1.85 min.

mTOR Kinase Assay (Echo): 0.0253μM

The following compounds were made in an analogous fashion from tert-butyl 4-cyclopropylsulfonyl-4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]piperidine-1-carboxylate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
21a		1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	515.6	1.71
21b		1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	545.7	1.56

Example	Structure	NAME	LCMS MH+	Retention time (min)
21c		1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	581.7	1.83

Example 21a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.68 - 0.74 (2H, m), 0.83 - 0.87 (2H, m), 1.23 (3H, d), 1.98 - 2.10 (2H, m), 2.32 - 2.49 (3H, m), 2.67 (3H, d), 2.82 – 2.97 (4H, m), 3.15 - 3.24 (1H, m), 3.47 – 3.57 (1H, m), 3.64 - 3.69 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.26 (1H, d), 4.50 – 4.59 (1H, m), 6.07 (1H, q), 6.81 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.0378μM

Example 21b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.69 – 0.76 (2H, m), 0.82 - 0.89 (2H, m), 1.23 (3H, d), 1.95 – 2.10 (2H, m), 2.31 - 2.49 (3H, m), 2.83 – 2.97 (4H, m), 3.15 – 3.26 (3H, m), 3.43 - 3.58 (3H, m), 3.64 - 3.69 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.26 (1H, d), 4.50 – 4.59 (1H, m), 4.74 (1H, t), 6.26 (1H, t), 6.81 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.81 (1H, s).

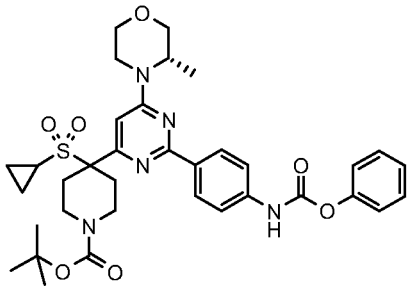
mTOR Kinase Assay (Echo): 0.0133μM

Example 21c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.73 (2H, br, s), 0.87 (2H, d), 1.23 (3H, d), 1.99 – 2.11 (2H, m), 2.33 - 2.48 (3H, m), 2.83 – 2.98 (4H, m), 3.15 – 3.20 (1H, m), 3.45 – 3.56 (1H, m), 3.68 (1H, d), 3.74 – 3.83 (4H, m), 3.99 (1H, d), 4.27 (1H, d), 4.55 (1H, br, s), 6.82 (1H, s), 7.38 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.26 (2H, d), 8.42 (1H, s), 8.86 (1H, s).

mTOR Kinase Assay (Echo): 0.0234μM

The preparation of tert-butyl 4-cyclopropylsulfonyl-4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]piperidine-1-carboxylateis described below.

tert-Butyl 4-cyclopropylsulfonyl-4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]piperidine-1-carboxylate

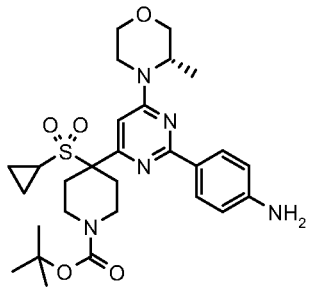


Phenyl chloroformate (0.235 mL, 1.87 mmol) was added to tert-butyl 4-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-cyclopropylsulfonylpiperidine-1-carboxylate (950 mg, 1.70 mmol) and sodium hydrogen carbonate (215 mg, 2.56 mmol) in dioxane (15 mL) at RT. The resulting slurry was stirred at RT for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 25% - 80% ethyl acetate in isohexane. The isolated material was triturated with diethyl ether to give the desired material as a near colourless dry film (1.06 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.80 - 0.85 (2H, m), 0.94 - 1.06 (2H, m), 1.35 (3H, d), 1.44 (9H, s), 2.14 - 2.22 (1H, m), 2.25 - 2.39 (2H, m), 2.69 - 2.95 (4H, m), 3.33 (1H, dt), 3.62 (1H, dt), 3.76 (1H, dd), 3.84 (1H, d), 4.03 - 4.31 (4H, m), 4.39 - 4.49 (1H, m), 6.68 (1H, s), 7.11 (1H, br, s), 7.19 - 7.28 (3H, m), 7.41 (2H, t), 7.54 (2H, d), 8.37 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 678; HPLC tR = 3.18 min.

tert-Butyl 4-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-cyclopropylsulfonylpiperidine-1-carboxylate



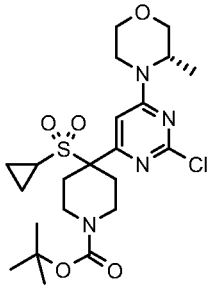
A stream of nitrogen was passed through tert-butyl 4-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-cyclopropylsulfonylpiperidine-1-carboxylate (0.94 g, 1.88 mmol), 4-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.534 g, 2.44 mmol) and 2M aqueous sodium carbonate (3.38 mL, 6.75 mmol) in DMF (3.75 mL), DME (5 mL), ethanol (5 mL) and water (12.5 mL) at RT for 15 minutes. The reaction mixture was treated with dichlorobis(triphenylphosphine)-palladium(II) (0.066 g, 0.09 mmol) and the mixture was stirred at 80°C for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% - 50% ethyl acetate in DCM. The isolated material was triturated with diethyl ether to give the desired material as a pale brown solid (0.990 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.77 - 0.85 (2H, m), 0.95 - 1.04 (2H, m), 1.32 (3H, d), 1.42 (9H, s), 2.14 - 2.21 (1H, m), 2.24 - 2.37 (2H, m), 2.69 - 2.93 (4H, m), 3.29 (1H, dt), 3.60 (1H, dt), 3.75 (1H, dd), 3.81 (1H, d), 3.90 (2H, s), 4.04 (1H, dd), 4.07 - 4.30 (3H, m), 4.39 - 4.48 (1H, m), 6.61 (1H, s), 6.61 (2H, d), 8.20 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 558; HPLC tR = 2.64 min.

tert-Butyl 4-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-cyclopropylsulfonylpiperidine-1-carboxylate

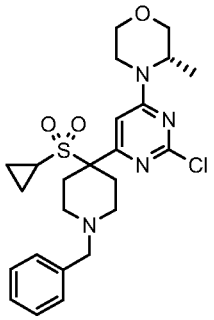


1-Chloroethyl chloroformate (0.971 mL, 9.00 mmol) was added to a solution of 4-(1-benzyl-4-cyclopropylsulfonylpiperidin-4-yl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.21 g, 4.50 mmol) in DCM (15 mL). The solution was heated at reflux for 1.5 hours. The mixture was diluted with methanol (15 mL) and heating was continued for 2 hours. The mixture was treated with di-tert-butyl dicarbonate (2.16 g, 9.90 mmol) and DIPEA (1.6 mL, 9.0 mmol) and this solution was stirred at RT for 1 hour. The solution was partitioned between DCM and water. The organic phase was concentrated under reduced pressure and the residue was purified by chromatography on silica, eluting with 10% - 30% ethyl acetate in DCM, to give the desired material as a colourless solid (1.9 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.93 - 1.00 (4H, m), 1.32 (3H, d), 1.44 (9H, s), 2.19 - 2.30 (3H, m), 2.62 - 2.80 (4H, m), 3.29 (1H, dt), 3.55 (1H, dt), 3.69 (1H, dd), 3.79 (1H, d), 3.95 - 4.37 (5H, m), 6.65 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 501, 503; HPLC tR = 2.70 min.

4-(1-Benzyl-4-cyclopropylsulfonylpiperidin-4-yl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



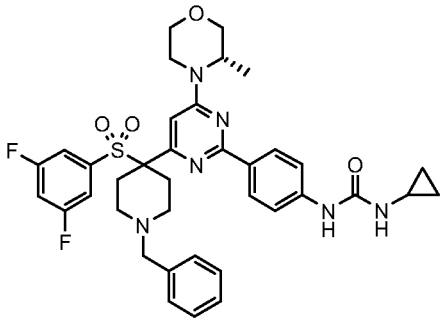
A solution of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2 g, 6.03 mmol) in NMP (18 mL) was treated with sodium hydride (0.796 g, 19.89 mmol). The mixture was stirred at RT for 10 minutes before being treated with tetrabutylammonium bromide (2.91 g, 9.04 mmol) and *N*-benzyl-2-chloro-*N*-(2-chloroethyl)ethanamine hydrochloride (1.781 g, 6.63 mmol). The reaction mixture was stirred for 5 minutes, warmed to 50°C for 1 hour then warmed to 80°C for 1.5 hours. The mixture was then allowed to cool to RT. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution and then extracted with ethyl acetate. The organic solution was washed three times with water then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% - 70% ethyl acetate in DCM, to give the desired material as a colourless foam (2.23 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.92 - 0.96 (2H, m), 0.97 - 1.02 (2H, m), 1.32 (3H, d), 1.92 - 2.00 (2H, m), 2.24 - 2.31 (1H, m), 2.40 - 2.49 (2H, m), 2.68 - 2.74 (2H, m), 2.88 - 2.92 (2H, m), 3.29 (1H, dt), 3.40 (2H, s), 3.55 (1H, dt), 3.70 (1H, dd), 3.79 (1H, d), 3.98 - 4.09 (2H, m), 4.28 (1H,br, s), 6.63 (1H, s), 7.21 - 7.33 (5H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 491, 493; HPLC tR = 2.71 min.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 22: 1-[4-[4-[1-Benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea



A stream of nitrogen was passed through [4-(3-cyclopropylureido)phenylboronic acid, pinacol ester (121 mg, 0.40 mmol), 4-[1-benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (225 mg, 0.40 mmol) and 2M aqueous sodium carbonate (0.719 mL, 1.44 mmol) in DMF (0.8 mL), DME (5 mL), ethanol (5 mL) and water (12.5 mL) at 25ºC for 15 minutes. The reaction mixture was treated with dichlorobis(triphenylphosphine)-palladium(II) (14.02 mg, 0.02 mmol) and the mixture was stirred at 80°C for 2 hours. The mixture was partitioned between DCM and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by ion exchange chromatography using an SCX column, eluting with 2M ammonia in methanol. The isolated material was further purified by chromatography on silica, eluting with 10% - 60% ethyl acetate in DCM, to give the desired material as a colourless dry film (125 mg).

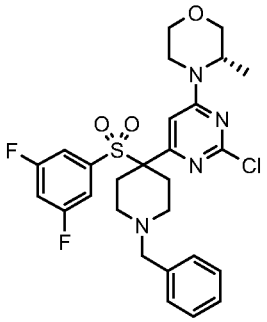
NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.67 - 0.71 (2H, m), 0.85 - 0.90 (2H, m), 1.36 (3H, d), 1.77 - 1.98 (2H, m), 2.47 - 2.67 (3H, m), 2.74 (2H, t), 2.85 - 2.96 (2H, m), 3.30 - 3.38 (3H, m), 3.64 (1H, dt), 3.76 - 3.87 (2H, m), 4.08 (1H, dd), 4.16 (1H, d), 4.40 - 4.51 (1H, m), 4.92 (1H, s), 6.63 (1H, s), 6.80 - 6.86 (1H, m), 6.95 - 7.03 (3H, m), 7.20 - 7.31 (5H, m), 7.39 (2H, d), 7.93 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 703.6; HPLC tR = 2.97 min.

mTOR Kinase Assay (Echo): 0.503μM

The preparation of 4-[1-benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine is described below.

4-[1-Benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



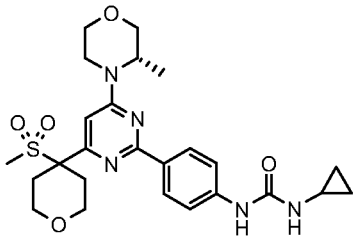
A mixture of 2-chloro-4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (874 mg, 2.16 mmol) in NMP (10 mL) was treated with sodium hydride (299 mg, 7.47 mmol) and stirred for 5 minutes at RT. Tetrabutylammonium bromide (698 mg, 2.16 mmol) and *N*-benzyl-2-chloro-*N*-(2-chloroethyl)ethanamine hydrochloride (669 mg, 2.49 mmol) were added and the mixture heated at 80ºC for 2 hours. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution and then extracted with ethyl acetate. The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% -50% ethyl acetate in isohexane, to give the desired material as a colourless solid (582 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.35 (3H, d), 1.85 - 1.93 (2H, m), 2.41 - 2.49 (2H, m), 2.55 (2H, d), 2.88 - 2.93 (2H, m), 3.32 (1H, dt), 3.38 (2H, s), 3.59 (1H, dt), 3.74 (1H, dd), 3.81 (1H, d), 3.98 - 4.08 (2H, m), 4.31 (1H, br, s), 6.64 (1H, s), 6.97 - 7.11 (3H, m), 7.22 - 7.33 (5H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 563, 565; HPLC tR = 3.18 min.

The preparation of 2-chloro-4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 23: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea



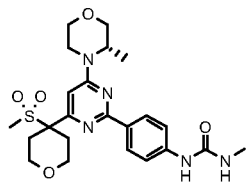
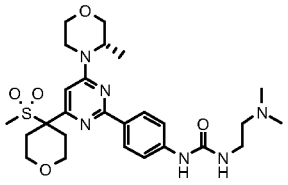
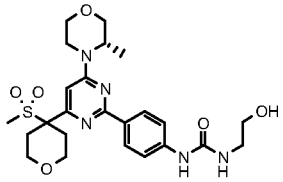
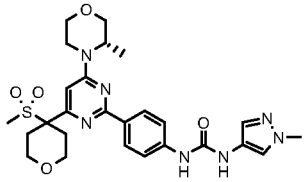
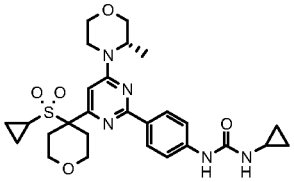
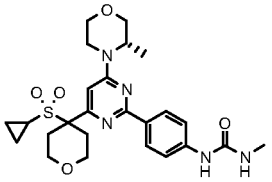
Cyclopropylamine (0.100 mL, 1.45 mmol) was added to phenyl N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.18 mmol) in DMF (2 mL). The resulting solution was stirred at 60°C for 4 hours. The mixture was evaporated to dryness and the residue was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (67 mg).

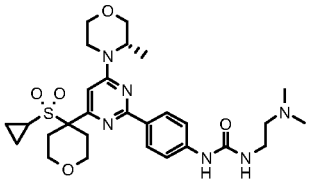
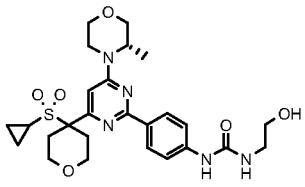
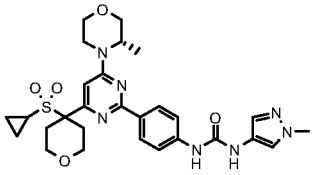
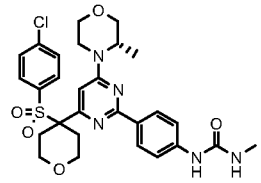
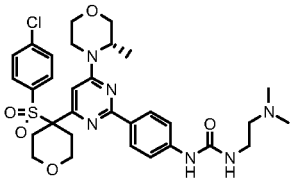
NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.71 (2H, ddd), 0.89 (2H, ddd), 1.35 (3H, d), 2.54 (3H, ddd), 2.64 (1H, m), 2.71 (3H, s), 2.72 (2H, br.d), 3.34 (1H, ddd), 3.42 (1H, ddd), 3.62 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.05 (3H, m), 4.20 (1H, d), 4.46 (1H, br.d), 4.89 (1H, s), 6.64 (1H, s), 7.00 (1H, s), 7.51 (2H, d), 8.31 (2H, d).

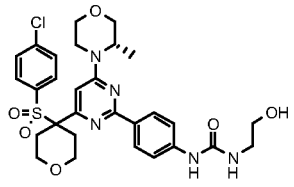
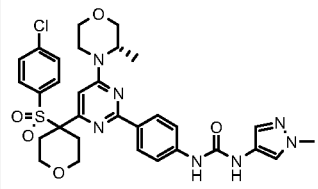
LCMS Spectrum: m/z (ESI+)(M+H)+ = 516; HPLC tR = 1.92 min.

mTOR Kinase Assay (Echo): 0.00492μM

The following compounds were made in an analogous fashion from either phenyl N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]carbamate, phenyl N-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl N-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
23a		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea	490	1.77
23b		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea	547	1.84
23c		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea	520	1.61
23d		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	554 (M-H)-	1.83
23e		3-cyclopropyl-1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	542	2.07
23f		1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	516	1.89

Example	Structure	NAME	LCMS MH+	Retention time (min)
23g		1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	573	1.96
23h		1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	546	1.72
23i		1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	580 (M-H)-	1.93
23j		1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	586	2.26
23k		1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	643	2.31

Example	Structure	NAME	LCMS MH+	Retention time (min)
23l		1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	616	2.05
23m		1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	652	2.26

Example 23a: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.54 (2H, ddd), 2.71 (3H, s), 2.72 (2H, d), 2.89 (3H, d), 3.35 (1H, ddd), 3.41 (2H, dd), 3.62 (1H, ddd), 3.76 (1H, dd), 3.84 (1H, d), 4.0-4.1 (3H, m), 4.19 (1H, d), 4.46 (1H, br.d), 4.62 (1H, br.q), 6.32 (1H, s), 6.64 (1H, s), 7.40 (2H, d), 8.31 (2H, d).

mTOR Kinase Assay (Echo): 0.00459μM

Example 23b: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.32 (6H, s), 2.5-2.6 (4H, m), 2.71 (3H, s), 2.72 (2H, d), 3.3-3.4 (3H, m), 3.41 (2H, ddd), 3.62 (1H, ddd), 3.76 (1H, dd), 3.84 (1H, d), 4.0-4.1 (3H, m), 4.19 (1H, d), 4.46 (1H, br.d), 5.22 (1H, br.t), 6.62 (1H, s), 7.44 (2H, d), 8.28 (2H, d).

mTOR Kinase Assay (Echo): 0.197μM

Example 23c: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.5-2.6 (3H, m), 2.71 (3H, s), 2.72 (2H, d), 3.34 (1H, ddd), 3.41 (2H, dd), 3.45 (4H, dt), 3.62 (1H, ddd), 3.76 (1H, dd), 3.78 (2H, m), 3.84 (1H, d), 4.0-4.1 (3H, m), 4.19 (1H, d), 4.45 (1H, br.d), 5.25 (1H, t), 6.64 (1H, s), 6.86 (1H, s), 7.41 (2H, d), 8.30 (2H, d).

mTOR Kinase Assay (Echo): 0.000831μM

Example 23d: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.54 (2H, ddd), 2.72 (3H, s), 2.72 (2H, m), 3.33 (1H, ddd), 3.41 (2H, dd), 3.61 (1H, ddd), 3.75 (1H, dd), 3.83 (1H, d), 3.90 (3H, s), 4.0-4.1 (3H, m), 4.18 (1H, d), 4.45 (1H, br.d), 6.25 (1H, br.s), 6.64 (1H, s), 6.78 (1H, s), 7.41 (1H, s), 7.44 (2H, d), 7.61 (1H, s), 8.29 (2H, d).

mTOR Kinase Assay (Echo): 0.00534μM

Example 23e: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.71 (2H, ddd), 0.83 (2H, m), 0.89 (2H, ddd), 1.02 (2H, m), 1.34 (3H, d), 2.18 (1H, tt), 2.53 (2H, ddd), 2.64 (1H, tt), 2.82 (2H, br.d), 3.34 (2H, ddd), 3.43 (3H, ddd), 3.63 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.02 (2H, m), 4.06 (1H, dd), 4.19 (1H, d), 4.46 (1H, br.d), 4.86 (1H, s), 6.67 (1H, s), 6.97 (1H, s), 7.51 (2H, d), 8.33 (2H, d).

mTOR Kinase Assay (Echo): 0.00876μM

Example 23f: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.83 (2H, m), 1.02 (2H, m), 1.34 (3H, d), 2.18 (1H, tt), 2.52 (2H, m), 2.82 (2H, br.d), 2.86 (3H, d), 3.33 (1H, ddd), 3.42 (2H, ddd), 3.62 (1H, ddd), 3.76 (1H, dd), 3.83 (1H, d), 4.01 (2H, m), 4.05 (1H, dd), 4.18 (1H, d), 4.45 (1H, br.d), 4.83 (1H, q), 6.63 (1H, s), 6.67 (1H, s), 7.40 (2H, d), 8.31 (2H, d).

mTOR Kinase Assay (Echo): 0.0199μM

Example 23g: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.82 (2H, m), 1.01 (2H, m), 1.34 (3H, d), 2.18 (1H, tt), 2.32 (6H, s), 2.52 (4H, m), 2.82 (2H, d), 3.32 (3H, m), 3.43 (2H, ddd), 3.62 (1H, ddd), 3.76 (1H, dd), 3.83 (1H, d), 4.01 (2H, m), 4.05 (2H, dd), 4.18 (1H, d), 4.46 (1H, br.d), 5.30 (1H, br.t), 6.66 (1H, s), 7.44 (2H, d), 8.30 (2H, d).

mTOR Kinase Assay (Echo): 1.21μM

Example 23h: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.83 (2H, m), 1.02 (2H, m), 1.34 (3H, d), 2.18 (1H, tt), 2.53 (3H, m), 2.82 (2H, br.d), 3.33 (1H, ddd), 3.43 (2H, dd), 3.46 (2H, t), 3.62 (1H, ddd), 3.76 (1H, dd), 3.78 (2H, t), 3.83 (1H, d), 4.01 (2H, m), 4.05 (1H, dd), 4.18 (1H, d), 4.45 (1H, br.d), 5.26 (1H, t), 6.67 (1H, s), 6.85 (1H, s), 7.40 (2H, d), 8.32 (2H, d).

mTOR Kinase Assay (Echo): 0.00808μM

Example 23i: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.84 (2H, m), 1.03 (2H, m), 1.34 (3H, d), 2.19 (1H, tt), 2.53 (2H, m), 2.82 (2H, br.d), 3.33 (1H, ddd), 3.42 (2H, ddd), 3.61 (1H, ddd), 3.76 (1H, dd), 3.83 (1H, d), 3.92 (3H, s), 4.02 (2H, m), 4.05 (1H, dd), 4.17 (1H, d), 4.45 (1H, br.d), 6.03 (1H, s), 6.60 (1H, s), 6.67 (1H, s), 7.42 (2H, d), 7.43 (1H, s), 7.60 (1H, s), 8.31 (2H, d).

mTOR Kinase Assay (Echo): 0.0254μM

Example 23j: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.36 (3H, d), 2.55 (2H, td), 2.64 (2H, br.d), 2.87 (3H, d), 3.30 (1H, ddd), 3.34 (1H, ddd), 3.65 (1H, ddd), 3.79 (1H, dd), 3.86 (1H, d), 3.99 (2H, m), 4.08 (1H, dd), 4.16 (1H, d), 4.45 (1H, br.d), 4.64 (1H, br.q), 6.29 (1H, s), 6.62 (1H, s), 7.27 (4H, m), 7.39 (2H, d), 7.83 (2H, d).

mTOR Kinase Assay (Echo): 0.0314μM

Example 23k: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.36 (3H, d), 2.32 (6H, s), 2.52 (2H, t), 2.55 (2H, ddd), 2.63 (2H, d), 3.26 - 3.37 (5H, m), 3.64 (1H, ddd), 3.79 (1H, dd), 3.85 (1H, d), 3.98 (2H, m), 4.07 (1H, dd), 4.17 (1H, d), 4.45 (1H, br.d), 5.18 (1H, br.t), 6.61 (1H, s), 7.27 (2H, d), 7.32 (2H, d), 7.39 (2H, d), 7.80 (2H, d).

mTOR Kinase Assay (Echo): 1.14μM

Example 23l: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.36 (3H, d), 2.37 (1H, t), 2.55 (4H, ddd), 2.64 (2H, br.d), 3.26 - 3.37 (3H, m), 3.46 (2H, dt), 3.64 (1H, ddd), 3.77 - 3.81 (3H, m), 3.86 (1H, d), 3.99 (2H, m), 4.08 (1H, dd), 4.16 (1H, d), 4.45 (1H, br.d), 5.07 (1H, t), 6.49 (1H, s), 6.63 (1H, s), 7.26 (2H, d), 7.28 (2H, d), 7.39 (2H, d), 7.84 (2H, d).

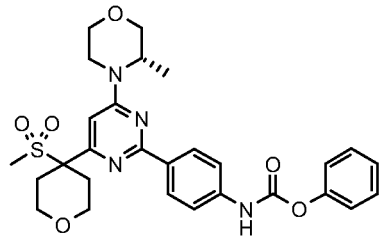
mTOR Kinase Assay (Echo): 0.00888μM

Example 23m: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.53 (3H, ddd), 2.64 (2H, br.d), 3.26 - 3.37 (3H, m), 3.64 (1H, ddd), 3.78 (21H, dd), 3.85 (1H, d), 3.91 (3H, s), 3.99 (2H, m), 4.07 (1H, dd), 4.15 (1H, d), 4.44 (1H, br.d), 6.11 (1H, s), 6.61 (1H, s), 6.63 (1H, s), 7.28 (2H, d), 7.32 (2H, d), 7.41 (2H, d), 7.42 (1H, s), 7.61 (1H, s), 7.84 (2H, d).

mTOR Kinase Assay (Echo): 0.0577μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]carbamate



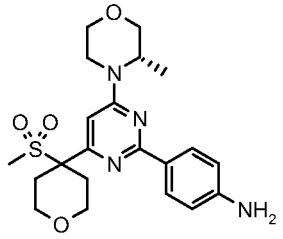
Phenyl chloroformate (0.196 mL, 1.56 mmol) was added dropwise to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]aniline (615 mg, 1.42 mmol) and sodium hydrogen carbonate (179 mg, 2.13 mmol) in dioxane (50 mL) at RT. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was concentrated, diluted with ethyl acetate (100 mL) and washed sequentially with water (2 x 100 mL) and

saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 40 to 80% ethyl acetate in *iso*-hexane, to afford the desired material as a white solid (714 mg).

NMR Spectrum: ^1H NMR (399.902 MHz, $CDCl_3$) δ 1.36 (3H, d), 2.55 (2H, m), 2.71 (3H, s), 2.73 (2H, d), 3.35 (1H, ddd), 3.42 (2H, ddd), 3.62 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.02 - 4.08 (3H, m), 4.20 (1H, d), 4.47 (1H, br.d), 6.66 (1H, s), 7.11 (1H, s), 7.21 (2H, d), 7.26 (1H, dd), 7.41 (2H, dd), 7.54 (2H, d), 8.35 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 553; HPLC tR = 2.57 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]aniline

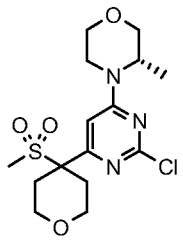


Sodium carbonate (2M in water, 5.75 mL, 11.49 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.839 g, 3.83 mmol) and 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidine (1.200 g, 3.19 mmol) in a mixture of ethylene glycol diethyl ether (10 mL), ethanol (10 mL), DMF (10 mL) and water (20 mL) at RT under nitrogen. The mixture was degassed and purged with nitrogen. Bis(triphenylphosphine)palladium(II) chloride (0.112 g, 0.16 mmol) was added and the mixture was degassed and purged with nitrogen. The resulting suspension was stirred under nitrogen at 80°C for 90 minutes. The reaction mixture was concentrated and diluted with ethyl acetate (150 mL) and washed sequentially with water (2 x 150 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 40 to 100% ethyl acetate in *iso*-hexane, to afford the desired material as a white solid (690 mg).

NMR Spectrum: ^1H NMR (399.902 MHz, $CDCl_3$) δ 1.34 (3H, d), 2.53 (2H, ddd), 2.70 (3H, s), 2.72 (2H, br.d), 3.33 (1H, ddd), 3.41 (2H, ddd), 3.61 (1H, ddd), 3.76 (1H, dd), 3.83 (1H, d), 3.93 (2H, s), 4.03 (3H, m), 4.18 (1H, d), 4.45 (1H, br.d), 6.58 (1H, s), 6.71 (2H, d), 8.18 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 433; HPLC tR = 1.98 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidine



Sodium *tert*-butoxide (1.38 g, 14.39 mmol) was added portionwise to a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (2.00 g, 6.54 mmol) and bis(2-bromoethyl) ether (2.055 mL, 16.35 mmol) in DMF (75 mL) at 0ºC over a period of 10 minutes under nitrogen. The resulting solution was allowed to warm to RT and stirred for 7 hours. Further sodium *tert*-butoxide (629 mg, 6.54 mmol) was added portionwise and the solution was stirred at RT for a further 45 hours. The reaction mixture was concentrated, diluted with ethyl acetate (200 mL) and washed sequentially with water (2 x 200 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 40 to 100% ethyl acetate in *iso*-hexane. Pure fractions were evaporated to dryness and the residue crystallised from ethyl acetate / *iso*-hexane to afford the desired material as a white crystalline solid (1.42 g).

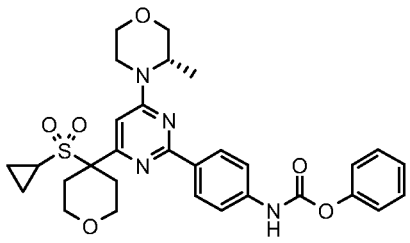
NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.34 (3H, d), 2.50 (2H, m), 2.55 (2H, m), 2.73 (3H, s), 3.33 (3H, m), 3.56 (1H, ddd), 3.71 (1H, dd), 3.80 (1H, d), 4.01 (4H, m), 4.31 (1H, br.s), 6.62 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 376, 378; HPLC tR = 1.85 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

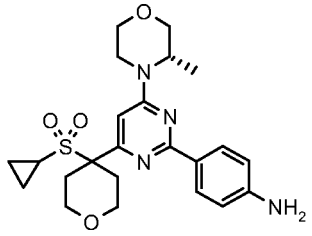
Phenyl *N*-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.211 mL, 1.68 mmol) was added to 4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (700 mg, 1.53 mmol) and sodium hydrogen carbonate (192 mg, 2.29 mmol) in 1,4-dioxane (50 mL) at RT. The resulting suspension was stirred at RT for 16 hours. The reaction mixture was concentrated and diluted with ethyl acetate (75 mL) and washed sequentially with water (75 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 70% ethyl acetate in *iso*-hexane, to afford the desired material as a white solid (850 mg).

NMR Spectrum: ^1H NMR (399.902 MHz, $CDCl_3$) δ 0.83 (2H, m), 1.02 (2H, m), 1.35 (3H, d), 2.18 (1H, tt), 2.54 (2H, m), 2.83 (2H, d), 3.34 (2H, ddd), 3.43 (2H, dd), 3.63 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.02 (2H, m), 4.06 (1H, dd), 4.20 (1H, d), 4.47 (1H, br.d), 6.69 (1H, s), 7.08 (1H, s), 7.21 (2H, d), 7.26 (1H, dd), 7.41 (2H, dd), 7.54 (2H, d), 8.37 (2H, d).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 579.5; HPLC tR = 2.72 min.

4-[4-(4-Cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



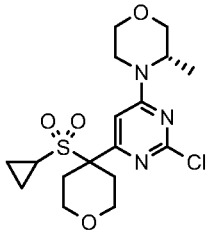
Sodium carbonate (2M in water, 7.48 mL, 14.96 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.092 g, 4.99 mmol) and 2-chloro-4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (1.67 g, 4.16 mmol) in a mixture of ethylene glycol diethyl ether (10 mL), ethanol (10 mL), DMF (10 mL) and water (20 mL) at RT under nitrogen. The mixture was degassed and purged with nitrogen. Bis(triphenylphosphine)palladium(II) chloride (0.146 g, 0.21 mmol) was added and the

mixture was degassed and purged with nitrogen. The resulting suspension was stirred under nitrogen at 80°C for 90 minutes. The reaction mixture was concentrated and diluted with ethyl acetate (150 mL) and washed sequentially with water (2 x 150 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 40 to 70% ethyl acetate in *iso*-hexane, to afford the desired material as a white solid (740 mg).

NMR Spectrum: ^1H NMR (399.902 MHz, $CDCl_3$) δ 0.82 (2H, m), 1.01 (2H, m), 1.33 (3H, d), 2.17 (1H, tt), 2.51 (2H, m), 2.82 (2H, br.d), 3.32 (1H, ddd), 3.43 (2H, ddd), 3.62 (1H, ddd), 3.76 (1H, dd), 3.83 (1H, d), 3.91 (2H, s), 3.98 (2H, m), 4.05 (1H, dd), 4.17 (1H, d), 4.45 (1H, br.d), 6.62 (1H, s), 6.71 (2H, d), 8.21 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 459; HPLC tR = 2.05 min.

2-Chloro-4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine



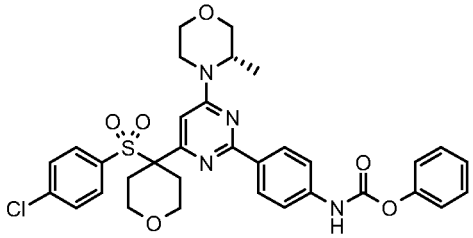
Sodium *tert*-butoxide (1.738 g, 18.08 mmol) was added portionwise to 2-choro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.00 g, 6.03 mmol) and bis(2-bromoethyl) ether (2.273 mL, 18.08 mmol) in DMF (75 mL) at RT over a period of 5 minutes under nitrogen. The resulting solution was stirred at RT for 5 hours. Further bis(2-bromoethyl) ether (0.758 mL, 6.03 mmol), and sodium *tert*-butoxide (0.579 g, 6.03 mmol) were added and the solution was stirred at RT for a further 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (0.5 mL), concentrated, diluted with ethyl acetate (200 mL) and washed sequentially with water (2 x 200 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 40 to 60% ethyl acetate in *iso*-hexane, to afford the desired material as a colourless oil which crystallised on standing (1.734 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.01 (2H, m), 1.01 (2H, m), 1.33 (3H, d), 2.22 (1H, tt), 2.47 (2H, ddd), 2.64 (2H, br.d), 3.30 (1H, ddd), 3.36 (2H, dd), 3.56 (1H, ddd), 3.71 (1H, dd), 3.80 (1H, d), 3.97 - 4.04 (4H, m), 4.30 (1H, br.d), 6.66 (1H, s).
LCMS Spectrum: m/z (ESI-)(M-H)- = 400.4; HPLC tR = 2.04 min.

The preparation of 2-choro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

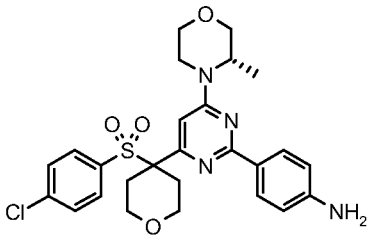
The preparation of phenyl *N*-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.198 mL, 1.58 mmol) was added to 4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (759 mg, 1.43 mmol) and sodium hydrogen carbonate (181 mg, 2.15 mmol) in 1,4-dioxane (50 mL) at RT. The resulting suspension was stirred at RT for 16 hours. The reaction mixture was concentrated and diluted with ethyl acetate (75 mL) and washed sequentially with water (75 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 70% ethyl acetate in *iso*-hexane, to afford the desired material as a white dry film (780 mg).
NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.36 (3H, d), 2.56 (2H, ddd), 2.64 (2H, br.d), 3.31 (2H, ddd), 3.35 (1H, ddd), 3.65 (1H, ddd), 3.80 (1H, dd), 3.86 (1H, d), 4.00 (2H, m), 4.08 (1H, dd), 4.18 (1H, d), 4.45 (1H, br.d), 6.64 (1H, s), 7.04 (1H, s), 7.21 (2H, d), 7.22 (1H, dd), 7.27 (2H, d), 7.39 (2H, d), 7.40 (2H, dd), 7.43 (2H, d), 7.87 (2H, d).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 649, 651; HPLC tR = 3.02 min.

4-[4-[4-(4-Chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

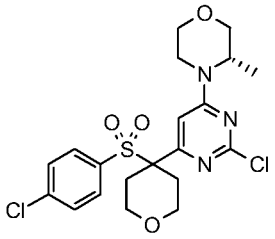


Sodium carbonate (2M in water, 4.02 mL, 8.05 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (490 mg, 2.24 mmol) and 2-chloro-4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (1056 mg, 2.24 mmol) in a mixture of ethanol (10 mL), water (20 mL), DMF (10 mL) and ethylene glycol diethyl ether (10 mL) at RT under nitrogen. The mixture was degassed and purged with nitrogen. Bis(triphenylphosphine)palladium(II) chloride (78 mg, 0.11 mmol) was added and the mixture degassed and purged with nitrogen. The resulting suspension was stirred at 80°C for 2 hours. The reaction mixture was concentrated and diluted with ethyl acetate (100 mL) and water (100 mL). The resulting precipitate was removed by filtration. The organic layer was washed sequentially with water (100 mL) and saturated brine (100 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in *iso*-hexane, to afford the desired material as a white dry film (790 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.54 (2H, ddd), 2.63 (2H, d), 3.27 - 3.35 (3H, m), 3.64 (1H, ddd), 3.79 (1H, dd), 3.85 (1H, d), 3.87 (2H, s), 3.98 (2H, m), 4.06 (1H, dd), 4.16 (1H, d), 4.44 (1H, br.d), 6.56 (1H, s), 6.60 (2H, d), 7.27 (2H, d), 7.39 (2H, d), 7.69 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 529.5, 531.5; HPLC tR = 2.49 min.

2-Chloro-4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine

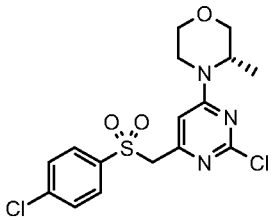


Sodium *tert*-butoxide (1.566 g, 16.30 mmol) was added portionwise to 2-chloro-4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.873 g, 4.66 mmol) and bis(2-bromoethyl) ether (1.463 mL, 11.64 mmol) in DMF (75 mL) at RT over a period of 5 minutes under nitrogen. The resulting solution was stirred at RT for 6 hours. Further sodium *tert*-butoxide (0.895 g, 9.31 mmol) was added and the solution was stirred at RT for a further 4 days. The reaction mixture was concentrated and diluted with ethyl acetate (200 mL), and washed sequentially with water (2 x 200 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 40 to 50% ethyl acetate in *iso*-hexane, to afford the desired material as a white dry film (1.0 g).

NMR Spectrum: ^1H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.45 - 2.49 (4H, m), 3.22 - 3.35 (3H, m), 3.59 (1H, ddd), 3.73 (1H, dd), 3.82 (1H, d), 3.95 - 4.00 (3H, m), 4.04 (1H, dd), 4.31 (1H, br.s), 6.67 (1H, s), 7.39 (2H, d), 7.45 (2H, d).

LCMS Spectrum: m/z (ESI-)(M-H)- = 470, 472; HPLC tR = 2.62 min.

2-Chloro-4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



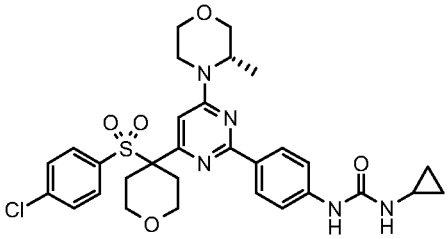
4-Chlorobenzenesulphinic acid sodium salt (5.39 g, 27.15 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (8.00 g, 22.63 mmol) in acetonitrile (400 mL) at RT. The resulting suspension was stirred at 85ºC under reflux for 5 hours. The reaction mixture was concentrated and diluted with DCM (400 mL) and washed with water (400 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 25 to 40% ethyl acetate in isohexane, to give the desired material as a white solid (6.90 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.33 (3H, d), 3.30 (1H, ddd), 3.55 (1H, ddd), 3.70 (1H, dd), 3.80 (1H, d), 4.02 (2H, m), 4.28 (1H, br.s), 4.29 (2H, s), 6.55 (1H, s), 7.51 (2H, d), 7.70 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 402, 404; HPLC tR = 2.26 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 24: 1-[4-[4-[4-(4-Chlorophenyl)sulfonyloxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea



Sodium carbonate (0.381 mL, 0.76 mmol) was added to 2-chloro-4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (100 mg, 0.21 mmol) and 4-(3-cyclopropylureido)phenylboronic acid (47 mg, 0.21 mmol) in DME (2 mL), ethanol (2 mL), DMF (2 mL) and water (4 mL) at RT under nitrogen. The mixture was degassed and purged with nitrogen then bis(triphenylphosphine)palladium(II) chloride (7.4 mg, 0.011 mmol) added and the mixture stirred at 85°C for 2 hours. The reaction mixture was concentrated, diluted with ethyl acetate (25 mL) and washed sequentially with water (2 x 25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane. The isolated material was further purified trituration with diethyl ether to afford the desired material as a white solid (26 mg).

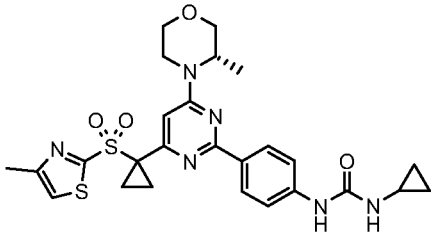
NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.70 (2H, m), 0.88 (2H, m), 1.36 (3H, d), 2.58 (5H, m), 3.31 (2H, m), 3.34 (1H, ddd), 3.65 (1H, ddd), 3.79 (1H, dd), 3.86 (1H, d), 3.99 (2H, m), 4.08 (1H, dd), 4.17 (1H, d), 4.45 (1H, d), 4.88 (1H, s), 6.63 (1H, s), 6.94 (1H, s), 7.27 (2H, d), 7.39 (2H, d), 7.39 (2H, d), 7.84 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 612, 6144; HPLC tR = 2.48 min.

mTOR Kinase Assay (Echo): 0.00517μM

The preparation of 2-chloro-4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 25: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea



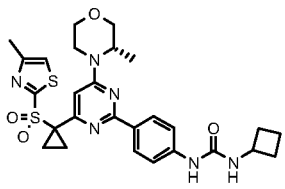
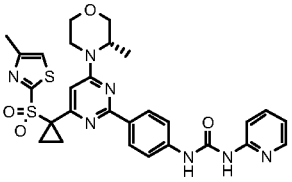
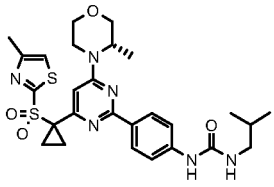
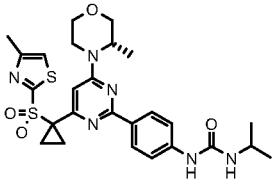
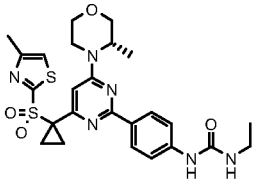
To cyclopropylamine (57 mg, 1 mmol) was added a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) in DMF (1.5 mL). Triethylamine (0.082 mL, 0.59 mmol) was then added and the resultant mixture was heated to 50°C and stirred overnight (~18 hours). The reaction mixture was cooled then purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) in acetonitrile as eluents, to give the desired material as a white solid (50 mg).

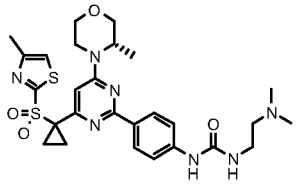
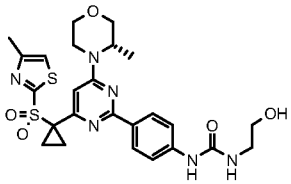
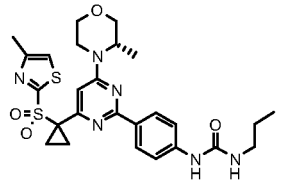
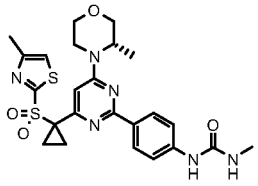
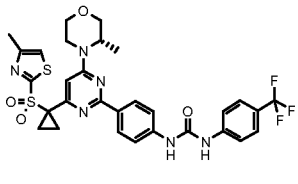
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.21 (3H, d), 1.75 - 1.80 (2H, m), 1.93 - 1.97 (2H, m), 2.47 - 2.49 (3H, m), 2.51 - 2.58 (1H, m), 3.17 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.10 - 4.20 (1H, m), 4.41 - 4.48 (1H, m), 6.41 (1H, d), 6.77 (1H, s), 7.41 - 7.44 (2H, m), 7.83 (1H, d), 7.87 - 7.90 (2H, m), 8.52 (1H, s).

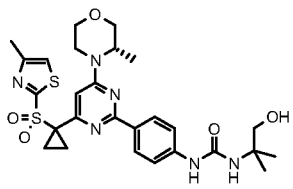
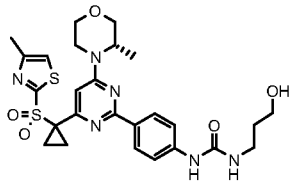
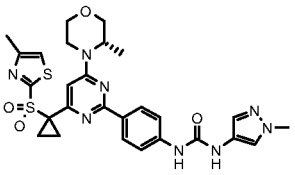
LCMS Spectrum: m/z (ESI+)(M+H)+ = 555; HPLC tR = 2.13 min.

mTOR Kinase Assay (Echo): 0.00155μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
25a		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	569.6	1.90
25b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea	592.4	2.51
25c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	571.4	2.42
25d		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea	557.4	2.26
25e		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	543.4	2.08

Example	Structure	NAME	LCMS MH+	Retention time (min)
25f		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	586.4	1.98
25g		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	559.3	1.78
25h		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-1-propylurea	557.4	2.26
25i		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	529.3	1.94
25j		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	659.3	2.9

Example	Structure	NAME	LCMS MH+	Retention time (min)
25k		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	587.4	2.05
25l		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	573.4	1.82
25m		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	595.4	1.99

Example 25a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.56 - 1.67 (2H, m), 1.75 - 1.79 (2H, m), 1.82 - 1.88 (2H, m), 1.93 - 1.95 (2H, m), 2.16 - 2.24 (2H, m), 2.48 (3H, s), 3.17 (1H, td), 3.46 (1H, td), 3.61 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.08 - 4.20 (2H, m), 4.41 - 4.49 (1H, m), 6.45 (1H, d), 6.77 (1H, s), 7.39 (2H, d), 7.83 - 7.88 (3H, m), 8.57 (1H, s).

mTOR Kinase Assay (Echo): 0.00224μM

Example 25b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.78 - 1.82 (2H, m), 1.95 - 1.99 (2H, m), 2.49 - 2.50 (3H, m), 3.20 (1H, td), 3.48 (1H, td), 3.63 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.13 - 4.21 (1H, m), 4.43 - 4.50 (1H, m), 6.81 (1H, s), 7.02 - 7.05 (1H, m), 7.53 - 7.62 (3H, m), 7.75 - 7.79 (1H, m), 7.85 - 7.87 (1H, m), 7.96 - 7.99 (2H, m), 8.29 - 8.31 (1H, m), 9.42 (1H, s), 10.53 (1H, s).

mTOR Kinase Assay (Echo): 0.000817μM

Example 25c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (6H, d), 1.21 (3H, d), 1.65 - 1.75 (1H, m), 1.75 - 1.80 (2H, m), 1.93 - 1.98 (2H, m), 2.48 - 2.49 (3H, m), 2.94 (2H, t), 3.18 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 - 4.20 (1H, m), 4.41 - 4.49 (1H, m), 6.22 (1H, t), 6.77 (1H, s), 7.39 - 7.42 (2H, m), 7.83 - 7.84 (1H, m), 7.87 - 7.90 (2H, m), 8.62 (1H, s).

mTOR Kinase Assay (Echo): 0.00385μM

Example 25d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.21 (3H, d), 1.76 - 1.80 (2H, m), 1.93 - 1.97 (2H, m), 2.48 - 2.49 (3H, m), 3.18 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.73 - 3.81 (2H, m), 3.97 (1H, dd), 4.12 - 4.19 (1H, m), 4.41 - 4.48 (1H, m), 6.03 (1H, d), 6.77 (1H, s), 7.38 - 7.41 (2H, m), 7.84 - 7.84 (1H, m), 7.87 - 7.90 (2H, m), 8.51 (1H, s).

mTOR Kinase Assay (Echo): 0.00157μM

Example 25e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.21 (3H, d), 1.76 - 1.80 (2H, m), 1.94 - 1.97 (2H, m), 2.48 - 2.49 (3H, m), 3.09 - 3.21 (3H, m), 3.47 (1H, td), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 - 4.19 (1H, m), 4.41 - 4.49 (1H, m), 6.15 (1H, t), 6.77 (1H, s), 7.39 - 7.43 (2H, m), 7.83 - 7.84 (1H, m), 7.86 - 7.90 (2H, m), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.000277μM

Example 25f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.26 (3H, d), 1.81 - 1.85 (2H, m), 1.99 - 2.02 (2H, m), 2.23 (6H, s), 2.39 (2H, t), 2.53 - 2.54 (3H, m), 3.19 - 3.27 (3H, m), 3.52 (1H, td), 3.67 (1H, dd), 3.81 (1H, d), 4.02 (1H, dd), 4.17 - 4.24 (1H, m), 4.47 - 4.53 (1H, m), 6.20 (1H, t), 6.82 (1H, s), 7.44 - 7.47 (2H, m), 7.88 - 7.90 (1H, m), 7.92 - 7.95 (2H, m), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.0547μM

Example 25g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.76 - 1.80 (2H, m), 1.93 - 1.97 (2H, m), 2.47 - 2.48 (3H, m), 3.13 - 3.21 (3H, m), 3.43 - 3.50 (3H, m), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 - 4.19 (1H, m), 4.41 - 4.49 (1H, m), 4.73 (1H, t), 6.23 (1H, t), 6.77 (1H, s), 7.39 - 7.42 (2H, m), 7.83 - 7.84 (1H, m), 7.87 - 7.90 (2H, m), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00119μM

Example 25h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.21 (3H, d), 1.46 (2H, sextet), 1.76 - 1.80 (2H, m), 1.94 - 1.97 (2H, m), 2.48 - 2.49 (3H, m), 3.06 (2H, q), 3.14 - 3.21 (1H, m), 3.47 (1H, td), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 - 4.19 (1H, m), 4.41 - 4.49 (1H, m), 6.19 (1H, t), 6.77 (1H, s), 7.39 - 7.43 (2H, m), 7.83 - 7.84 (1H, m), 7.86 - 7.90 (2H, m), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.000993μM

Example 25i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.76 - 1.80 (2H, m), 1.94 - 1.97 (2H, m), 2.48 – 2.49(3H, m), 2.66 (3H, d), 3.18 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 - 4.20 (1H, m), 4.40 - 4.50 (1H, m), 6.05 (1H, q), 6.77 (1H, s), 7.40 - 7.44 (2H, m), 7.83 - 7.84 (1H, m), 7.86 - 7.90 (2H, m), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.001μM

Example 25j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.77 - 1.81 (2H, m), 1.95 - 1.99 (2H, m), 2.48 - 2.49 (3H, m), 3.19 (1H, td), 3.48 (1H, td), 3.63 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.13 - 4.21 (1H, m), 4.42 - 4.51 (1H, m), 6.80 (1H, s), 7.49 - 7.52 (2H, m), 7.63 - 7.70 (4H, m), 7.85 - 7.86 (1H, m), 7.95 - 7.98 (2H, m), 9.03 (1H, s), 9.12 (1H, s).

mTOR Kinase Assay (Echo): 0.00576μM

Example 25k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.24 (6H, s), 1.76 - 1.79 (2H, m), 1.94 - 1.97 (2H, m), 2.48 - 2.49 (3H, m), 3.18 (1H, td), 3.39 (2H, d), 3.47 (1H, td), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 - 4.19 (1H, m), 4.41 - 4.48 (1H, m), 4.95 (1H, t), 5.98 (1H, s), 6.76 (1H, s), 7.34 - 7.39 (2H, m), 7.84 - 7.89 (3H, m), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.00292μM

Example 25l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.60 (2H, quintet), 1.76 - 1.80 (2H, m), 1.94 - 1.97 (2H, m), 2.48 - 2.49 (3H, m), 3.14 - 3.21 (3H, m), 3.44 - 3.50 (3H, m), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 - 4.19 (1H, m), 4.42 - 4.49 (2H, m), 6.18 (1H, t), 6.77 (1H, s), 7.39 - 7.43 (2H, m), 7.83 - 7.84 (1H, m), 7.86 - 7.90 (2H, m), 8.69 (1H, s).

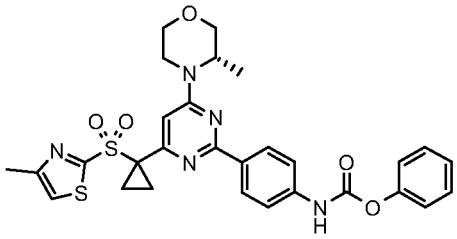
mTOR Kinase Assay (Echo): 0.000956μM

Example 25m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.77 - 1.80 (2H, m), 1.94 - 1.98 (2H, m), 2.48 - 2.49 (3H, m), 3.15 - 3.22 (1H, m), 3.48 (1H, td), 3.62 (1H, dd), 3.75 - 3.79 (4H, m), 3.97 (1H, dd), 4.13 - 4.20 (1H, m), 4.42 - 4.49 (1H, m), 6.79 (1H, s), 7.38 - 7.39 (1H, m), 7.44 - 7.49 (2H, m), 7.77 (1H, s), 7.84 - 7.85 (1H, m), 7.90 - 7.94 (2H, m), 8.38 (1H, s), 8.83 (1H, s).

mTOR Kinase Assay (Echo): 0.00025μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate

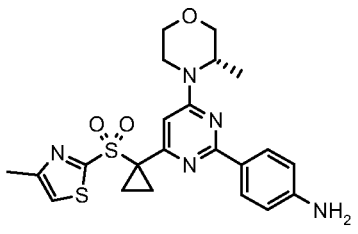


A solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]aniline (1.56 g, 3.31 mmol) in 1,4-dioxane (18 mL) was treated with sodium bicarbonate (0.445 g, 5.29 mmol). Phenyl chloroformate (0.5 mL, 3.99 mmol) was then added dropwise and the resulting suspension was stirred at RT, under nitrogen for 150 minutes. The reaction mixture was evaporated to dryness and the residue partitioned between DCM (100 mL) and water (50 mL). The organic layer washed with brine, dried ($MgSO_4$), filtered and evaporated to an amber gum/foam which was triturated under isohexane / diethyl ether (~1:1 v/v,~100 mL) with sonication and resultant solid collected by suction filtration and dried, under vacuum, at 50°C, to give the desired material as a beige solid (1.72 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.71 - 1.75 (2H, m), 1.87 - 1.91 (2H, m), 2.40 - 2.41 (3H, m), 3.12 (1H, td), 3.40 (1H, td), 3.55 (1H, dd), 3.69 (1H, d), 3.90 (1H, dd), 4.07 - 4.14 (1H, m), 4.35 - 4.44 (1H, m), 6.75 (1H, s), 7.16 - 7.23 (3H, m), 7.35 - 7.40 (2H, m), 7.47 - 7.50 (2H, m), 7.76 - 7.77 (1H, m), 7.90 - 7.93 (2H, m), 10.32 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 592.1; HPLC tR = 2.87 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]aniline

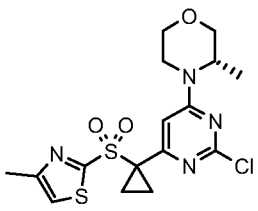


A mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidine (1.9 g, 4.58 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.36 g, 6.21 mmol) and 2M aqueous sodium carbonate solution (5.72 mL, 11.45 mmol) in a mixture of ethanol (5.50 mL), DME (11 mL), water (5.50 mL) and DMF (0.7 mL) was purged with nitrogen for 10 minutes before addition of bis(triphenylphosphine)palladium(II) chloride (0.161 g, 0.23 mmol). The reaction mixture was then heated to 85°C and stirred for 3 hours. The reaction mixture was cooled and partitioned between ethyl acetate (150 mL) and water (250 mL), the organic layer separated and aqueous re-extracted with ethyl acetate (100 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered and evaporated to dryness to afford the crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane. The isolated material was further purified by trituration with hot isohexane and diethyl ether to give the desired material as a beige solid (1.6 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.73 - 1.77 (2H, m), 1.92 - 1.95 (2H, m), 2.48 - 2.49 (3H, m), 3.15 (1H, td), 3.46 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.08 - 4.16 (1H, m), 4.37 - 4.45 (1H, m), 5.52 (2H, s), 6.50 - 6.54 (2H, m), 6.67 (1H, s), 7.70 - 7.74 (2H, m), 7.82 - 7.84 (1H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 472.1; HPLC tR = 2.24 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidine



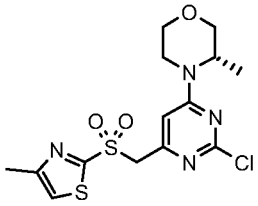
A solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (3.29 g, 8.46 mmol) in toluene (45 mL) was treated with 1,2-dibromoethane (1.4 mL, 16.25 mmol). Tetrabutylammonium bromide (0.273 g, 0.85 mmol) was then added followed by a solution of sodium hydroxide (3.4 g, 85.01 mmol) in water (3.4 mL). The resulting mixture was heated to 65°C, under an atmosphere of nitrogen, for 1 hour then at 75°C for 2.5 hours. The mixture was allowed to cool and partitioned between ethyl acetate (60 mL) and water (30 mL). The organic layer was separated, washed with brine,

dried ($MgSO_4$), filtered and evaporated to a brown gum. The crude product was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired material as a yellow gum (2.76 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.12 (3H, d), 1.63 - 1.66 (2H, m), 1.81 - 1.85 (2H, m), 2.39 - 2.41 (3H, m), 3.11 (1H, td), 3.32 - 3.38 (1H, m), 3.49 (1H, dd), 3.65 (1H, d), 3.82 - 3.92 (2H, m), 4.16 - 4.27 (1H, m), 6.83 (1H, s), 7.81 - 7.84 (1H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 415.10; HPLC tR = 2.12 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine

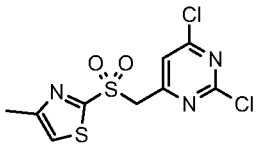


A solution of 2,4-dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (8.35 g, 25.76 mmol) in DCM (100 mL) was cooled to 4°C. Triethylamine (4.3 mL, 30.85 mmol) was then added and mixture stirred for 5 minutes before dropwise addition, over 10 minutes, of a solution of (S)-3-methylmorpholine (2.9 g, 28.67 mmol) in DCM (25 mL). The reaction mixture was then stirred in cooling bath for 45 minutes then at RT overnight. Water (200 mL) was added to reaction mixture and stirred for10 minutes before the organic layer was separated and aqueous layer extracted with DCM (50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated to afford the crude product, which was purified by flash silica chromatography, eluting with 50% ethyl acetate in isohexane, to give the desired material as a yellow gum (5.80 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 2.49 - 2.50 (3H, m), 3.18 (1H, td), 3.43 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.88 - 3.96 (2H, m), 4.15 - 4.29 (1H, m), 4.82 (2H, s), 6.80 (1H, s), 7.89 - 7.90 (1H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ =389.2; HPLC tR = 1.87min.

2,4-Dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine

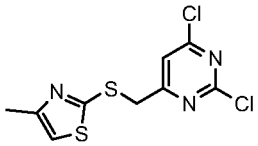


A solution of 2,4-dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfanylmethyl]pyrimidine (7.39 g, 25.29 mmol) in DCM (130 ml) was cooled to 4°C and treated portionwise, over 15 minutes with 3-chloroperoxybenzoic acid (13.60 g, 60.70 mmol). The resulting suspension was stirred in cooling bath for 15 minutes then at RT for 24 hours. A saturated aqueous solution of sodium bicarbonate (200 mL) was added to the reaction mixture and stirred for 30 minutes. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and evaporated to give the desired material as an oil which solidified on standing (8.40 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.47 - 2.49 (3H, m), 5.19 (2H, s), 7.84 (1H, s), 7.93 - 7.95 (1H, m).

LCMS Spectrum: m/z (ESI-) (M-H)- = 322.0; HPLC tR = 1.53 min.

2,4-Dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfanylmethyl]pyrimidine

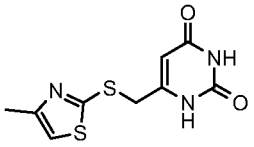


A suspension of 6-[(4-methyl-1,3-thiazol-2-yl)sulfanylmethyl]-1*H*-pyrimidine-2,4-dione (14.4 g, 56.40 mmol) in phosphorus oxychloride (60 mL, 643.70 mmol) was warmed to 100°C and stirred for 6 hours. The reaction mixture cooled before evaporating to a brown oil and partitioning between DCM (100 mL) and water (100 mL). With stirring solid sodium hydrogen carbonate was then added carefully to adjust the mixture to pH8, additional aliquots of water (100 mL) and DCM (100 mL) were added during this time. Additional DCM (100 mL) and water (100 mL) were added and the organic layer separated and the aqueous layer re-extracted with DCM (2 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to dryness to give the desired material as a tan solid (15.76 g). the material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.30 - 2.32 (3H, m), 4.55 (2H, s), 7.22 - 7.24 (1H, m), 7.84 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 292.1; HPLC tR = 2.36min.

6-[(4-Methyl-1,3-thiazol-2-yl)sulfanylmethyl]-1*H*-pyrimidine-2,4-dione

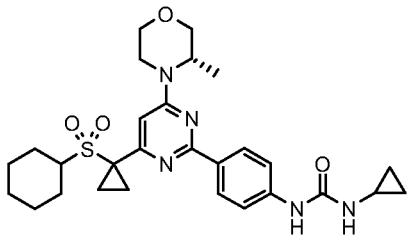


To a solution of 4-methylthiazole-2-thiol (10 g, 76.21 mmol) in DMF (150 mL) at RT was added DBU (14 mL, 93.80 mmol) dropwise over 5 minutes. The resulting solution was stirred at RT for 30 minutes. 6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (10 g, 62.28 mmol) was then added portionwise over a period of 20 minutes under nitrogen. The resulting solution was stirred at RT for 19 hours then the reaction mixture evaporated to dryness and the residue partitioned between DCM (150 mL) and water (150 mL). The solid precipitate was collected by filtration to give the desired material as a cream solid (11.1 g). Additional desired material (4.3 g) was obtained after the filtrate was acidified with 2M hydrochloric acid and the resultant precipitate collected by filtration.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.34 (3H, s), 4.08 (2H, s), 5.43 (1H, s), 7.27 (1H, s), 10.98 (2H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 256.2; HPLC tR = 0.58 min.

Example 26: 1-[4-[4-(1-Cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea



To cyclopropylamine (56 mg, 0.98 mmol) was added a solution of phenyl *N*-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (79.5 mg, 0.14 mmol) in DMF (2 mL). Triethylamine (0.067 mL, 0.48 mmol) was then added and the resultant mixture was heated to 50°C and stirred for 2 hours.

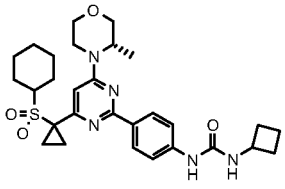
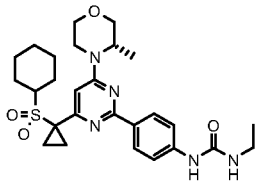
The reaction mixture was cooled and purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% TFA) and acetonitrile as eluants, followed by purification by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) in acetonitrile as eluants, to give the desired material as a white solid (28 mg).

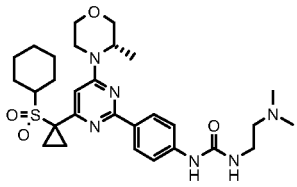
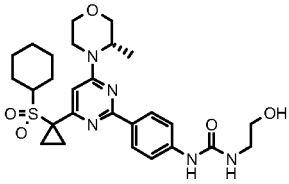
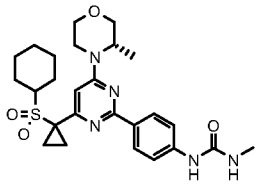
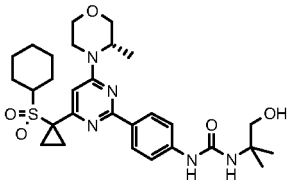
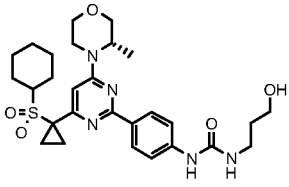
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.13 - 1.29 (6H, m), 1.37 - 1.66 (7H, m), 1.82 - 1.88 (2H, m), 2.26 - 2.34 (2H, m), 2.53 - 2.59 (1H, m), 3.16 - 3.25 (1H, m), 3.44 - 3.53 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.26 (1H, m), 4.49 - 4.59 (1H, m), 6.47 (1H, d), 6.76 (1H, s), 7.50 - 7.54 (2H, m), 8.19 - 8.23 (2H, m), 8.58 (1H, s).

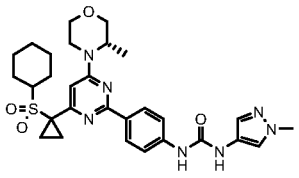
LCMS Spectrum: m/z (ESI+) (M+H)+ = 540; HPLC tR = 2.57 min.

mTOR Kinase Assay (Echo): 0.00605μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
26a		3-cyclobutyl-1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	554	2.81
26b		3-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	528	2.56

Example	Structure	NAME	LCMS MH+	Retention time (min)
26c		1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	571	2.53
26d		1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	544	2.15
26e		1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	514	2.39
26f		1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	572	2.27
26g		1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	558	2.21

Example	Structure	NAME	LCMS MH+	Retention time (min)
26h		1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	580	2.40

Example 26a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 - 1.28 (6H, m), 1.37 - 1.69 (9H, m), 1.81 - 1.92 (4H, m), 2.17 - 2.25 (2H, m), 2.26 - 2.34 (2H, m), 3.20 (1H, td), 3.44 - 3.52 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.09 - 4.25 (2H, m), 4.50 - 4.58 (1H, m), 6.49 (1H, d), 6.76 (1H, s), 7.47 - 7.50 (2H, m), 8.19 - 8.22 (2H, m), 8.60 (1H, s).
mTOR Kinase Assay (Echo): 0.00672μM

Example 26b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.13 - 1.29 (6H, m), 1.36 - 1.66 (7H, m), 1.81 - 1.89 (2H, m), 2.26 - 2.35 (2H, m), 3.09 - 3.16 (2H, m), 3.20 (1H, td), 3.45 - 3.53 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.25 (1H, m), 4.50 - 4.58 (1H, m), 6.20 (1H, t), 6.76 (1H, s), 7.48 - 7.52 (2H, m), 8.18 - 8.23 (2H, m), 8.70 (1H, s).
mTOR Kinase Assay (Echo): 0.0039μM

Example 26c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.12 - 1.29 (6H, m), 1.36 - 1.66 (7H, m), 1.82 - 1.88 (2H, m), 2.18 (6H, s), 2.27 - 2.35 (4H, m), 3.16 - 3.24 (3H, m), 3.44 - 3.52 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.25 (1H, m), 4.50 - 4.58 (1H, m), 6.17 (1H, t), 6.76 (1H, s), 7.47 - 7.51 (2H, m), 8.19 - 8.23 (2H, m), 8.90 (1H, s).
mTOR Kinase Assay (Echo): 0.119μM

Example 26d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 - 1.28 (6H, m), 1.38 - 1.65 (7H, m), 1.81 - 1.88 (2H, m), 2.27 - 2.34 (2H, m), 3.16 - 3.24 (3H, m), 3.44 - 3.52 (4H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.25 (1H, m), 4.50 - 4.58 (1H, m), 4.73 (1H, t), 6.27 (1H, t), 6.76 (1H, s), 7.48 - 7.51 (2H, m), 8.19 - 8.23 (2H, m), 8.83 (1H, s).
mTOR Kinase Assay (Echo): 0.0012μM

Example 26e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 - 1.29 (6H, m), 1.37 - 1.66 (7H, m), 1.82 - 1.88 (2H, m), 2.27 - 2.34 (2H, m), 2.66 (3H, d), 3.20 (1H, td), 3.45 - 3.53 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.25 (1H, m), 4.50 - 4.59 (1H, m), 6.09 (1H, q), 6.76 (1H, s), 7.49 - 7.53 (2H, m), 8.19 - 8.22 (2H, m), 8.77 (1H, s).

mTOR Kinase Assay (Echo): 0.00395μM

Example 26f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.12 - 1.29 (12H, m), 1.37 - 1.67 (7H, m), 1.82 - 1.88 (2H, m), 2.27 - 2.34 (2H, m), 3.20 (1H, td), 3.39 (2H, d), 3.45 - 3.53 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.25 (1H, m), 4.49 - 4.59 (1H, m), 4.95 (1H, t), 6.01 (1H, s), 6.75 (1H, s), 7.44 - 7.47 (2H, m), 8.18 - 8.22 (2H, m), 8.77 (1H, s).

mTOR Kinase Assay (Echo): 0.00457μM

Example 26g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 - 1.29 (6H, m), 1.37 - 1.66 (9H, m), 1.81 - 1.88 (2H, m), 2.27 - 2.34 (2H, m), 3.14 - 3.24 (3H, m), 3.44 - 3.52 (4H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.18 - 4.24 (1H, m), 4.47 (1H, t), 4.50 - 4.58 (1H, m), 6.23 (1H, t), 6.76 (1H, s), 7.48 - 7.52 (2H, m), 8.19 - 8.22 (2H, m), 8.74 (1H, s).

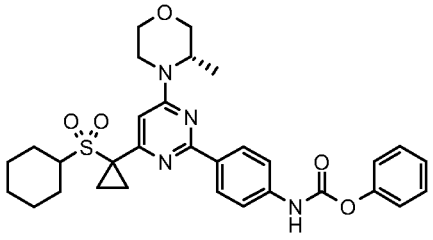
mTOR Kinase Assay (Echo): 0.00746μM

Example 26h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 - 1.30 (6H, m), 1.37 - 1.67 (7H, m), 1.82 - 1.89 (2H, m), 2.28 - 2.34 (2H, m), 3.21 (1H, td), 3.45 - 3.53 (2H, m), 3.64 (1H, dd), 3.74 - 3.79 (4H, m), 3.98 (1H, dd), 4.18 - 4.26 (1H, m), 4.51 - 4.59 (1H, m), 6.77 (1H, s), 7.39 (1H, d), 7.54 - 7.57 (2H, m), 7.77 (1H, s), 8.23 - 8.26 (2H, m), 8.42 (1H, s), 8.87 (1H, s).

mTOR Kinase Assay (Echo): 0.004μM

The preparation of phenyl *N*-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



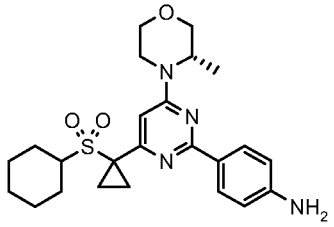
A suspension of 4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (615 mg, 1.35 mmol) in 1,4-dioxane (7 mL) was treated with sodium bicarbonate (182 mg, 2.17 mmol). Phenyl chloroformate (0.20 mL, 1.59 mmol) was then added dropwise and resultant mixture left to stir under nitrogen at RT overnight (~16 hours). The reaction mixture was evaporated to dryness and the residue partitioned between

DCM (10 mL) and water (10 mL). The organic layer was separated and evaporated to an amber gum which was azeotroped with diethyl ether to give the desired material as a beige solid (726 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 - 1.29 (6H, m), 1.37 - 1.48 (2H, m), 1.50 - 1.65 (5H, m), 1.81 - 1.87 (2H, m), 2.26 - 2.34 (2H, m), 3.22 (1H, td), 3.44 - 3.52 (2H, m), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.20 - 4.29 (1H, m), 4.52 - 4.60 (1H, m), 6.83 (1H, s), 7.23 - 7.30 (3H, m), 7.42 - 7.47 (2H, m), 7.63 - 7.67 (2H, m), 8.28 - 8.32 (2H, m), 10.45 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 577.1; HPLC tR = 3.12min.

4-[4-(1-Cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



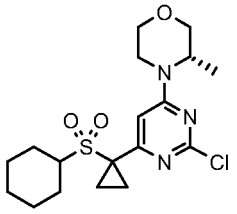
A mixture of 2-chloro-4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.78 g, 4.45 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.474 g, 6.73 mmol) in a mixture of DMF (8 mL), ethanol (8 mL), DME (8 mL) and water (20 mL) was treated with 2M aqueous sodium carbonate solution (11 mL, 22.00 mmol). The resulting mixture was purged with nitrogen for 10 minutes before addition of bis(triphenylphosphine)palladium(II) chloride (0.156 g, 0.22 mmol). The mixture was heated to 85°C and stirred, under nitrogen for 4 hours before being cooled and partitioned between ethyl acetate (100 mL) and water (100 mL). The biphasic mixture was filtered and the organic layer was separated. The aqueous layer was re-extracted with ethyl acetate (2 x 50 mL) and the combined organics were washed with brine, dried ($MgSO_4$) and evaporated to afford the crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired material as a beige solid (0.627 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 - 1.21 (6H, m), 1.31 - 1.49 (6H, m), 1.53 - 1.58 (1H, m), 1.74 - 1.82 (2H, m), 2.19 - 2.26 (2H, m), 3.07 - 3.14 (1H, m), 3.37 -

3.47 (2H, m), 3.55 (1H, dd), 3.68 (1H, d), 3.89 (1H, dd), 4.07 - 4.14 (1H, m), 4.40 - 4.48 (1H, m), 5.50 (2H, s), 6.54 (2H, d), 6.58 (1H, s), 7.98 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 457.3; HPLC tR = 2.55 min.

2-Chloro-4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

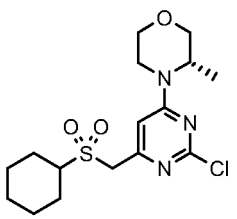


A solution of 2-chloro-4-(cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.8 g, 7.49 mmol) in toluene (40 mL) was treated with 1,2-dibromoethane (1.3 mL, 15.09 mmol). Tetrabutylammonium bromide (0.241 g, 0.75 mmol) was then added followed by a solution of sodium hydroxide (3.00 g, 74.89 mmol) in water (3 mL). The resulting mixture was heated to 64°C and stirred for 90 minutes. The reaction mixture was cooled before addition of ethyl acetate (50 mL) and water (20 mL). The mixture was stirred for 5 minutes then the organic layer separated, washed with brine (30 mL) and evaporated to afford the crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired compound as a pale yellow oil which crystallised on standing (1.785 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10 - 1.41 (8H, m), 1.48 - 1.55 (4H, m), 1.60 - 1.66 (1H, m), 1.77 - 1.84 (2H, m), 2.14 - 2.20 (2H, m), 3.16 - 3.24 (1H, m), 3.32 - 3.47 (2H, m), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 3.99 - 4.07 (1H, m), 4.32 - 4.43 (1H, m), 6.93 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 400.3; HPLC tR = 2.56 min.

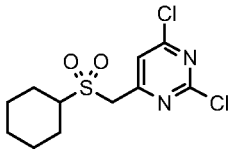
2-Chloro-4-(cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



To a solution of 2,4-dichloro-6-(cyclohexylsulfonylmethyl)pyrimidine (1.7g, 5.50 mmol) in DCM (25 ml), cooled with a water / ice bath, was added triethylamine (0.85 mL, 6.10 mmol). The resulting solution was treated, dropwise over 5 minutes, with a solution of (S)-3-methylmorpholine (0.658 g, 6.51 mmol) in DCM (5 mL). The mixture was stirred in cooling bath for 30 minutes then at RT for 3 hours. Water (25 mL) was added to the reaction mixture and stirred for 15 minutes. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to give the crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired material as a yellow oil which crystallised on standing (1.3 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 - 1.45 (8H, m), 1.63 - 1.69 (1H, m), 1.81 - 1.87 (2H, m), 2.11 - 2.17 (2H, m), 3.16 - 3.25 (2H, m), 3.45 (1H, td), 3.60 (1H, dd), 3.73 (1H, d), 3.92 - 4.05 (2H, m), 4.26 - 4.34 (1H, m), 4.40 (2H, s), 6.90 (1H, s).
LCMS Spectrum: m/z (ESI+) (M+H)+ =374.3; HPLC tR = 2.22 min.

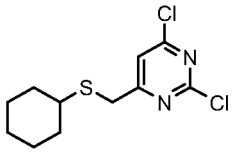
2,4-Dichloro-6-(cyclohexylsulfonylmethyl)pyrimidine



To a solution of 2,4-dichloro-6-(cyclohexylsulfanylmethyl)pyrimidine (4.23 g, 15.26 mmol) in DCM (90 mL), cooled in a water / ice bath, was added 3-chloroperoxybenzoic acid (8.55 g, 38.15 mmol) over a period of 30 minutes under nitrogen, so as to control temperature below 10°C. The resulting suspension was stirred at RT for 3 hours. Saturated aqueous sodium hydrogen carbonate solution (120 mL) was then carefully added portionwise and reaction mixture stirred for 30 minutes before separating the organic layer, drying ($MgSO_4$) and evaporating to give the desired material as an off white solid (4.90 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 - 1.46 (5H, m), 1.62 - 1.68 (1H, m), 1.81 - 1.87 (2H, m), 2.10 - 2.16 (2H, m), 3.22 (1H, tt), 4.74 (2H, s), 7.85 (1H, s).
LCMS Spectrum: m/z (ESI-) (M-H)- = 307.2; HPLC tR = 2.22 min.

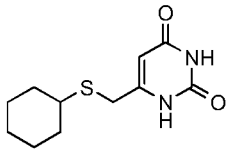
2,4-Dichloro-6-(cyclohexylsulfanylmethyl)pyrimidine



A suspension of 6-(cyclohexylsulfanylmethyl)-1*H*-pyrimidine-2,4-dione (6.4 g, 26.63 mmol) in phosphorus oxychloride (25 mL, 268.2 mmol) was warmed to 100°C, over a period of 15 minutes. The resulting dark orange solution was stirred at 100°C for 7 hours before being cooled and evaporated to a brown oil. The oil was partitioned between DCM (150 mL) and water (150 mL). With stirring solid sodium hydrogen carbonate was then added carefully to adjust the mixture to pH8, aliquots of water (100 mL) and DCM (50 mL) were added during addition. The organic layer was separated, the aqueous layer was re-extracted with more DCM (2 x 75 mL) and the combined organic layers washed with brine (200 mL), dried ($MgSO_4$) and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 15% ethyl acetate in isohexane, to give the desired material as an orange liquid (4.24 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 - 1.31 (5H, m), 1.51 - 1.57 (1H, m), 1.64 - 1.72 (2H, m), 1.86 - 1.92 (2H, m), 2.71 - 2.77 (1H, m), 3.85 (2H, s), 7.82 (1H, s).
LCMS Spectrum: m/z (ESI-) (M-H)- = 275.2 & 277.2 HPLC tR = 3.01 min.

6-(Cyclohexylsulfanylmethyl)-1*H*-pyrimidine-2,4-dione



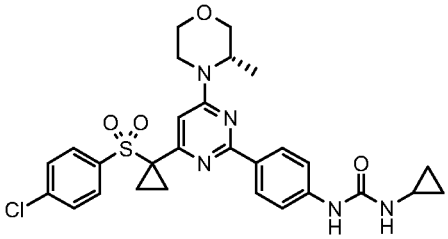
A solution of cyclohexanethiol (10 mL, 81.74 mmol) in DMF (150 mL) at RT was treated with DBU (14 mL, 93.80 mmol). The resulting solution was stirred at RT for 20 minutes then 6-(chloromethyl)-1*H*-pyrimidine-2,4-dione (10 g, 62.28 mmol) added portionwise over a period of 30 minutes, under nitrogen, so as to maintain the internal temperature below 35°C. The resulting solution was stirred at RT overnight. The reaction mixture was evaporated to dryness and the residue was partitioned between DCM (100 mL) and water (150 mL). On mixing a precipitate formed, this was removed by filtration to give the desired material as a

white solid (6.45 g). Additional desired material (3.62 g) was obtained by separating the filtrate, adjusting the aqueous layer to pH2 and collecting the resultant precipitate by filtration.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 - 1.34 (5H, m), 1.51 - 1.58 (1H, m), 1.63 - 1.72 (2H, m), 1.87 - 1.96 (2H, m), 2.65 - 2.72 (1H, m), 3.41 (2H, s), 5.49 (1H, s), 10.75 - 10.96 (2H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 241.3; HPLC tR = 0.99min.

Example 27: 1-[4-[4-[1-(4-Chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea



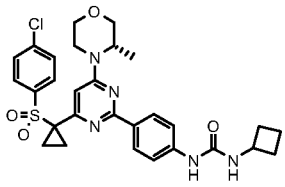
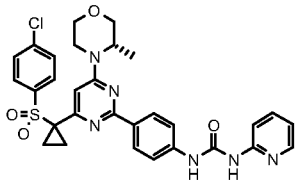
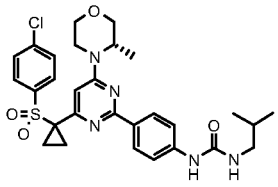
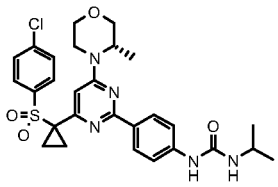
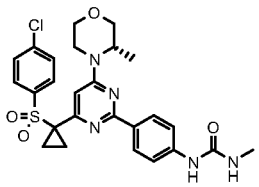
Cyclopropylamine (0.137 mL, 1.98 mmol) was added to phenyl *N*-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.25 mmol) in DMF (2 mL). The resulting solution was stirred at 60°C for 4 hours. The mixture was evaporated to dryness and the residue was partitioned between ethyl acetate (15 mL) and water (15 mL). The organic layer was washed with 1M aqueous citric acid (15 mL) and water (15 mL) and evaporated to dryness. The residue was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to afford the desired material as a white solid (62 mg).

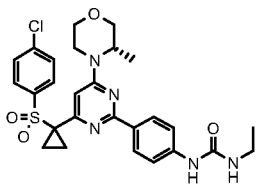
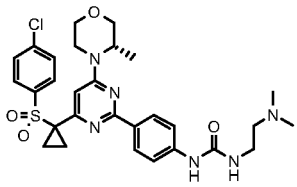
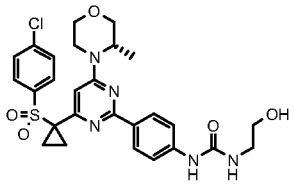
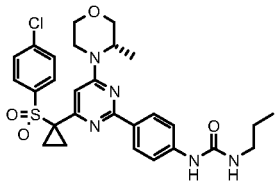
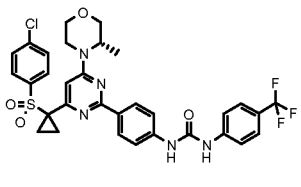
NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.69 (2H, m), 0.87 (2H, m), 1.32 (3H, d), 1.57 (1H, ddd), 1.64 (1H, ddd), 1.98 (2H, m), 2.63 (1H, m), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 4.04 (1H, dd), 4.14 (1H, d), 4.41 (1H, br.d), 4.87 (1H, s), 6.77 (1H, s), 6.93 (1H, s), 7.40 (2H, d), 7.42 (2H, d), 7.68 (2H, d), 7.99 (2H, d).

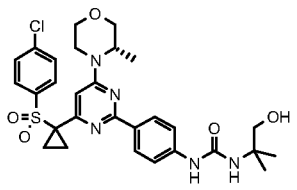
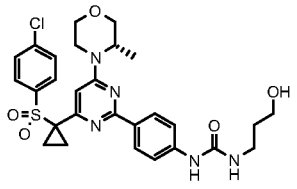
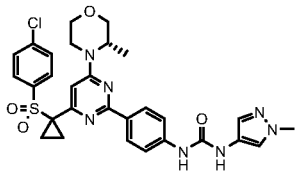
LCMS Spectrum: m/z (ESI+)(M+H)+ = 568, 570; HPLC tR = 2.33 min.

mTOR Kinase Assay (Echo): 0.00144μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
27a		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutylurea	582, 584	2.55
27b		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea	605, 607	2.73
27c		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	584, 586	2.63
27d		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea	570, 572	2.47
27e		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	542, 544	2.17

Example	Structure	NAME	LCMS MH+	Retention time (min)
27f		3-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	556, 558	2.33
27g		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	599, 601	2.23
27h		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	572, 574	2.00
27i		3-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea	570, 572	2.48
27j		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	672, 674	3.09

Example	Structure	NAME	LCMS MH+	Retention time (min)
27k		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	600, 602	2.28
27l		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	586, 588	2.04
27m		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	608, 610	2.38

Example 27a: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.59 (2H, m), 1.71 (2H, m), 1.84 (2H, m), 1.98 (2H, m), 2.38 (2H, m), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 4.04 (1H, dd), 4.13 (1H, d), 4.30 (1H, tt), 4.41 (1H, br.d), 4.82 (1H, d), 6.26 (1H, s), 6.76 (1H, s), 7.30 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

mTOR Kinase Assay (Echo): 0.00388μM

Example 27b: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.59 (1H, ddd), 1.66 (1H, ddd), 1.99 (2H, m), 3.30 (1H, ddd), 3.61 (1H, ddd), 3.75 (1H, dd), 3.83 (1H, d), 4.05 (1H, dd), 4.15 (1H, d), 4.42 (1H, m), 6.71 (1H, d), 6.78 (1H, s), 6.98 (1H, dd), 7.25 (1H, s), 7.41 (2H, d), 7.60 (2H, d), 7.66 (1H, ddd), 7.69 (2H, d), 8.03 (2H, d), 8.30 (1H, d), 11.92 (1H, s).

mTOR Kinase Assay (Echo): 0.00425μM

Example 27c: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.94 (6H, d), 1.31 (3H, d), 1.56 (1H, ddd), 1.63 (1H, ddd), 1.80 (1H, m), 1.98 (2H, m), 3.10 (2H, dd), 3.29 (1H, ddd), 3.59 (1H, ddd),

3.74 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.13 (1H, d), 4.41 (1H, br.d), 4.81 (1H, t), 6.41 (1H, s), 6.75 (1H, s), 7.30 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

mTOR Kinase Assay (Echo): 0.014μM

Example 27d: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.19 (6H, d), 1.31 (3H, d), 1.56 (1H, ddd), 1.63 (1H, ddd), 1.98 (2H, m), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.82 (1H, d), 4.03 (2H, m), 4.13 (1H, d), 4.41 (1H, d), 4.54 (1H, br.d), 6.31 (1H, s), 6.75 (1H, s), 7.29 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.97 (2H, d).

mTOR Kinase Assay (Echo): 0.00307μM

Example 27e: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.56 (1H, ddd), 1.62 (1H, ddd), 1.98 (2H, m), 2.87 (3H, d), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 4.04 (1H, dd), 4.13 (1H, d), 4.41 (1H, br.d), 4.65 (1H, q), 6.31 (1H, s), 6.76 (1H, s), 7.30 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

mTOR Kinase Assay (Echo): 0.000719μM

Example 27f: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.17 (3H, t), 1.31 (3H, d), 1.56 (1H, ddd), 1.62 (1H, ddd), 1.98 (2H, m), 3.28 (3H, ddd), 3.32 (3H, dq), 3.59 (1H, ddd), 3.74 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.13 (1H, d), 4.41 (1H, br.d), 4.71 (1H, t), 6.38 (1H, s), 6.75 (1H, s), 7.30 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

mTOR Kinase Assay (Echo): 0.000959μM

Example 27g: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.56 (1H, ddd), 1.63 (1H, ddd), 1.97 (2H, m), 2.31 (6H, s), 2.51 (2H, t), 3.28 (3H, ddd), 3.32 (3H, dt), 3.59 (1H, ddd), 3.74 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.14 (1H, d), 4.41 (1H, br.d), 5.25 (1H, br.t), 6.74 (1H, s), 7.26 (1H, s), 7.35 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.95 (2H, d).

mTOR Kinase Assay (Echo): 0.0189μM

Example 27h: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.56 (1H, ddd), 1.62 (1H, ddd), 1.98 (2H, m), 2.64 (1H, br.s), 3.28 (1H, ddd), 3.43 (2H, dt), 3.59 (1H, ddd), 3.73 (1H, dd), 3.75 (2H, m), 3.82 (1H, d), 4.04 (1H, dd), 4.12 (1H, d), 4.40 (1H, br.d), 5.27 (1H, t), 6.73 (1H, s), 6.81 (1H, s), 7.31 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

mTOR Kinase Assay (Echo): 0.0000856μM

Example 27i: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.94 (3H, t), 1.31 (3H, d), 1.56 (2H, m), 1.56 (1H, ddd), 1.63 (1H, ddd), 1.98 (2H, m), 3.24 (2H, dt), 3.30 (1H, dd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.13 (1H, d), 4.41 (1H, br.d), 4.74 (1H, t), 6.36 (1H, s), 6.75 (1H, s), 7.30 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

mTOR Kinase Assay (Echo): 0.00302μM

Example 27j: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.57 (1H, ddd), 1.63 (1H, ddd), 1.99 (2H, m), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 4.04 (1H, dd), 4.12 (1H, d), 4.40 (1H, br.d), 6.72 (1H, s), 6.77 (1H, s), 6.88 (1H, s), 7.37 (2H, d), 7.41 (2H, d), 7.50 (2H, d), 7.55 (2H, d), 7.69 (2H, d), 8.03 (2H, d).

mTOR Kinase Assay (Echo): 0.00761μM

Example 27k: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.57 (1H, ddd), 1.63 (1H, ddd), 1.98 (2H, m), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.64 (2H, d), 3.73 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.13 (1H, d), 4.40 (1H, br.d), 4.45 (1H, t), 4.88 (1H, s), 6.54 (1H, s), 6.75 (1H, s), 7.27 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.99 (2H, d).

mTOR Kinase Assay (Echo): 0.00462μM

Example 27l: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.56 (1H, ddd), 1.62 (1H, ddd), 1.71 (2H, tt), 1.98 (2H, m), 2.94 (1H, br.s), 3.28 (1H, ddd), 3.44 (2H, dt), 3.59 (1H, ddd), 3.72 (1H, br.s), 3.73 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.12 (1H, d), 4.40 (1H, br.d), 5.13 (1H, t), 6.62 (1H, s), 6.74 (1H, s), 7.30 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

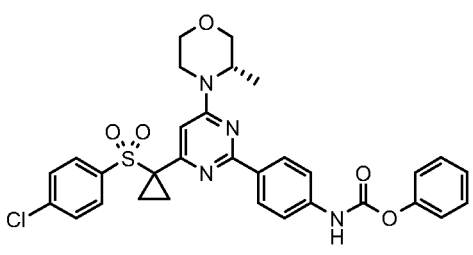
mTOR Kinase Assay (Echo): 0.00112μM

Example 27m: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.57 (1H, ddd), 1.63 (1H, ddd), 1.98 (2H, m), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 3.90 (3H, s), 4.04 (1H, dd), 4.13 (1H, d), 4.40 (1H, br.d), 6.12 (1H, s), 6.63 (1H, s), 6.76 (1H, s), 7.35 (2H, d), 7.40 (2H, d), 7.41 (1H, s), 7.60 (1H, s), 7.67 (2H, d), 7.99 (2H, d).

mTOR Kinase Assay (Echo): 0.00144μM

The preparation of phenyl *N*-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

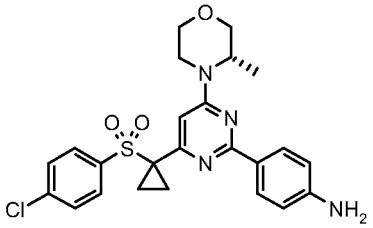


Phenyl chloroformate (0.829 mL, 6.60 mmol) was added dropwise to 4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (3.20 g, 6.60 mmol) and sodium hydrogen carbonate (0.554 g, 6.60 mmol) in 1,4-dioxane (150 mL) at RT. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (400 mL) and washed with water (2 x 400 mL) and saturated brine (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to afford the desired material as a white dry film (3.78 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.57 (1H, ddd), 1.64 (1H, ddd), 1.99 (2H, m), 3.30 (1H, ddd), 3.60 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 4.05 (1H, dd), 4.15 (2H, br.d), 4.42 (1H, br.d), 6.78 (1H, s), 7.04 (1H, s), 7.20 (2H, d), 7.25 (2H, dd), 7.40 (2H, d), 7.40 (2H, dd), 7.45 (2H, d), 7.68 (2H, d), 8.02 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 605, 607; HPLC tR = 3.15 min.

4-[4-[1-(4-Chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

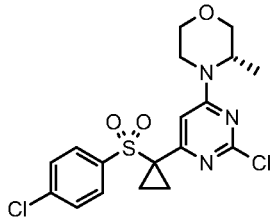


Sodium carbonate (13.45 mL, 26.89 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.637 g, 7.47 mmol), 2-chloro-4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.20 g, 7.47 mmol) in a mixture of DME (20 mL), DMF (20 mL), ethanol (20 mL) and water (40 mL) at RT under nitrogen. The mixture was degassed and purged with nitrogen before bis(triphenylphosphine)palladium(II) chloride (0.262 g, 0.37 mmol) was added and the mixture stirred at 80°C under nitrogen for 90 minutes. The reaction mixture was concentrated and diluted with ethyl acetate (250 mL), and washed sequentially with water (2 x 200 mL) and saturated brine (150 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 45% ethyl acetate in isohexane, to afford the desired material as a beige dry film (3.32 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.30 (3H, d), 1.56 (1H, ddd), 1.62 (1H, ddd), 1.96 (2H, m), 3.27 (1H, ddd), 3.59 (1H, ddd), 3.73 (1H, dd), 3.81 (1H, d), 3.86 (2H, s), 4.03 (1H, dd), 4.13 (1H, br.d), 4.41 (1H, br.d), 6.63 (2H, d), 6.70 (1H, s), 7.40 (2H, d), 7.67 (2H, d), 7.85 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 485, 487; HPLC tR = 2.70 min.

2-Chloro-4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



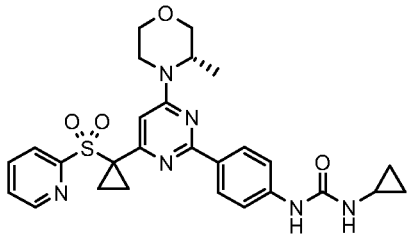
10N Sodium hydroxide solution (7.46 mL, 74.57 mmol) was added to 2-chloro-4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.00 g, 7.46 mmol), 1,2-dibromoethane (1.285 mL, 14.91 mmol) and tetrabutylammonium bromide (0.240 g, 0.75 mmol) in toluene (50 mL). The resulting solution was stirred at 60°C for 1 hour. The reaction mixture was concentrated, diluted with ethyl acetate (300 mL), washed with water (2 x 300 mL) and saturated brine (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to afford the desired material as a white dry film (2.85 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.54 (1H, ddd), 1.60 (1H, ddd), 1.95 (2H, m), 3.27 (1H, ddd), 3.54 (1H, ddd), 3.69 (1H, dd), 3.79 (1H, d), 4.01 (2H, m), 4.27 (1H, br.s), 6.87 (1H, s), 7.46 (2H, d), 7.64 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 428, 430; HPLC tR = 2.51 min.

The preparation of 2-chloro-4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 28: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea

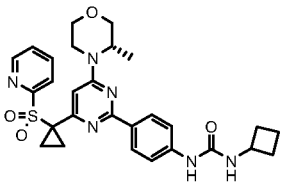


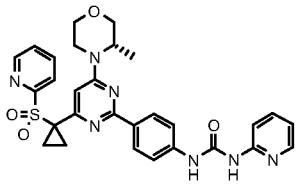
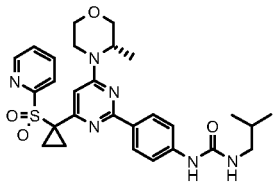
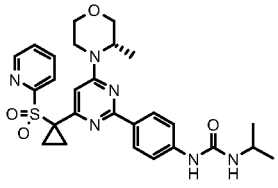
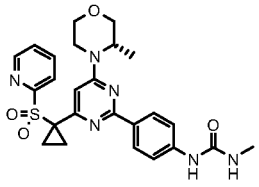
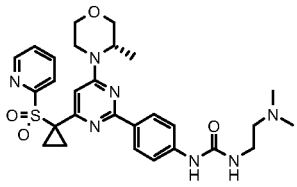
Cyclopropylamine (0.76 mmol) was added in one portion to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (104 mg, 0.19 mmol), in DMF (2 mL) at RT under nitrogen. The resulting solution was stirred at RT for 60 minutes. The reaction mixture was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to afford the desired material as a white solid (49 mg).

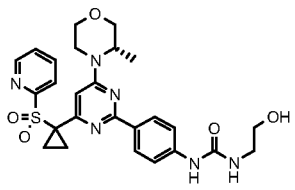
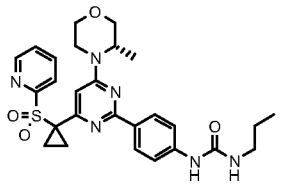
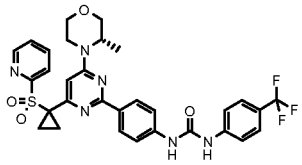
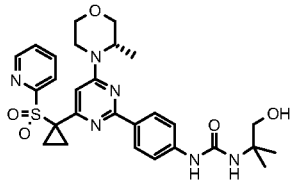
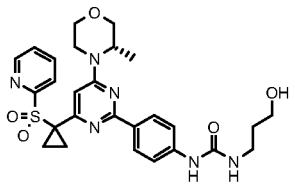
NMR Spectrum: ^{1}H NMR (399.902 DMSO-d_6) δ 0.33 (2H, s), 0.54 - 0.60 (2H, m), 1.06 - 1.10 (3H, m), 1.62 - 1.70 (2H, m), 1.92 (2H, s), 3.01 - 3.11 (1H, m), 3.37 (1H, t), 3.52 (1H, d), 3.66 (1H, d), 3.87 (1H, d), 4.00 - 4.11 (1H, m), 4.32 (1H, s), 6.33 (1H, s), 6.59 (1H, s), 7.29 (2H, d), 7.61 - 7.69 (3H, m), 7.89 - 7.93 (1H, m), 7.98 - 8.03 (1H, m), 8.41 (1H, s), 8.75 (1H, s); LCMS Spectrum: m/z (ESI+)(M+H)+ = 535.4; HPLC tR = 1.91 min.

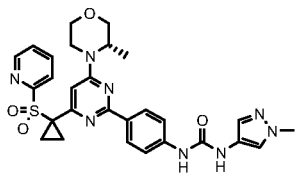
mTOR Kinase Assay (Echo): 0.000816μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
28a		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	549.4	2.13

Example	Structure	NAME	LCMS MH+	Retention time (min)
28b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea	572.4	2.32
28c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	551.4	2.22
28d		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-ylurea	537.9	2.06
28e		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	509.4	1.73
28f		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	564.4	1.81

Example	Structure	NAME	LCMS MH+	Retention time (min)
28g		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	539.4	1.6
28h		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-propylurea	537.4	2.07
28i		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	639.4	2.82
28j		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	567.4	1.87
28k		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	553.4	1.63

Example	Structure	NAME	LCMS MH+	Retention time (min)
28l		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	575.4	1.8

Example 28a: ^{1}H NMR (399.902 DMSO-d_6) δ 1.16 (d, 3H), 1.57 - 1.68 (m, 2H), 1.70 - 1.78 (m, 2H), 1.80 - 1.92 (m, 2H), 1.96 - 2.04 (m, 2H), 2.17 - 2.26 (m, 2H), 3.10 - 3.18 (m, 1H), 3.41 - 3.49 (m, 1H), 3.57 - 3.63 (m, 1H), 3.75 (d, 1H), 3.93 - 3.98 (m, 1H), 4.09 - 4.19 (m, 2H), 4.40 (s, 1H), 6.44 (d, 1H), 6.67 (s, 1H), 7.34 (d, 2H), 7.72 (d, 2H), 7.73 - 7.77 (m, 1H), 7.99 (d, 1H), 8.06 - 8.11 (m, 1H), 8.52 (s, 1H), 8.81 - 8.84 (m, 1H).

mTOR Kinase Assay (Echo): 0.00253μM

Example 28b: ^{1}H NMR (399.902 DMSO-d_6) δ 1.18 (d, 3H), 1.71 - 1.82 (m, 2H), 1.98 - 2.05 (m, 2H), 3.11 - 3.21 (m, 1H), 3.42 - 3.51 (m, 1H), 3.59 - 3.64 (m, 1H), 3.76 (d, 1H), 3.94 - 4.00 (m, 1H), 4.15 (d, 1H), 4.42 (s, 1H), 6.71 (s, 1H), 7.02 - 7.07 (m, 1H), 7.50 (d, 2H), 7.56 - 7.60 (m, 1H), 7.75 - 7.80 (m, 2H), 7.81 (d, 2H), 7.99 - 8.02 (m, 1H), 8.08 - 8.13 (m, 1H), 8.29 - 8.32 (m, 1H), 8.83 - 8.85 (m, 1H), 9.42 - 9.44 (m, 1H), 10.53 (s, 1H).

mTOR Kinase Assay (Echo): 0.00149μM

Example 28c: ^{1}H NMR (399.902 DMSO-d_6) δ 0.79 (d, 6H), 1.07 (d, 3H), 1.57 - 1.68 (m, 3H), 1.88 - 1.92 (m, 2H), 2.84 (t, 2H), 3.00 - 3.09 (m, 1H), 3.31 - 3.40 (m, 1H), 3.48 - 3.53 (m, 1H), 3.65 (d, 1H), 3.84 - 3.89 (m, 1H), 4.00 - 4.07 (m, 1H), 4.30 (s, 1H), 6.13 (t, 1H), 6.57 (s, 1H), 7.24 - 7.28 (m, 2H), 7.62 (d, 2H), 7.64 - 7.67 (m, 1H), 7.88 - 7.91 (m, 1H), 7.97 - 8.02 (m, 1H), 8.51 (s, 1H), 8.72 - 8.74 (m, 1H).

mTOR Kinase Assay (Echo): 0.00847μM

Example 28d: ^{1}H NMR (399.902 DMSO-d_6) δ 1.11 (d, 6H), 1.16 (d, 3H), 1.70 - 1.79 (m, 2H), 1.96 - 2.04 (m, 2H), 3.10 - 3.18 (m, 1H), 3.41 - 3.49 (m, 1H), 3.57 - 3.63 (m, 1H), 3.72 - 3.83 (m, 2H), 3.93 - 3.99 (m, 1H), 4.13 (d, 1H), 4.40 (s, 1H), 6.04 (d, 1H), 6.67 (s, 1H), 7.34 (d, 2H), 7.72 (d, 2H), 7.74 - 7.77 (m, 1H), 7.98 - 8.01 (m, 1H), 8.06 - 8.12 (m, 1H), 8.49 (s, 1H), 8.82 - 8.84 (m, 1H).

mTOR Kinase Assay (Echo): 0.00237μM

Example 28e: ^{1}H NMR (399.902 DMSO-d_6) δ 1.16 (d, 3H), 1.70 - 1.80 (m, 2H), 1.96 - 2.03 (m, 2H), 2.66 (d, 3H), 3.10 - 3.18 (m, 1H), 3.41 - 3.49 (m, 1H), 3.58 - 3.63 (m, 1H), 3.75 (d, 1H), 3.93 - 3.98 (m, 1H), 4.13 (d, 1H), 4.41 (s, 1H), 6.05 (q, 1H), 6.67 (s, 1H), 7.37 (d, 2H), 7.72 (d, 2H), 7.73 - 7.77 (m, 1H), 7.99 (d, 1H), 8.07 - 8.12 (m, 1H), 8.70 (s, 1H), 8.82 - 8.84 (m, 1H).

mTOR Kinase Assay (Echo): 0.000434μM

Example 28f: ^{1}H NMR (399.902 DMSO-d_6) δ 1.17 (d, 3H), 1.69 - 1.80 (m, 2H), 1.97 - 2.03 (m, 2H), 2.19 (s, 6H), 2.34 (t, 3H), 3.10 - 3.22 (m, 3H), 3.41 - 3.49 (m, 1H), 3.58 - 3.63 (m, 1H), 3.75 (d, 1H), 3.94 - 3.98 (m, 1H), 4.12 (d, 1H), 4.40 (s, 1H), 6.15 (t, 1H), 6.67 (s, 1H), 7.35 (d, 2H), 7.72 (d, 2H), 7.74 - 7.78 (m, 1H), 8.00 (d, 1H), 8.09 (t, 1H), 8.81 - 8.87 (m, 2H).

mTOR Kinase Assay (Echo): 0.0674μM

Example 28g: ^{1}H NMR (399.902 DMSO-d_6) δ 1.14 - 1.21 (m, 3H), 1.70 - 1.79 (m, 2H), 1.97 - 2.04 (m, 2H), 3.10 - 3.24 (m, 3H), 3.41 - 3.51 (m, 3H), 3.57 - 3.65 (m, 1H), 3.75 (d, 1H), 3.93 - 3.99 (m, 1H), 4.13 (d, 1H), 4.41 (s, 1H), 4.73 (t, 1H), 6.23 (t, 1H), 6.67 (s, 1H), 7.35 (d, 2H), 7.70 - 7.77 (m, 3H), 7.99 (d, 1H), 8.09 (t, 1H), 8.76 (s, 1H), 8.83 (d, 1H).

mTOR Kinase Assay (Echo): 0.0118μM

Example 28h: ^{1}H NMR (399.902 DMSO-d_6) δ 0.87 - 0.94 (m, 3H), 1.15 - 1.21 (m, 3H), 1.42 - 1.52 (m, 2H), 2.01 (s, 2H), 3.03 - 3.20 (m, 3H), 3.47 (t, 1H), 3.62 (d, 1H), 3.76 (d, 1H), 3.97 (d, 1H), 4.15 (d, 1H), 4.42 (s, 1H), 6.20 (s, 1H), 6.69 (s, 1H), 7.37 (d, 2H), 7.70 - 7.79 (m, 3H), 7.98 - 8.03 (m, 1H), 8.07 - 8.14 (m, 1H), 8.63 (s, 1H), 8.84 (s, 1H).

mTOR Kinase Assay (Echo): 0.00093μM

Example 28i: ^{1}H NMR (399.902 DMSO-d_6) δ 1.18 (d, 4H), 1.72 - 1.79 (m, 2H), 2.00 - 2.02 (m, 2H), 3 (d, 1H), 3.11 - 3.20 (m, 1H), 3.43 - 3.50 (m, 2H), 3.59 - 3.64 (m, 1H), 3.75 (d, 1H), 3.94 - 3.99 (m, 2H), 4.14 (d, 1H), 4.42 (s, 1H), 6.70 (s, 1H), 7.45 (d, 2H), 7.67 (q, 4H), 7.74 - 7.82 (m, 3H), 8.08 - 8.13 (m, 1H), 8.82 - 8.85 (m, 1H), 9.01 (s, 1H), 9.11 (s, 1H).

mTOR Kinase Assay (Echo): 0.00153μM

Example 28j: ^{1}H NMR (399.902 DMSO-d_6) δ 1.16 (d, 3H), 1.24 (s, 6H), 1.68 - 1.80 (m, 2H), 1.96 - 2.04 (m, 2H), 3.09 - 3.18 (m, 1H), 3.39 (d, 2H), 3.41 - 3.49 (m, 1H), 3.58 - 3.63 (m, 1H), 3.75 (d, 1H), 3.93 - 3.98 (m, 1H), 4.13 (d, 1H), 4.40 (s, 1H), 4.96 (t, 1H), 5.98 (s, 1H), 6.67 (s, 1H), 7.32 (d, 2H), 7.71 (d, 2H), 7.74 - 7.78 (m, 1H), 7.99 (d, 1H), 8.09 (t, 1H), 8.70 (s, 1H), 8.82 - 8.85 (m, 1H).

mTOR Kinase Assay (Echo): 0.00557μM

Example 28k: ^{1}H NMR (399.902 DMSO-d_6) δ 1.17 (d, 3H), 1.56 - 1.64 (m, 2H), 1.69 - 1.80 (m, 2H), 1.96 - 2.04 (m, 2H), 3.10 - 3.20 (m, 3H), 3.41 - 3.51 (m, 3H), 3.58 - 3.63 (m, 1H), 3.74 (d, 1H), 3.93 - 3.98 (m, 1H), 4.13 (d, 1H), 4.40 (s, 1H), 4.48 (t, 1H), 6.19 (t, 1H), 6.67 (s, 1H), 7.36 (d, 2H), 7.72 (d, 2H), 7.73 - 7.77 (m, 1H), 7.99 (d, 1H), 8.09 (t, 1H), 8.67 (s, 1H), 8.82 - 8.84 (m, 1H).

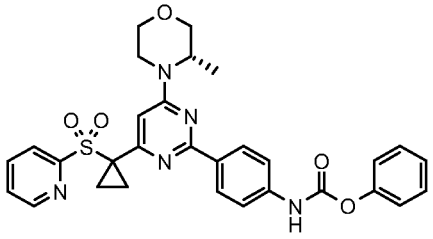
mTOR Kinase Assay (Echo): 0.000954μM

Example 28l: ^{1}H NMR (399.902 DMSO-d_6) δ 1.17 (d, 3H), 1.69 - 1.81 (m, 2H), 1.96 - 2.05 (m, 2H), 3.10 - 3.19 (m, 1H), 3.42 - 3.50 (m, 1H), 3.58 - 3.64 (m, 1H), 3.75 (d, 1H), 3.79 (s, 3H), 3.93 - 3.99 (m, 1H), 4.14 (d, 1H), 4.41 (s, 1H), 6.68 (s, 1H), 7.38 - 7.44 (m, 3H), 7.73 - 7.78 (m, 4H), 8.00 (d, 1H), 8.07 - 8.12 (m, 1H), 8.37 (s, 1H), 8.80 (s, 1H), 8.82 - 8.85 (m, 1H).

mTOR Kinase Assay (Echo): 0.000442μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate

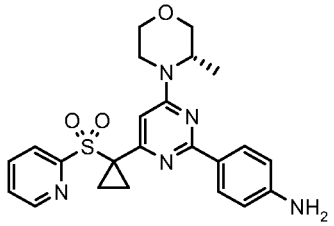


Phenyl chloroformate (0.693 g, 4.43 mmol) was added dropwise to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (2.0 g, 4.43 mmol) and sodium hydrogen carbonate (0.744 g, 8.86 mmol) in dioxane (40 mL) at RT. The resulting slurry was stirred at RT for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 0% - 20% ethyl acetate in DCM, to afford the desired material as a yellow gum (2.07 g).

NMR spectrum: ^{1}H NMR (399.902 $CDCl_3$) δ 1.23 (5H, d), 1.61 - 1.71 (2H, m), 2.06 - 2.15 (2H, m), 3.17 - 3.24 (1H, m), 3.47 - 3.54 (1H, m), 3.75 (1H, d), 4.05 - 4.11 (2H, m), 4.35 (1H, s), 6.82 (1H, s), 6.95 (1H, s), 7.13 (2H, m), 7.16 - 7.21 (1H, m), 7.31 - 7.37 (4H, m), 7.38 - 7.43 (1H, m), 7.73 - 7.77 (1H, m), 7.86 (1H, d), 7.93 - 7.97 (2H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 572.6; HPLC tR = 2.81 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline

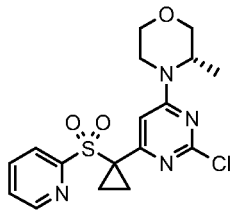


Sodium carbonate (20.51 mL, 41.03 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.498 g, 11.4 mmol) and 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidine (4.5 g, 11.40 mmol) in a mixture of DME (20 mL), ethanol (20 mL), DMF (20 mL) and water (40 mL). The mixture was purged with nitrogen then bis(triphenylphosphine)palladium(II) chloride (0.4 g, 0.57 mmol) was added and the resulting suspension was stirred at 80°C for 90 minutes. The reaction mixture was concentrated, diluted with ethyl acetate (150 mL), and washed sequentially with water (2 x 150 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 45% ethyl acetate in DCM, to afford the desired material as a beige solid (3.64 g).

NMR spectrum: ^{1}H NMR (399.902 $CDCl_3$) δ 1.20 (3H, d), 1.60 - 1.72 (2H, m), 2.04 - 2.12 (2H, m), 3.14 - 3.22 (1H, m), 3.46 - 3.53 (1H, m), 3.71 - 3.78 (3H, m), 3.92 - 3.96 (1H, m), 4.02 - 4.08 (1H, m), 4.33 (1H, s), 6.53 (2H, d), 6.76 (1H, s), 7.37 - 7.41 (1H, m), 7.72 - 7.77 (1H, m), 7.78 - 7.86 (3H, m), 8.64 - 8.66 (1H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 452.6; HPLC tR = 1.40 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidine

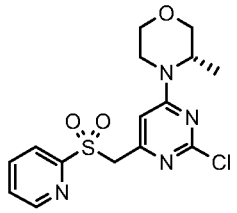


1,2-Dibromoethane (5.61 mL, 65.08 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine (6 g, 16.27 mmol), 10N sodium hydroxide solution (32.5 mL, 325.35 mmol) and tetrabutylammonium bromide (0.524 g, 1.63 mmol) in toluene (400 mL). The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was concentrated and diluted with ethyl acetate (150 mL), then washed with water (2 x 100 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 20% ethyl acetate in DCM, to afford the desired material as a white dry film (3.02 g).

NMR spectrum: ^{1}H NMR (399.902 $CDCl_3$) δ 1.22 (3H, d), 1.56 - 1.67 (2H, m), 1.97 - 2.07 (2H, m), 3.14 - 3.22 (1H, m), 3.41 - 3.49 (1H, m), 3.58 - 3.62 (1H, m), 3.70 (1H, d), 3.89 - 3.99 (2H, m), 4.21 (1H, s), 7.02 (1H, s), 7.44 - 7.48 (1H, m), 7.81 - 7.89 (2H, m), 8.62 - 8.64 (1H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 395.4; HPLC tR = 1.98 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine



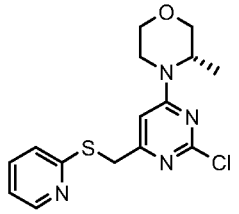
A 35% aqueous solution of hydrogen peroxide (8.26 mL, 93.53 mmol) was added dropwise to a stirred solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfanylmethyl)pyrimidine (10.5g, 31.17 mmol), sodium tungstate dihydrate (0.206 g, 0.62 mmol) and 2N Sulfuric acid (0.6 mL) in dioxane (300 mL) and then the solution warmed to 55ºC. The solution was stirred at 55°C for 4 hours. Further hydrogen peroxide (8.26 mL) was added and the mixture stirred at 50ºC for 18 hours. 3-Chloroperoxybenzoic acid (5.38 g,

31.17 mmol) was added and the mixture stirred at RT for 2 hours. The solution was diluted with water (500 mL) and cooled to 20ºC. A 10% solution of sodium metabisulfite was added to destroy any remaining peroxide and the solution was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and filtered. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a yellow gum (10.5 g,).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.24 (d, 3H), 3.20 (m, 1H), 3.46 (m, 1H), 3.61 (d, 1H), 3.71 (d, 1H), 3.90 - 3.98 (m, 2H), 4.21 (s, 1H), 4.51 (s, 2H), 6.50 (s, 1H), 7.51 - 7.53 (m, 1H), 7.86 - 7.95 (m, 2H), 8.72 - 8.74 (m, 1H)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 369.4; HPLC tR = 1.73 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfanylmethyl)pyrimidine



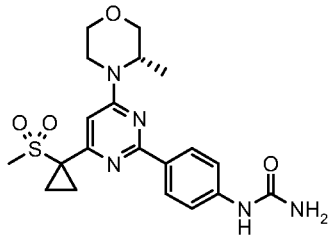
DIPEA (8.77 ml, 50.71 mmol) was added to 2-mercaptopyridine (3.80 g, 34.22 mmol), in DMF (300 mL) at RT in an atmosphere of nitrogen. The resulting solution was stirred at RT for 15 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (11 g, 31.11 mmol) was added portionwise over 5 minutes and the mixture stirred at RT for 3 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (200 mL) and washed sequentially with saturated sodium hydrogen carbonate solution (100 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a tan oil (10.50 g). NMR shows the presence of 0.6 eq. of 3-chlorobenzoic acid. This material was used in the subsequent step without further purification.

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.23 (d, 3H), 3.17 - 3.25 (m, 1H), 3.46 - 3.54 (m, 1H), 3.62 - 3.67 (m, 1H), 3.74 (d, 1H), 3.93 - 4.01 (m, 2H), 4.20 (s, 1H), 4.29 - 4.38 (m, 2H), 6.60 (s, 1H), 6.99 - 7.02 (m, 1H), 7.20 (d, 1H), 7.47 - 7.51 (m, 1H), 8.40 - 8.42 (m, 1H).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 337.5; HPLC tR = 2.19 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 29: [4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



6-Aminopyridin-2(1*H*)-one hydrochloride salt (0.218 g, 1.49 mmol) was added to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (0.151 g, 0.30 mmol) and triethylamine (0.249 mL, 1.78 mmol) in DMF (2 mL) at RT. The resulting solution was stirred at 50°C for 1 day. The solution was cooled and purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (0.094 g).

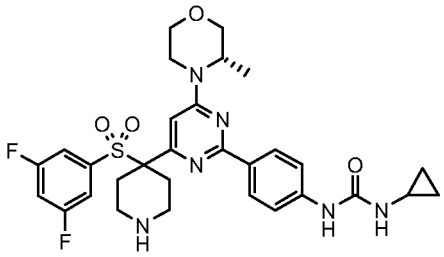
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22-1.25(3H, d), 1.55-1.58(2H, q), 1.66-1.69(2H, q), 3.17-3.26(1H, td), 3.30(3H, s), 3.45-3.52(1H, td), 3.62-3.65(1H, dd), 3.75-3.78(1H, d), 3.96-3.99(1H, dd), 4.20-4.23(1H, d), 4.57(1H, bs), 5.91(2H, s), 6.77(1H, s), 7.50-7.52(2H, q), 8.19-8.21(2H, q), 8.76(1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=432; HPLC tR=1.66 min.

mTOR Kinase Assay (Echo): 0.0042μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 30: 3-Cyclopropyl-1-[4-[4-[4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

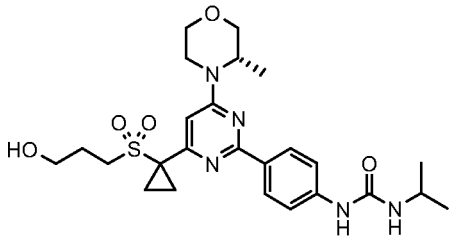


1-Chloroethyl chloroformate (0.015 mL, 0.14 mmol) and 1-[4-[4-[1-benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea (50 mg, 0.07 mmol) were dissolved in DCM (1 mL) and sealed into a microwave tube. The reaction was heated to 110°C for 5 minutes in a microwave reactor and then cooled to RT. Methanol (1 mL) was added and the mixture was heated to 110°C for 5 minutes in a microwave reactor and then cooled to RT. The mixture was purified by ion exchange chromatography using an SCX column, eluting with methanol followed by 2M ammonia in methanol. The isolated material was further purified by chromatography on silica, eluting with 2% methanol in DCM to 20% methanol in DCM containing 1% ammonia. The isolated material was triturated with diethyl ether to give the desired material as a colourless solid (26 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.68 - 0.72 (2H, m), 0.86 - 0.90 (2H, m), 1.36 (3H, d), 2.27 - 2.36 (2H, m), 2.52 - 2.65 (3H, m), 2.70 - 2.79(2H, m), 3.10 - 3.15 (2H, m), 3.34 (1H, dt), 3.64 (1H, dt), 3.77 - 3.87 (2H, m), 4.05 - 4.18 (2H, m), 4.43 - 4.52 (1H, m), 4.91 (1H, s), 6.65 (1H, s), 6.81 - 6.87 (1H, m), 6.95 - 7.02 (3H, m), 7.39 (2H, d), 7.93 (2H, d).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 613.5; HPLC tR = 2.16 min.
mTOR Kinase Assay (Echo): 0.025μM

The preparation of 1-[4-[4-[1-benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea was described earlier.

Example 31: 1-[4-[4-[1-(3-Hydroxypropylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea



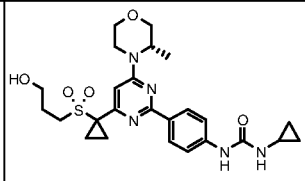
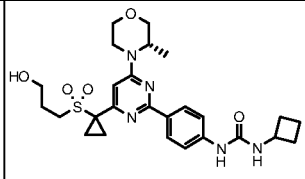
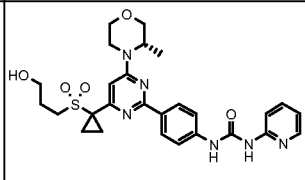
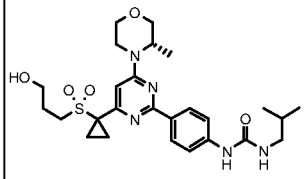
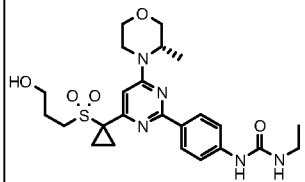
Triethylamine (0.126 mL, 0.90 mmol) was added to phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.18 mmol) and propan-2-amine (0.078 mL, 0.90 mmol) in NMP (2 mL) at RT under air. The resulting solution was stirred at RT for 1 hour. The crude product was purified by preparative, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (65 mg).

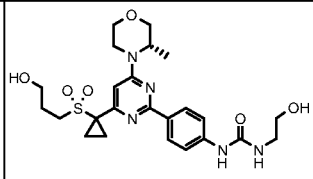
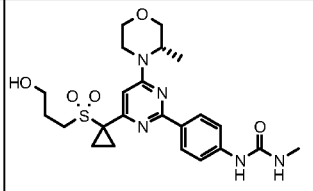
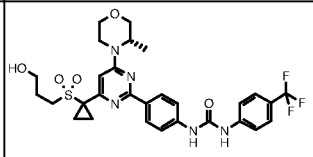
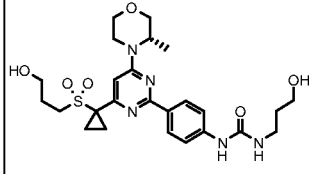
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.22 (3H, d), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 3.16 - 3.23 (1H, m), 3.31 - 3.34 (1H, m), 3.44 - 3.55 (4H, m), 3.61 - 3.64 (1H, m), 3.73 - 3.81 (2H, m), 3.95 - 3.99 (1H, m), 4.16 - 4.26 (1H, m), 4.52 - 4.59 (1H, m), 4.73 (1H, t), 6.08 (1H, d), 6.77 (1H, s), 7.47 (2H, d), 8.20 (2H, d), 8.57 (1H, s)

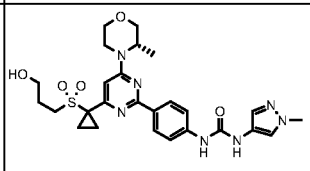
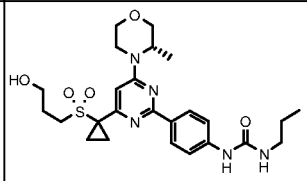
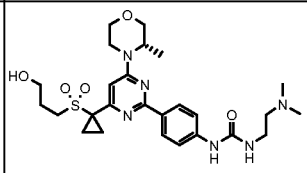
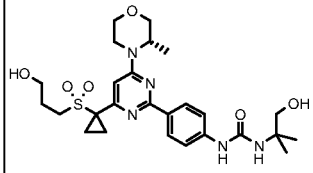
LCMS Spectrum: m/z (ESI+)(M+H)+ = 518; HPLC tR = 2.04min.

mTOR Kinase Assay (Echo): 0.00452μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
31a		3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	516	1.74
31b		3-cyclobutyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	530	1.94
31c		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea	553	2.10
31d		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	532	2.02
31e		1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	504	1.71

Example	Structure	NAME	LCMS MH+	Retention time (min)
31f		3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	520	1.49
31g		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	490	1.59
31h		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	620	2.54
31i		3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	534	1.52

Example	Structure	NAME	LCMS MH+	Retention time (min)
31j		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	556	1.66
31k		3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea	518	1.86
31l		3-(2-dimethylaminoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	547	1.66
31m		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.72

Example 31a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.22 (3H, d), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 2.53 - 2.58 (1H, m), 3.16 - 3.22 (1H, m), 3.44 - 3.55 (5H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 -

3.98 (1H, m), 4.17 - 4.25 (1H, m), 4.53 - 4.59 (1H, m), 4.73 (1H, t), 6.46 (1H, s), 6.77 (1H, s), 7.50 (2H, d), 8.21 (2H, d), 8.58 (1H, s).

mTOR Kinase Assay (Echo): 0.00265μM

Example 31b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.54 - 1.63 (6H, m), 1.81 - 1.97 (4H, m), 2.17 - 2.23 (2H, m), 3.17 - 3.22 (1H, m), 3.45 - 3.54 (5H, m), 3.61 - 3.63 (1H, m), 3.76 (1H, d), 3.96 - 3.98 (1H, m), 4.10 - 4.24 (2H, m), 4.51 - 4.58 (1H, m), 4.73 (1H, t), 6.48 (1H, d), 6.77 (1H, s), 7.47 (2H, d), 8.20 (2H, d), 8.60 (1H, s).

mTOR Kinase Assay (Echo): 0.00497μM

Example 31c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.62 - 1.66 (2H, m), 1.91 - 1.98 (2H, m), 3.18 - 3.25 (1H, m), 3.46 - 3.57 (5H, m), 3.62 - 3.65 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.20 - 4.27 (1H, m), 4.52 - 4.61 (1H, m), 4.75 (1H, t), 6.80 (1H, s), 7.02 - 7.05 (1H, m), 7.55 - 7.58 (1H, m), 7.64 (2H, d), 7.75 - 7.79 (1H, m), 8.29 - 8.31 (1H, m), 8.30 (2H, d), 9.49 (1H, s), 10.63 (1H, s).

mTOR Kinase Assay (Echo): 0.00131μM

Example 31d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (6H, d), 1.22 (3H, d), 1.54 - 1.56 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 2.94 (2H, t), 3.16 - 3.23 (1H, m), 3.45 - 3.55 (6H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.96 - 3.98 (1H, m), 4.16 - 4.26 (1H, m), 4.52 - 4.59 (1H, m), 4.73 (1H, t), 6.26 (1H, t), 6.77 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.00955μM

Example 31e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.22 (3H, d), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 3.09 - 3.23 (3H, m), 3.44 - 3.55 (5H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.18 - 4.24 (1H, m), 4.53 - 4.59 (1H, m), 4.73 (1H, t), 6.18 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00107μM

Example 31f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.54 - 1.64 (4H, m), 1.90 - 1.97 (2H, m), 3.15 - 3.19 (2H, m), 3.43 - 3.54 (8H, m), 3.61 - 3.63 (1H, m), 3.76 (1H, d), 3.95 - 3.98 (1H, m), 4.17 - 4.24 (1H, m), 4.51 - 4.59 (1H, m), 4.73 - 4.79 (2H, m), 6.28 (1H, t), 6.76 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.84 (1H, s).

mTOR Kinase Assay (Echo): 0.0016μM

Example 31g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 2.66 (3H, d), 3.16 - 3.23 (1H, m), 3.44 - 3.55 (5H, m), 3.61

- 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 - 4.23 (1H, m), 4.52 - 4.59 (1H, m), 4.73 (1H, t), 6.07 - 6.10 (1H, m), 6.77 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00323μM

Example 31h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.59 (2H, m), 1.62 - 1.65 (2H, m), 1.91 - 1.98 (2H, m), 3.17 - 3.25 (1H, m), 3.45 - 3.56 (5H, m), 3.62 - 3.65 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.18 - 4.26 (1H, m), 4.53 - 4.61 (1H, m), 4.75 (1H, t), 6.80 (1H, s), 7.58 (2H, d), 7.64 - 7.70 (4H, m), 8.29 (2H, d), 9.09 (1H, s), 9.17 (1H, s).

mTOR Kinase Assay (Echo): 0.000209μM

Example 31i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.54 - 1.64 (6H, m), 1.90 - 1.97 (2H, m), 3.14 - 3.23 (3H, m), 3.44 - 3.55 (7H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 - 4.25 (1H, m), 4.52 (1H, t), 4.53 - 4.59 (1H, m), 4.73 (1H, t), 6.22 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.00326μM

Example 31j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.58 (2H, m), 1.61 - 1.64 (2H, m), 1.90 - 1.98 (2H, m), 3.16 - 3.24 (1H, m), 3.46 - 3.56 (4H, m), 3.61 - 3.65 (1H, m), 3.79 (3H, s), 3.96 - 3.99 (1H, m), 4.18 - 4.25 (1H, m), 4.53 - 4.58 (1H, m), 4.74 (1H, t), 6.78 (1H, s), 7.39 (1H, s), 7.54 (2H, d), 7.77 (1H, s), 8.24 (2H, d), 8.43 (1H, s), 8.89 (1H, s).

mTOR Kinase Assay (Echo): 0.00103μM

Example 31k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (3H, t), 1.22 (3H, d), 1.41 - 1.50 (2H, m), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.88 - 1.97 (2H, m), 3.03 - 3.08 (2H, m), 3.16 - 3.23 (1H, m), 3.44 - 3.55 (5H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 - 4.24 (1H, m), 4.51 - 4.59 (1H, m), 4.73 (1H, t), 6.22 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.69 (1H, s).

mTOR Kinase Assay (Echo): 0.00191μM

Example 31l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 2.18 (6H, s), 2.33 (2H, t), 3.17 - 3.23 (3H, m), 3.44 - 3.55 (5H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 - 4.25 (1H, m), 4.50 - 4.60 (1H, m), 4.73 (1H, t), 6.17 (1H, t), 6.77 (1H, s), 7.48 (2H, d), 8.20 (2H, d), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.214μM

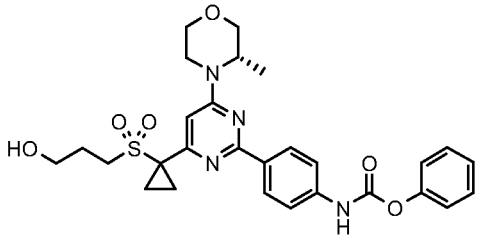
Example 31m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (6H, s), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 3.16 - 3.23 (1H, m), 3.38 (2H, d), 3.44 - 3.55 (5H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 - 4.25 (1H, m), 4.51 - 4.59 (1H,

m), 4.74 (1H, t), 4.99 (1H, t), 6.01 (1H, s), 6.76 (1H, s), 7.45 (2H, d), 8.19 (2H, d), 8.77 (1H, s).

mTOR Kinase Assay (Echo): 0.00591μM

The preparation of phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

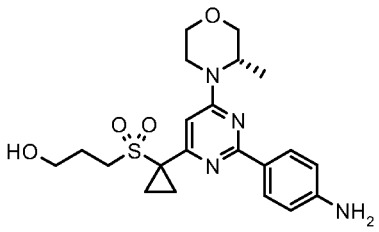


Phenyl chloroformate (0.581 mL, 4.63 mmol) was added to 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol (1.82 g, 4.21 mmol) and sodium bicarbonate (0.530 g, 6.31 mmol) in dioxane (100 mL) at 5°C under a nitrogen atmosphere. The resulting suspension was stirred overnight and allowed to come to RT. The reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford desired product as a gum. The gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (2.32 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.48 - 1.52 (2H, m), 1.55 - 1.61 (2H, m), 1.83 - 1.90 (2H, m), 3.11 - 3.18 (1H, m), 3.38 - 3.46 (4H, m), 3.54 - 3.58 (1H, m), 3.69 (1H, d), 3.75 - 3.94 (2H, m), 3.88 - 3.92 (1H, m), 4.14 - 4.18 (1H, m), 4.47 - 4.53 (1H, m), 6.75 (1H, s), 7.17 - 7.23 (3H, m), 7.36 - 7.39 (2H, m), 7.56 (2H, d), 8.23 (2H, d), 10.37 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 553; HPLC tR = 2.51min.

3-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol

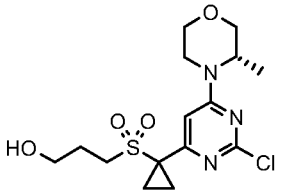


Dichlorobis(triphenylphosphine)palladium (II) (0.218 g, 0.31 mmol) was added to 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol (2.33 g, 6.20 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.766 g, 8.06 mmol) and 2M aqueous sodium carbonate solution (11.16 mL, 22.32 mmol) in DMF (15 mL), water (37.5 mL), ethanol (15 mL) and DME (15 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at 80°C for 17 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product as a brown solid. The crude product was purified by flash silica chromatography, eluting with 0 to 75% ethyl acetate in DCM, to give the desired material as a cream solid (1.82 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.52 - 1.54 (2H, m), 1.60 - 1.62 (2H, m), 1.90 - 1.97 (2H, m), 3.14 - 3.21 (1H, m), 3.44 - 3.52 (5H, m), 3.60 - 3.64 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.16 - 4.19 (1H, m), 4.48 - 4.55 (1H, m), 4.67 (1H, t), 5.56 (2H, s), 6.60 (2H, d), 6.67 (1H, s), 8.04 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 433; HPLC tR = 1.81min.

3-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol



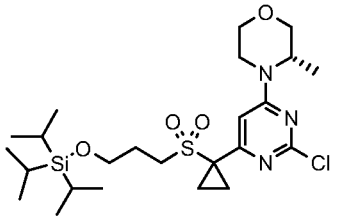
Tetrabutylammonium fluoride (1M in THF, 31 mL, 31 mmol) was added to 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropoxy-tri(propan-2-yl)silane (3.28 g, 6.16 mmol) in THF (30 mL) at RT. The resulting solution was stirred at RT for 1 hour then concentrated *in vacuo* and diluted with saturated ammonium chloride (10 mL)

and water. The mixture was extracted twice with ethyl acetate, the combined organic extracts washed with brine,dried ($MgSO_4$), filtered and evaporated to give the desired material as a gum (2.33 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.42 - 1.51 (4H, m), 2.07 - 2.14 (2H, m), 2.40 (1H, s), 3.28 - 3.32 (2H, m), 3.37 - 3.42 (3H, m), 3.51 - 3.57 (1H, m), 3.66 - 3.70 (1H, m), 3.77 - 3.80 (2H, m), 3.99 - 4.02 (1H, m), 4.28 - 4.38 (1H, m), 6.84 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 376; HPLC tR = 1.58min.

3-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropoxy-tri(propan-2-yl)silane

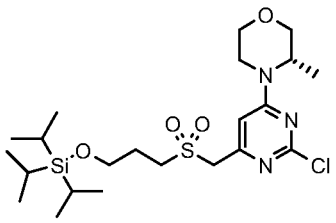


1,2-dibromoethane (1.723 mL, 20 mmol) was added to 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane (5.0 g, 9.88 mmol), 40% sodium hydroxide solution (10 mL, 98.78 mmol) and tetrabutylammonium bromide (0.645 g, 2 mmol) in toluene (50 mL) at RT under air. The resulting mixture was stirred at 60°C for 4 hours. The reaction mixture was evaporated to dryness and redissolved in ethyl acetate (100 mL) and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 20% ethyl acetate in DCM, to give the desired material as a colourless gum (2.86 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.00 - 1.05 (21H, m), 1.32 (3H, d), 1.49 - 1.52 (2H, m), 1.78 - 1.81 (2H, m), 2.02 - 2.09 (2H, m), 3.21 - 3.32 (3H, m), 3.50 - 3.56 (1H, m), 3.65 - 3.69 (1H, m), 3.77 - 3.80 (3H, m), 3.98 - 4.02 (2H, m), 4.28 - 4.36 (1H, m), 6.90 (1H, s)

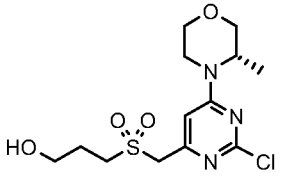
LCMS Spectrum: m/z (ESI+)(M+H)+ = 532; HPLC tR = 3.37min.

3-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane



3-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propan-1-ol (5.04 g, 14.41 mmol) in DMF (25 mL) was added to chlorotrisopropylsilane (3.70 mL, 17.29 mmol) and imidazole (2.354 g, 34.58 mmol) in DMF (25 mL) at RT over a period of 5 minutes under a nitrogen atmosphere. The resulting solution was stirred at RT for 18 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (200 mL) then washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as an oil (7.29 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.99 - 1.07 (21H, m), 1.33 (3H, d), 2.06 - 2.13 (2H, m), 3.20 - 3.24 (2H, m), 3.26 - 3.34 (1H, m), 3.50 - 3.57 (1H, m), 3.66 - 3.70 (1H, m), 3.77 - 3.83 (3H, m), 3.99 - 4.03 (2H, m), 4.16 (2H, s), 4.25 - 4.37 (1H, m), 6.54 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 506; HPLC tR = 3.42min.

3-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propan-1-ol

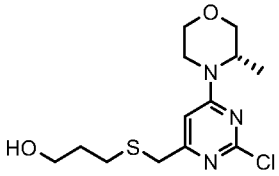


3-Chlorobenzoperoxoic acid (4.00 g, 23.16 mmol) was added to 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]propan-1-ol (3.68 g, 11.58 mmol) in DCM (100 mL) at RT over a period of 5 minutes. The resulting solution was stirred at RT for 3 hours. A further portion of 3-chlorobenzoperoxoic acid (2.00 g, 11.58 mmol) was added and the resulting solution was stirred at RT for an additional 1 hour. The reaction mixture was washed sequentially with 10% aqueous sodium metabisulphite solution (2 x 100 mL), a saturated aqueous solution of sodium hydrogen carbonate (100 mL), and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as a gum (4.05 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.34 (3H, d), 2.12 - 2.18 (2H, m), 3.27 (2H, t), 3.31 - 3.35 (1H, m), 3.51 - 3.57 (1H, m), 3.67 - 3.70 (1H, m), 3.77 - 3.82 (3H, m), 3.99 - 4.03 (1H, m), 4.18 (2H, s), 4.26 - 4.37 (1H, m), 6.51 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 350; HPLC tR = 1.30min.

3-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]propan-1-ol



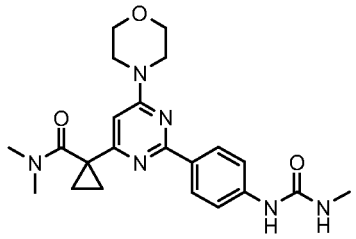
A solution of 2-chloro-4-(iodomethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (12.4 g, 35.07 mmol) in DCM (50 mL) was added to a stirred solution of 3-mercapto-1-propanol (3.64 mL, 42.08 mmol) and DIPEA (9.77 mL, 56.11 mmol) in DCM (100 mL) at RT, over a period of 40 minutes under a nitrogen atmosphere. The resulting solution was stirred at RT for 18 hours. The reaction mixture was washed sequentially with a saturated aqueous solution of sodium hydrogen carbonate (2 x 50 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product as a dark brown oil. The crude product was purified by flash silica chromatography, eluting with 0 to 75% ethyl acetate in DCM, to give the desired material as a yellow gum (5.86 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.84 - 1.90 (2H, m), 1.94 (1H, s), 2.69 (2H, t), 3.24 - 3.32 (1H, m), 3.51 - 3.58 (1H, m), 3.61 (2H, s), 3.67 - 3.71 (1H, m), 3.73 - 3.80 (3H, m), 3.98 - 4.04 (2H, m), 4.28 - 4.34 (1H, m), 6.45 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 318; HPLC tR = 1.55min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 32: *N,N*-Dimethyl-1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide



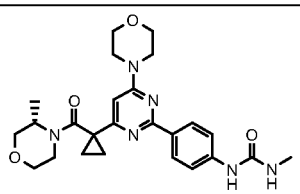
DIPEA (0.127 mL, 0.72 mmol) was added to a suspension of 1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid (96 mg, 0.24 mmol), dimethylamine (2.0M in THF, 0.36 mL, 0.72 mmol) and HBTU (138 mg, 0.36 mmol) in DMF (3 mL). The reactions were stirred at RT for 3 hours. The reaction mixture was passed down a SCX-2 ion exchange column, eluting with methanol followed by 7N ammonia in methanol. The isolated material was further purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (54 mg).

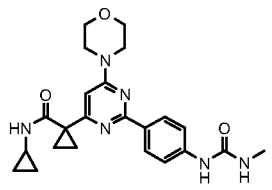
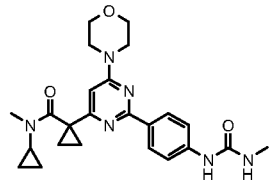
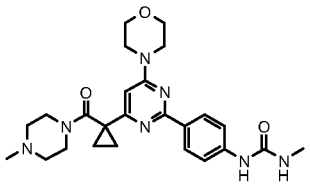
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.28 - 1.31 (2H, m), 1.51 - 1.54 (2H, m), 2.65 (3H, d), 2.87 - 2.89 (3H, s), 2.94 (3H, s), 3.64 (4H, m), 3.69 - 3.71 (4H, m), 6.08 (1H, d), 6.22 (1H, s), 7.46 - 7.49 (2H, m), 8.16 - 8.18 (2H, m), 8.76 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 425; HPLC tR = 1.45 min.

mTOR Kinase Assay (Echo): 0.00315μM

The following compounds were made in an analogous fashion from 1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
32a		3-methyl-1-[4-[4-[1-[(3S)-3-methylmorpholine-4-carbonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	481.4	1.53

Example	Structure	NAME	LCMS MH+	Retention time (min)
32b		N-cyclopropyl-1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide	437.4	1.5
32c		N-cyclopropyl-N-methyl-1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide	451.4	1.62
32d		3-methyl-1-[4-[4-[1-(4-methylpiperazine-1-carbonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	480.4	1.35

Example 32a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.31 (2H, d), 1.62 (2H, d), 2.65 - 2.66 (3H, m), 3.17 (1H, d), 3.48 (1H, d), 3.50 (1H, m), 3.66 (4H, s), 3.70 (4H, s), 3.70 (1H, s), 3.85 (1H, m), 4.23 (1H, d), 4.47 - 4.49 (1H, m), 6.07 (1H, q), 6.23 (1H, d), 7.48 (2H, d), 8.19 (2H, d), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.0425μM

Example 32b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.42 - 0.46 (2H, m), 0.60 - 0.65 (2H, m), 1.30 - 1.37 (4H, m), 2.66 (3H, d), 2.67 - 2.68 (1H, m), 3.67 (8H, s), 6.08 (1H, d), 6.46 (1H, s), 7.48 - 7.50 (2H, m), 8.14 - 8.17 (2H, m), 8.37 (1H, d), 8.77 (1H, s).

mTOR Kinase Assay (Echo): 0.00829μM

Example 32c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.64 (2H, s), 0.69 (2H, s), 1.32 (2H, s), 1.49 (2H, t), 2.33 (1H, t), 2.65 - 2.66 (3H, m), 2.73 - 2.76 (3H, m), 3.64 (4H, s), 3.69 - 3.71 (4H, m), 6.07 (1H, q), 6.30 (1H, s), 7.46 - 7.49 (2H, m), 8.16 - 8.18 (2H, m), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.00288μM

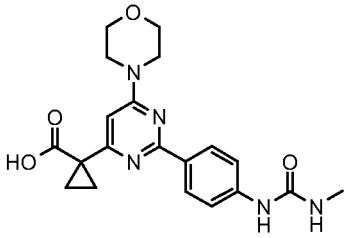
Example 32d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.29 - 1.32 (2H, m), 1.50 - 1.53 (2H, m), 2.11 - 2.11 (3H, m), 2.14 (2H, s), 2.33 (2H, t), 2.65 - 2.66 (3H, m), 3.30 (2H, s), 3.57 (2H, s),

3.67 - 3.70 (8H, m) 6.08 (1H, q), 6.26 (1H, s), 7.46 - 7.50 (2H, m), 8.17 - 8.20 (2H, m), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.0131μM

The preparation of 1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid is described below:

1-[2-[4-(Methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid

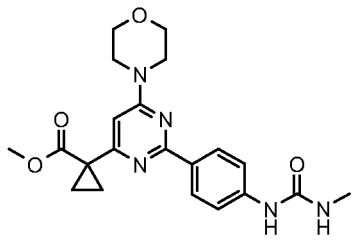


Lithium hydroxide-1-hydrate (59.5 mg, 1.42 mmol) was added in one portion to methyl 1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate (583 mg, 1.42 mmol) in methanol (8 mL) and water (8 mL). The resulting suspension was stirred at 60°C for 5 hours. The reaction mixture was evaporated to dryness, redissolved in water (25 mL), and washed with diethyl ether (25 mL). The aqueous layer was acidified with 2M hydrochloric acid and the precipitate was collected by filtration, washed with diethyl ether and dried under vacuum to give the desired material as a brown solid (486 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.51 - 1.58 (4H, m), 2.65 - 2.66 (3H, m), 3.70 (8H, s), 6.09 (1H, q), 6.73 (1H, s), 7.49 - 7.52 (2H, m), 8.13 - 8.15 (2H, m), 8.80 (1H, s), 14.09 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 398; HPLC tR = 1.21 min.

Methyl 1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate

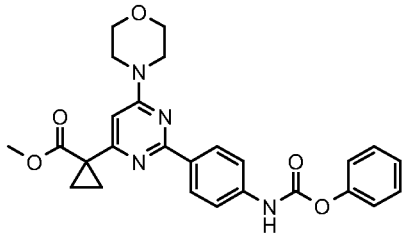


Methylamine (1.97 mL, 3.94 mmol) was added in one portion to methyl 1-[6-morpholin-4-yl-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]cyclopropane-1-carboxylate (934 mg, 1.97 mmol) in DMF (20 mL) The resulting solution was stirred at RT for 4 hours. The reaction mixture was evaporated to dryness and the residue purified by ion exchange chromatography using an SCX column, eluting with methanol followed by 7M ammonia in methanol, to give the desired material as a yellow solid (713 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.49 - 1.55 (4H, m), 2.66 (3H, d), 3.65 (3H, s), 3.69 (8H, s), 6.05 (1H, t), 6.83 (1H, s), 7.46 - 7.49 (2H, m), 8.16 - 8.19 (2H, m), 8.71 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 412; HPLC tR = 1.93 min.

Methyl 1-[6-morpholin-4-yl-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]cyclopropane-1-carboxylate

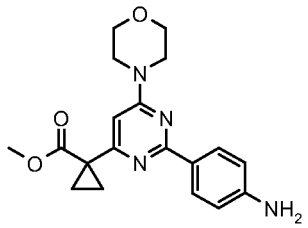


Phenyl chloroformate (0.53 mL, 4.20 mmol) was added dropwise to methyl 1-[2-(4-aminophenyl)-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate (1.49 g, 4.20 mmol) and sodium bicarbonate (0.53 g, 6.31 mmol) in dioxane (50 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (60 mL) and washed with water (60 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the desired material as a yellow solid (2.1 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.52 - 1.54 (4H, m), 3.57 (3H, s), 3.71 (8H, s), 6.89 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.62 (2H, d), 8.27 (2H, d), 10.46 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 475; HPLC tR = 2.83 min.

Methyl 1-[2-(4-aminophenyl)-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate

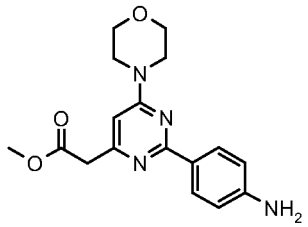


Sodium hydride (434 mg, 10.84 mmol) was added in one portion to methyl 2-[2-(4-aminophenyl)-6-morpholin-4-ylpyrimidin-4-yl]acetate (3.56 g, 10.84 mmol) in DMF (75 mL) cooled to 0ºC under nitrogen. The resulting solution was stirred at 0°C for 10 minutes then 1,2-dibromoethane (0.981 mL, 11.38 mmol) added and the reaction stirred at 0°C for 5 minutes. Further sodium hydride (434 mg, 10.84 mmol) was added in one portion and the reaction stirred at 0°C for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (10 mL). The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine solution (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was triturated with diethyl ether to give the desired material as a yellow solid (2.23 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.47 - 1.53 (4H, m), 3.64 (8H, t), 3.69 - 3.71 (3H, m), 5.50-5.60 (2H, s), 6.57 - 6.60 (2H, m), 6.73 (1H, s), 7.99 - 8.03 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 355; HPLC tR = 2.06 min.

Methyl 2-[2-(4-aminophenyl)-6-morpholin-4-ylpyrimidin-4-yl]acetate

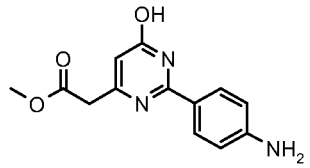


DBU (2.2 mL, 14.68 mmol) was added to methyl 2-[2-(4-aminophenyl)-6-hydroxypyrimidin-4-yl]acetate (3.46 g, 13.35 mmol) and *N*-phenyltrifluoromethanesulfonimide (5.24 g, 14.68 mmol) in DCM (120 mL). The resulting solution was stirred at RT for 2 hours. Morpholine (2.91 mL, 33.36 mmol) was added and the reaction stirred at RT for 2 hours. The reaction mixture was diluted with DCM (20 mL) and washed with a saturated aqueous solution of sodium hydrogen carbonate (100 mL). The organic layer was dried (MgSO4) filtered and concentrated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a yellow solid (3.65 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.62 (2H, d), 3.66 (8H,m), 3.72 - 3.73 (3H, m), 6.27 (1H, s), 6.61 - 6.64 (2H, m), 7.17 - 7.23 (2H, m), 8.12 - 8.16 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 329; HPLC tR = 1.74 min.

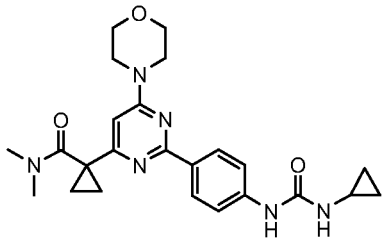
Methyl 2-[2-(4-aminophenyl)-6-hydroxypyrimidin-4-yl]acetate



To a stirred solution of dimethyl 3-oxopentanedioate (15.06g, 86.50 mmol) in methanol (125 mL) was added 4-aminobenzimidamide dihydrochloride (12 g, 57.67 mmol) and potassium carbonate (19.93 g, 144.17 mmol) and the reaction mixture heated at 90°C for 5 hours then allowed to cool to RT. The mixture was concentrated *in vacuo*, redissoved in water (150 mL) and extracted with DCM (150 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The aqueous layer was adjusted to pH5 using acetic acid and the precipitate formed was filtered and dried in a vacuum oven to give the desired material as a yellow solid (3.49g).

LCMS Spectrum: m/z (ES+)(M+H)+=260; HPLC tR=1.06 min.

Example 33: 1-[2-[4-(Cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N,N-dimethylcyclopropane-1-carboxamide



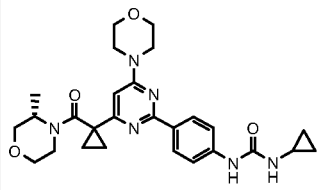
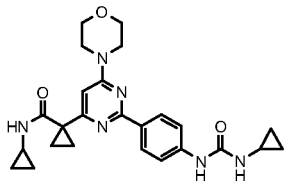
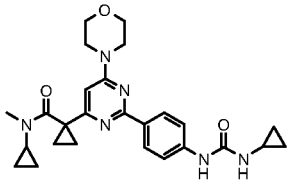
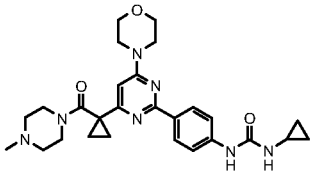
DIPEA (0.142 mL, 0.81 mmol) was added to a suspension of 1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid (115 mg, 0.27 mmol), dimethylamine (2.0M in THF, 0.405 mL, 0.81 mmol) and HBTU (155 mg, 0.36 mmol) in DMF (3 mL). The reactions were stirred at RT for 3 hours then purified on a ion exchange SCX-2 coulmn, eluting with methanol followed by 7N ammonia in methanol. The residue was further purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (20 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.28 - 1.31 (2H, m), 1.51 - 1.54 (2H, m), 2.54 - 2.56 (1H, m), 2.87 (3H, s), 2.94 (3H, s), 3.64 (4H, d), 3.69 - 3.71 (4H, m), 6.22 (1H, s), 6.44 (1H, d), 7.47 - 7.49 (2H, m), 8.16 - 8.19 (2H, m), 8.55 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 451; HPLC tR = 1.83 min.

mTOR Kinase Assay (Echo): 0.00929μM

The following compounds were made in an analogous fashion from 1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
33a		3-cyclopropyl-1-[4-[4-[1-[(3S)-3-methylmorpholine-4-carbonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	507	1.90
33b		N-cyclopropyl-1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide	463	1.88
33c		N-cyclopropyl-1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N-methylcyclopropane-1-carboxamide	477	2.00
33d		3-cyclopropyl-1-[4-[4-[1-(4-methylpiperazine-1-carbonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	506	1.72

Example 33a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.16 (1H, s), 1.23 (2H, d), 1.32 - 1.36 (2H, m), 1.40 (1H, d), 1.61 - 1.64 (2H, m), 2.52 - 2.57 (1H, m), 3.17 (1H, q), 3.15 - 3.21 (1H, m), 3.46 - 3.49 (1H, m), 3.66 - 3.66 (4H, m), 3.69 (4H, d), 3.71 (1H, s), 4.20 (1H, d), 4.48 (1H, d), 6.24 (1H, s), 6.45 (1H, d), 7.48 (2H, d), 8.19 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.0584μM

Example 33b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.41 - 0.45 (4H, m), 0.61 - 0.66 (4H, m), 1.31 - 1.35 (4H, m), 2.54 - 2.56 (1H, m), 2.71 (1H, d), 3.67 - 3.72 (8H, m), 6.45 (2H, d), 7.50 (2H, d), 8.15 - 8.17 (2H, m), 8.36 (1H, d), 8.56 (1H, s).

mTOR Kinase Assay (Echo): 0.012μM

Example 33c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.50 (2H, m), 0.63 - 0.65 (2H, m), 0.68 (2H, d), 1.32 -1.40 (2H, m), 1.49 (2H, t), 2.54 - 2.57 (1H, m), 2.75 (3H, d), 2.89 (1H, s), 3.64 (4H, d), 3.69 (4H, d), 6.31 (1H, s), 6.45 (1H, d), 7.48 (2H, d), 8.18 (2H, d), 8.54 (1H, s).

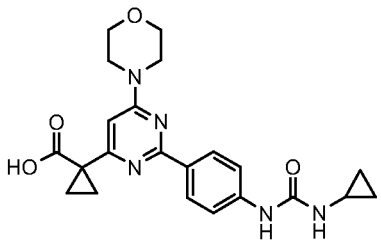
mTOR Kinase Assay (Echo): 0.00258μM

Example 33d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.30 - 1.32 (2H, m), 1.51 (2H, t), 2.12 (4H, s), 2.33 (3H, s), 2.53 - 2.56 (1H, m), 3.58 (4H, s), 3.67 - 3.71 (8H, d), 6.27 (1H, s), 6.45 (1H, d), 7.47 - 7.50 (2H, m), 8.18 - 8.20 (2H, m), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.133μM

The preparation of 1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid is described below:

1-[2-[4-(Cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid

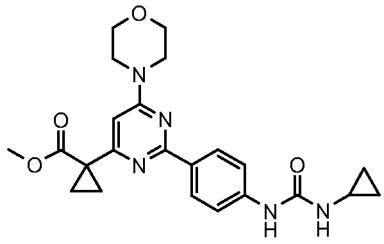


Lithium hydroxide-1-hydrate (67 mg, 1.59 mmol) was added in one portion to methyl 1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate (697 mg, 1.59 mmol) in methanol (8 mL) and water (8 mL) The resulting suspension was stirred at 80°C for 1 hour. The reaction mixture was evaporated to dryness, redissolved in water (25 mL), and washed with diethyl ether (25 mL). The aqueous layer was acidified with 2M hydrochloric acid, the precipitate collected by filtration, washed with diethyl ether and dried under vacuum to give the desired material as a brown solid (580 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.51 - 1.58 (4H, m), 2.53 - 2.57 (1H, m), 3.71 (8H, s), 6.48 (1H, d), 6.75 (1H, s), 7.51 (2H, d), 8.15 (2H, d), 8.63 (1H, s), 14.02 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 424; HPLC tR = 1.09 min.

Methyl 1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate



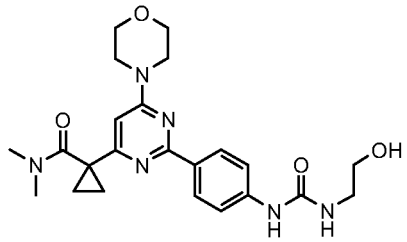
Cyclopropanamine (0.219 mL, 3.15 mmol) was added in one portion to methyl 1-[6-morpholin-4-yl-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]cyclopropane-1-carboxylate (998 mg, 2.10 mmol) in DMF (20 mL) The resulting solution was stirred at RT for 4 hours and the reaction mixture evaporated to dryness. The crude product was purified by ion exchange chromatography using an SCX column, eluting with methanol followed by 7M ammonia in methanol, to give the desired material as a yellow solid (757 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.50 - 1.53 (4H, m), 2.52 - 2.56 (1H, m), 3.64 (3H, s), 3.69 (8H, d), 6.43 (1H, d), 6.84 (1H, s), 7.47 - 7.49 (2H, m), 8.18 (2H, d), 8.55 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 438; HPLC tR = 2.10 min.

The preparation of methyl 1-[6-morpholin-4-yl-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]cyclopropane-1-carboxylate was described earlier.

Example 34: 1-[2-[4-(2-Hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N,N-dimethylcyclopropane-1-carboxamide



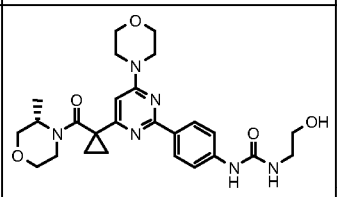
DIPEA (0.106 mL, 0.60 mmol) was added to a suspension of 1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid (86 mg, 0.20 mmol), dimethylamine (2.0M in THF, 0.30 mL, 0.60 mmol) and HBTU (115 mg, 0.30 mmol) in DMF (3 mL). The reactions were stirred at RT for 1 hour then purified by ion exchange using a SCX-2 column, eluting with methanol followed by 7N ammonia in methanol. The isolated material was further purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (56 mg).

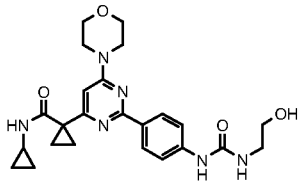
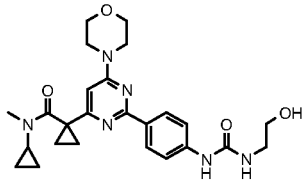
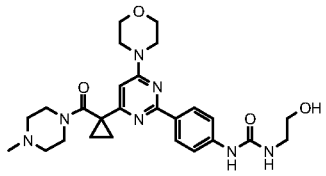
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.30 - 1.31 (2H, m), 1.53 (2H, d), 2.89 (3H, s), 2.94 (3H, s), 3.17 - 3.19 (2H, m), 3.47 (2H, d), 3.65 (4H, d), 3.70 -3.71 (4H, d), 4.74 (1H, s), 6.23 (2H, m), 7.47 (2H, d), 8.18 (2H, d), 8.79 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 455; HPLC tR = 1.52 min.

mTOR Kinase Assay (Echo): 0.00405μM

The following compounds were made in an analogous fashion from 1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
34a		3-(2-hydroxyethyl)-1-[4-[4-[1-[(3S)-3-methylmorpholine-4-carbonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	511	1.59

Example	Structure	NAME	LCMS MH+	Retention time (min)
34b		N-cyclopropyl-1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide	467	1.56
34c		N-cyclopropyl-1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N-methylcyclopropane-1-carboxamide	481	1.67
34d		3-(2-hydroxyethyl)-1-[4-[4-[1-(4-methylpiperazine-1-carbonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	510	1.44

Example 34a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.22 - 1.25 (3H, m), 1.33 (2H, d), 1.63 (2H, d), 3.16 - 3.20 (1H, m), 3.17 - 3.19 (3H, m), 3.46 (3H, m), 3.67 (4H, s), 3.71 (4H, d), 3.71 (2H, s), 4.20 (1H, d), 4.50(1H, s), 4.74 (1H, t), 6.25 (2H, m), 7.47 (2H, d), 8.20 (2H, d), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.0387μM

Example 34b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.44 - 0.46 (2H, m), 0.62 - 0.65 (2H, m), 1.32 - 1.37 (4H, m), 2.73 (1H, d), 3.18 (2H, d), 3.46 (2H, t), 3.68 (4H, d), 3.71 - 3.71 (4H, d), 4.74 (1H, t), 6.25 (1H, s), 6.46 (1H, s), 7.47 - 7.50 (2H, m), 8.15 - 8.18 (2H, m), 8.35 (1H, s), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.0109μM

Example 34c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.69 (4H, s), 1.50 (4H, m), 2.40 (1H, s), 2.80 (3H, m), 3.16 - 3.19 (2H, m), 3.47 (2H, q), 3.65 (4H, d), 3.70 - 3.72 (4H, m), 4.74 (1H, t), 6.25 (2H, m), 7.46 - 7.48 (2H, m), 8.17 - 8.19 (2H, m), 8.78 (1H, s).

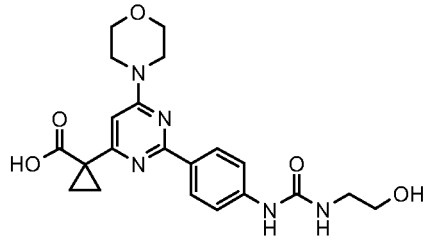
mTOR Kinase Assay (Echo): 0.00345μM

Example 34d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.30 - 1.33 (2H, m), 1.51 - 1.54 (2H, m), 2.10 - 2.15 (5H, m), 2.33 - 2.34 (1H, t), 3.18 - 3.19 (3H, m), 3.36 (1H, d), 3.47 (2H, q), 3.58 (3H, s), 3.66 - 3.71 (4H, m), 3.71 (4H, d), 4.74 (1H, t), 6.25 (1H, t), 6.27 (1H, s), 7.46 - 7.49 (2H, m), 8.18 - 8.21 (2H, m), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.0863μM

The preparation of 1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid is described below:

1-[2-[4-(2-Hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid

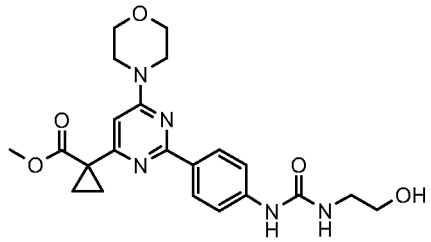


Lithium hydroxide-1-hydrate (67.2 mg, 1.60 mmol) was added in one portion to methyl 1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate (707 mg, 1.60 mmol) in methanol (8 mL) and water (8 mL). The resulting suspension was stirred at 80°C for 1 hour. The reaction mixture was evaporated to dryness, redissolved in water (25 mL), and washed with diethyl ether (25 mL). The aqueous layer was acidified with 2M hydrochloric acid, the precipitate collected by filtration, washed with diethyl ether and dried under vacuum to give the desired material as a beige solid (439 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.51 - 1.58 (4H, m), 3.17 (2H, q), 3.45 (2H, t), 3.70 (8H, s), 4.77 (1H, s), 6.28 (1H, t), 6.74 (1H, s), 7.48 - 7.50 (2H, m), 8.14 - 8.16 (2H, m), 8.86 (1H, s), 14.06 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 428; HPLC tR = 0.92 min.

Methyl 1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate



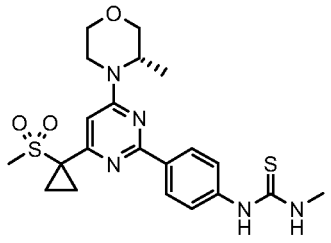
2-Aminoethanol (0.127 mL, 2.10 mmol) was added in one portion to methyl 1-[6-morpholin-4-yl-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]cyclopropane-1-carboxylate (998 mg, 2.10 mmol) in DMF (20 mL) The resulting solution was stirred at RT for 16 hours. The reaction mixture was evaporated to dryness and the crude product purified by ion exchange chromatography using an SCX column, eluting with methanol followed by 7N ammonia in methanol, to give the desired material as a yellow solid (767 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.50 - 1.52 (4H, m), 3.17 (2H, q), 3.45 (2H, q), 3.64 (3H, s), 3.70 (8H, s), 4.77 (1H, t), 6.25 (1H, t), 6.83 (1H, s), 7.45 - 7.47 (2H, m), 8.16 - 8.19 (2H, m), 8.81 (1H, s)

LCMS Spectrum. m/z (ESI+) (M+H)+ = 442; HPLC tR = 1.71 min.

The preparation of methyl 1-[6-morpholin-4-yl-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]cyclopropane-1-carboxylate was described earlier.

Example 35: 3-Methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea



To a solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (60mg, 0.16 mmol) in DCM (2 mL) and THF (1 mL) was added a solution of di(imidazol-1-yl)methanethione (37 mg, 0.21 mmol) in

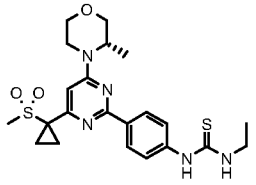
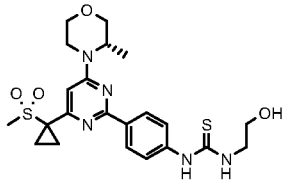
DCM (1 mL) and the resulting solution stirred at RT for 3 hours. Methylamine (2M in THF, 0.4 mL, 0.80 mmol) was added followed by triethylamine (0.022 mL, 0.16mmol) and the solution stirred for 1 hour at RT. The solvent was evaporated and the crude product purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (19 mg).

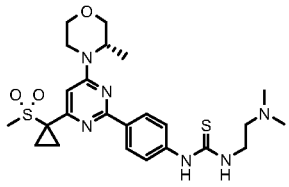
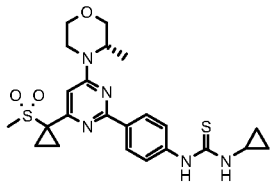
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 – 1.58 (2H, m), 1.66 – 1.69 (2H, m), 2.95 (3H, d), 3.16 (3H, s), 3.21 – 3.26 (1H, m), 3.45 – 3.52 (1H, m), 3.61 – 3.65 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.20 – 4.23 (1H, m), 4.55 – 4.63 (1H, m), 6.80 (1H, s), 7.55 (2H, d), 7.84 (1H, s), 8.26 (2H, d), 9.73 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 462; HPLC tR = 1.86min.

mTOR Kinase Assay (Echo): 0.00531μM

The compounds below were prepared in an analogous fashion from 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
35a		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	476	1.94
35b		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	492	1.68

Example	Structure	NAME	LCMS MH+	Retention time (min)
35c		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	519	1.99
35d		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	488	1.89

Example 35a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.14 (3H, t), 1.24 (3H, d), 1.55 – 1.58 (2H, m), 1.66 – 1.69 (2H, m), 3.17 – 3.25 (1H, m), 3.29 (3H, s), 3.45 – 3.51 (3H, m), 3.61 – 3.65 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.20 – 4.23 (1H, m), 4.55 – 4.62 (1H, m), 6.80 (1H, s), 7.57 (2H, d), 7.88 (1H, s), 8.25 (2H, d), 9.63 (1H, s).

mTOR Kinase Assay (Echo): 0.00552μM

Example 35b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.66 - 1.69 (2H, m), 3.17 - 3.25 (1H, m), 3.29 (3H, s), 3.45 - 3.52 (1H, m), 3.57 (4H, s), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 - 4.23 (1H, m), 4.55 - 4.62 (1H, m), 4.77 - 4.85 (1H, m), 6.80 (1H, s), 7.63 (2H, d), 7.86 (1H, s), 8.26 (2H, d), 9.81 (1H, s).

mTOR Kinase Assay (Echo): 0.000577μM

Example 35c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.66 - 1.69 (2H, m), 2.20 (6H, s), 2.45 (2H, t), 3.18 - 3.25 (1H, m), 3.26 (3H, s), 3.45 - 3.52 (1H, m), 3.56 (2H, s), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.21 (1H, d), 4.56 - 4.61 (1H, m), 6.80 (1H, s), 7.65 (2H, d), 7.77 (1H, s), 8.25 (2H, d), 9.90 (1H, s).

mTOR Kinase Assay (Echo): 0.108μM

Example 35d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.58 - 0.62 (2H, m), 0.74 - 0.79 (2H, m), 1.24 (3H, d), 1.55 - 1.59 (2H, m), 1.67 - 1.69 (2H, m), 2.89 - 2.97 (1H, m), 3.17 - 3.27 (1H, m), 3.30 (3H, s), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.21 - 4.24 (1H, m), 4.60 (1H, s), 6.81 (1H, s), 7.62 (2H, d), 8.14 (1H, s), 8.25 (2H, d), 9.51 (1H, s).

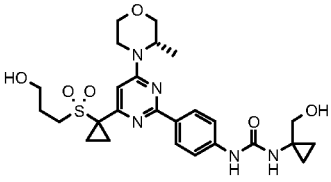
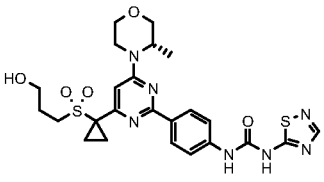
mTOR Kinase Assay (Echo): 0.00411μM

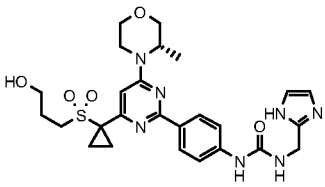
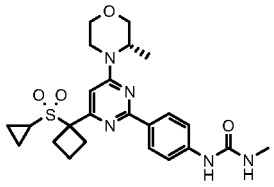
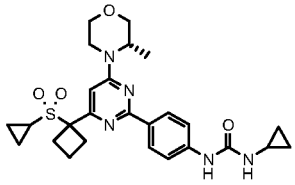
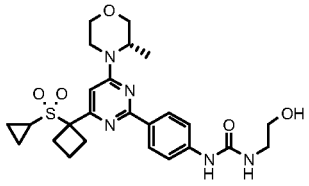
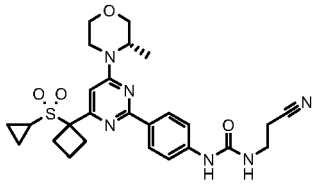
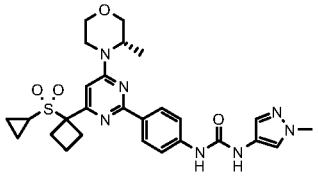
The preparation of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline was described earlier.

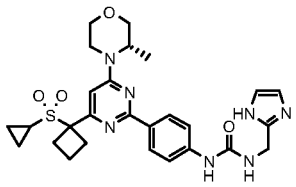
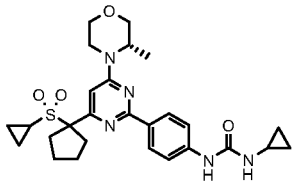
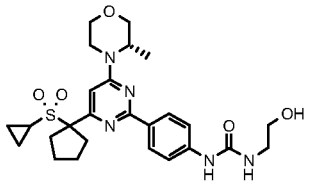
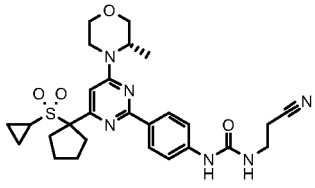
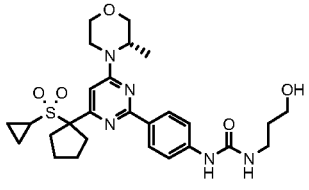
Example 36

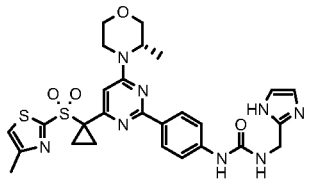
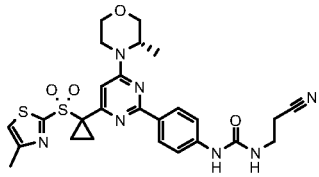
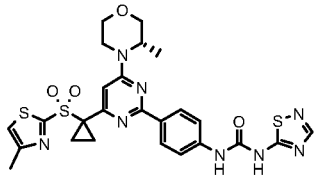
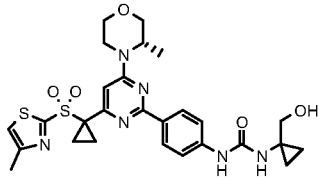
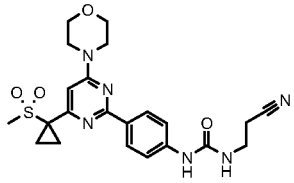
The following compounds were prepared according to the following general procedure:

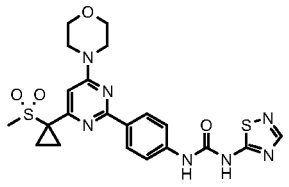
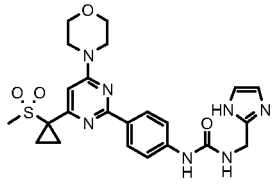
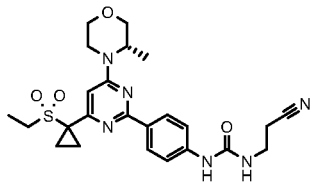
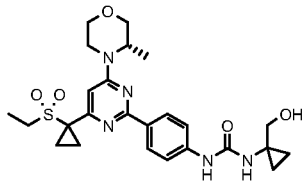
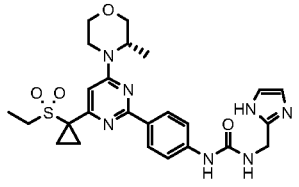
The appropriate phenyl carbamate and an excess of both triethylamine and the appropriate amine were dissolved in either DMF, NMP or DMA and stirred at 50°C – 70°C for between 2 – 18 hours (unless otherwise specified). The materials were purifed by preparative HPLC except where specified.

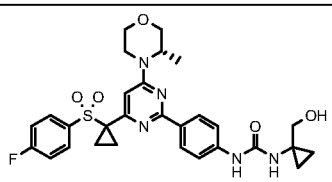
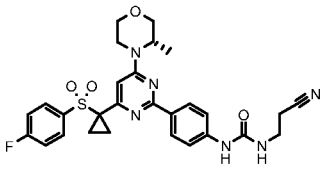
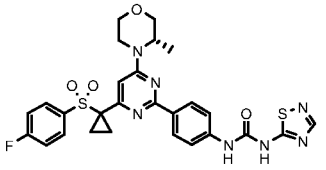
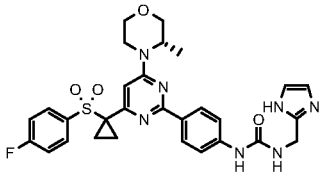
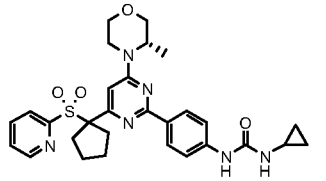
Example	Structure	NAME	LCMS MH+	Retention time (min)
36a		3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	546	1.67
36b		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	560	1.41

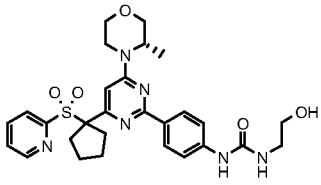
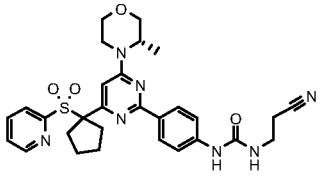
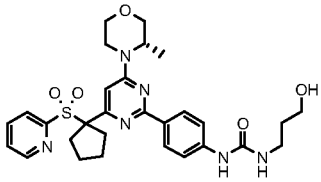
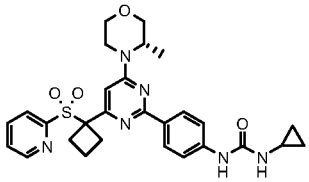
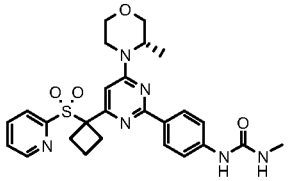
Example	Structure	NAME	LCMS MH+	Retention time (min)
36c		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	556	1.65
36d		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	486	1.92
36e		3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	512	2.16
36f		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	516	1.84
36g		3-(2-cyanoethyl)-1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	525	2.07
36h		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	552	2.04

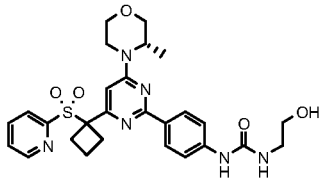
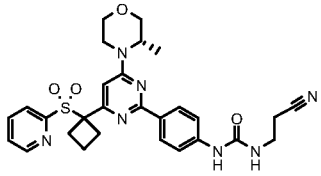
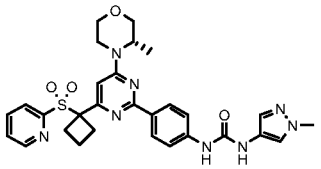
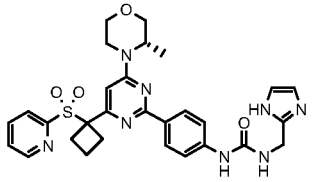
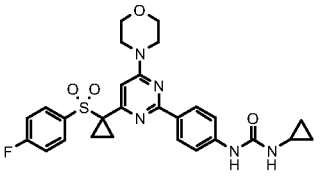
Example	Structure	NAME	LCMS MH+	Retention time (min)
36i		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	552	1.99
36j		3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	526	2.34
36k		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	530	1.97
36l		3-(2-cyanoethyl)-1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	539	2.19
36m		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	544	1.99

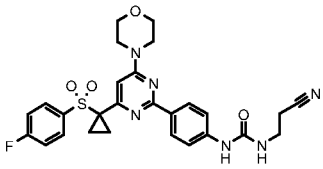
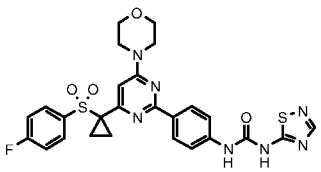
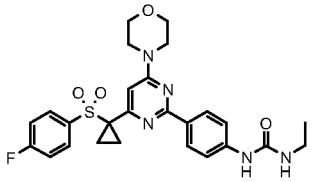
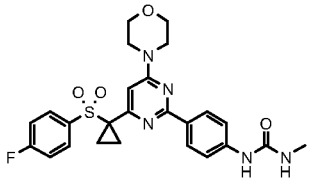
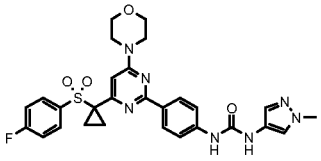
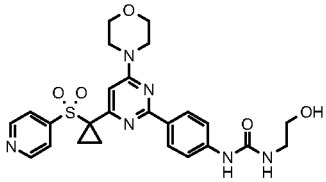
Example	Structure	NAME	LCMS MH+	Retention time (min)
36n		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	595	2.07
36o		3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	568	2.25
36p		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	599	1.81
36q		3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	585	2.09
36r		3-(2-cyanoethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	471.5	1.66

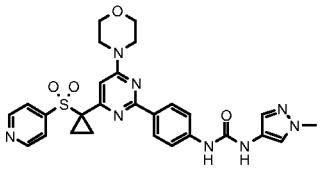
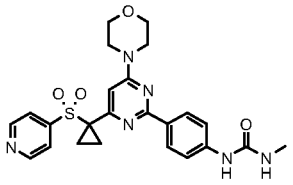
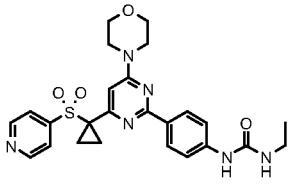
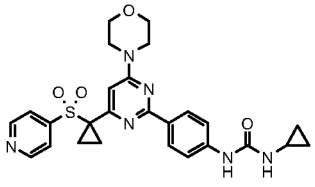
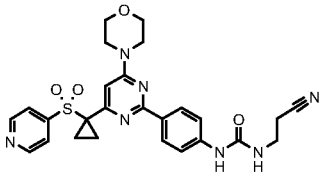
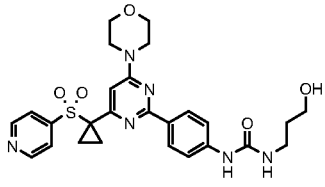
Example	Structure	NAME	LCMS MH+	Retention time (min)
36s*		1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	502	1.61
36t		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	498.6	2.02
36u		3-(2-cyanoethyl)-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	499.1	2.10
36v		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea	516.1	1.97
36w		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	526.1	1.94

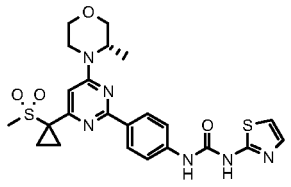
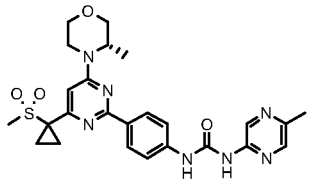
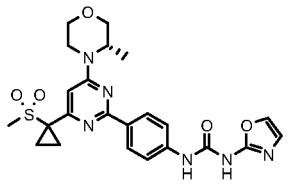
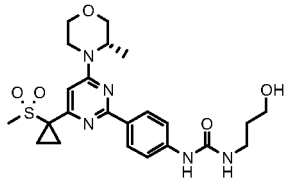
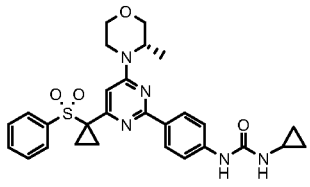
Example	Structure	NAME	LCMS MH+	Retention time (min)
36x		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea	582	2.17
36y		3-(2-cyanoethyl)-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	565	2.40
36z		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	596	1.49
36aa		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	592	2.07
36ab		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	563	2.38

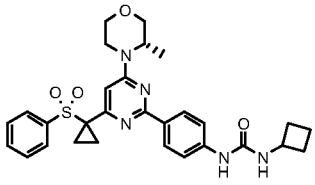
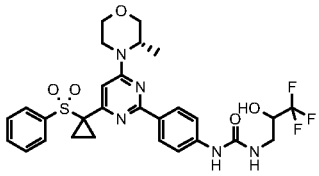
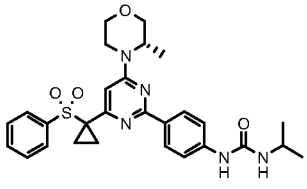
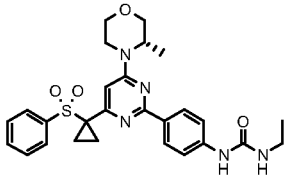
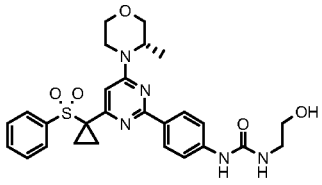
Example	Structure	NAME	LCMS MH+	Retention time (min)
36ac		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	567	2.01
36ad		3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	576	2.28
36ae		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	581	2.05
36af		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	549	2.25
36ag		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	523	2.08

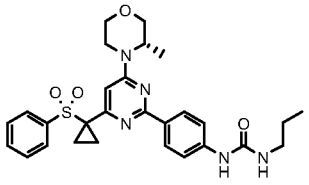
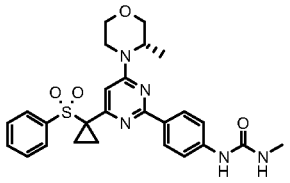
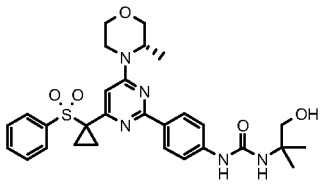
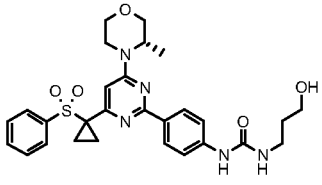
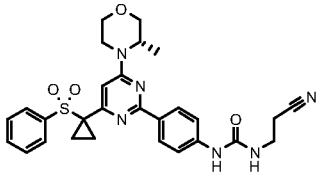
Example	Structure	NAME	LCMS MH+	Retention time (min)
36ah		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	553	1.89
36ai		3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	562	2.15
36aj		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	589	2.11
36ak		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	589	2.34
36al**		3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	538	2.36

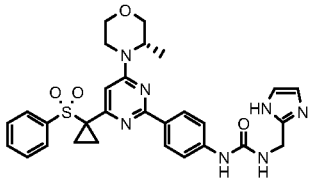
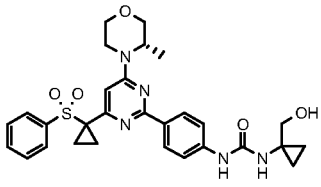
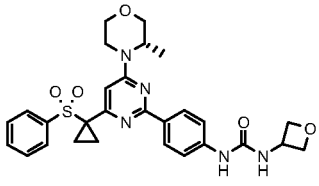
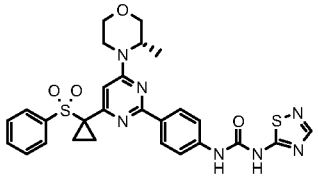
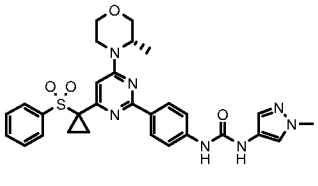
Example	Structure	NAME	LCMS MH+	Retention time (min)
36am**		3-(2-cyanoethyl)-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	551	2.27
36an		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	542	1.41
36ao		1-ethyl-3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	526	2.14
36ap		3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-methylurea	512	1.99
36aq		3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-(1-methylpyrazol-4-yl)urea	578	2.04
36ar		3-(2-hydroxyethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	525	1.66

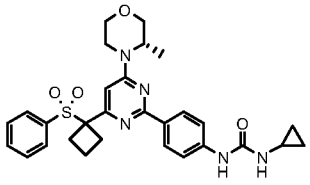
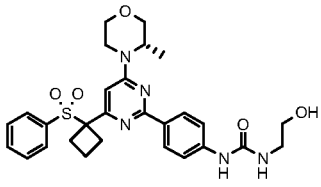
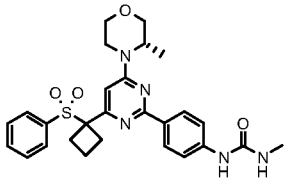
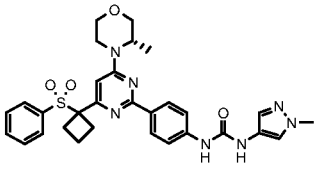
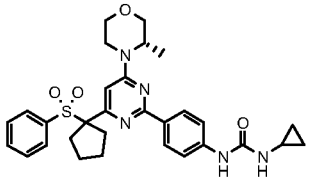
Example	Structure	NAME	LCMS MH+	Retention time (min)
36as		1-(1-methylpyrazol-4-yl)-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	561	1.81
36at		1-methyl-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	495	1.81
36au		1-ethyl-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	509	1.99
36av		3-cyclopropyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	521	1.95
36aw		3-(2-cyanoethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	534	1.89
36ax		3-(3-hydroxypropyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	539	1.72

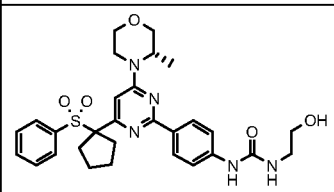
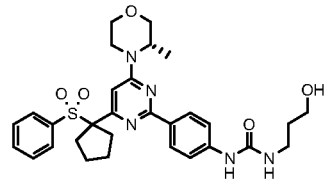
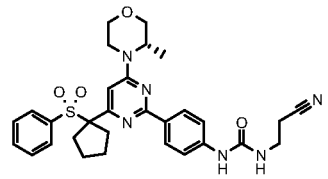
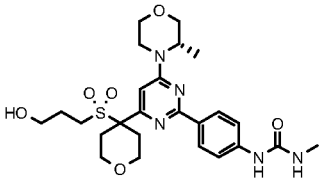
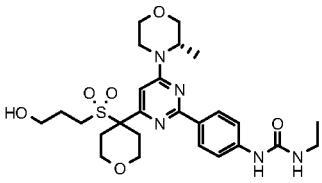
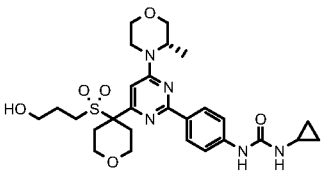
Example	Structure	NAME	LCMS MH+	Retention time (min)
36ay		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea	515	2.19
36az		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-(5-methylpyrazin-2-yl)urea	524	2.35
36ba		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,3-oxazol-2-yl)urea	499	1.99
36bb		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	490	1.75
36bc		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	534	2.39

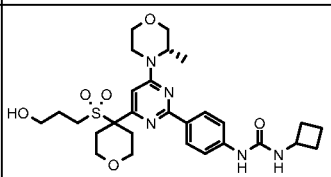
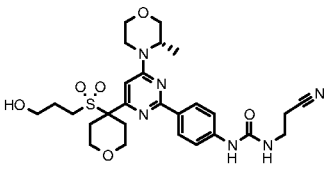
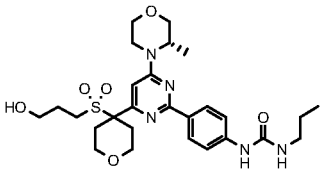
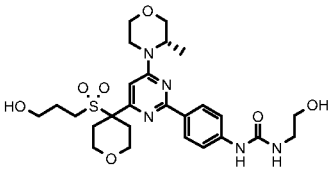
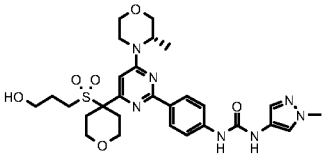
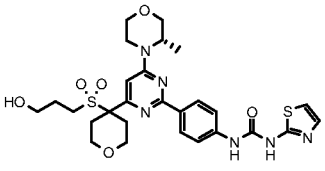
Example	Structure	NAME	LCMS MH+	Retention time (min)
36bd		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutylurea	548	2.61
36be		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3,3,3-trifluoro-2-hydroxypropyl)urea	606	2.45
36bf		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea	536	2.51
36bg		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	522	2.32
36bh		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	538	1.98

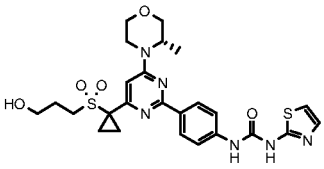
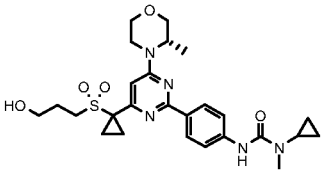
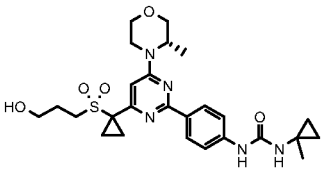
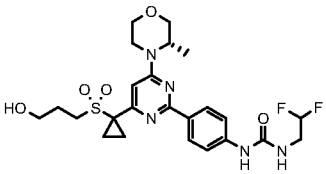
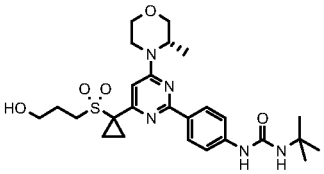
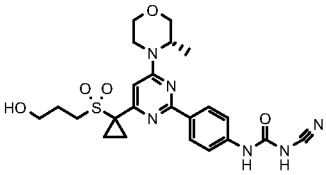
Example	Structure	NAME	LCMS MH+	Retention time (min)
36bi		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea	536	2.49
36bj		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	508	2.16
36bk		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	566	2.28
36bl		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	552	2.03
36bm		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea	547	2.24

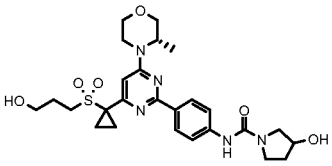
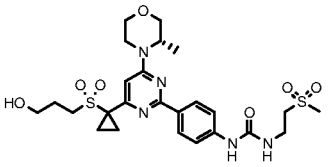
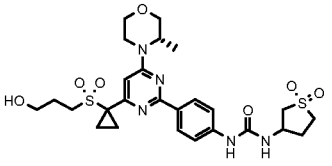
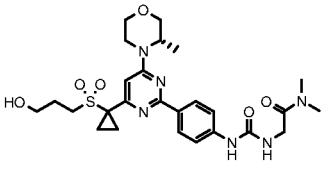
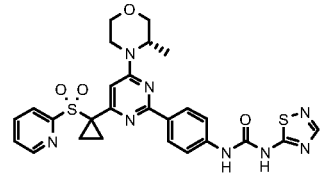
Example	Structure	NAME	LCMS MH+	Retention time (min)
36bn		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	574	2.12
36bo		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea	564	2.11
36bp		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(oxetan-3-yl)urea	550	2.13
36bq		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	578	1.35
36br		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	574	2.21

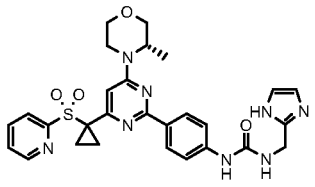
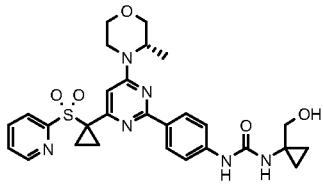
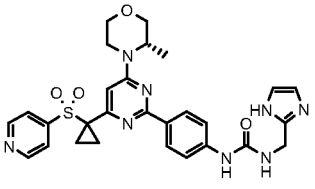
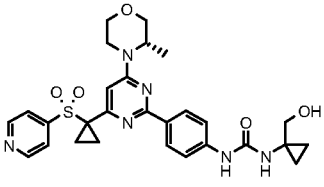
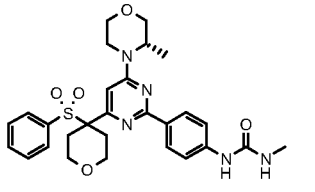
Example	Structure	NAME	LCMS MH+	Retention time (min)
36bs		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	548	2.53
36bt		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	552	2.14
36bu		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	522	2.35
36bv		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	588	2.37
36bw		1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	562	2.75

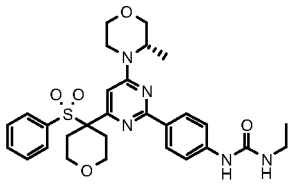
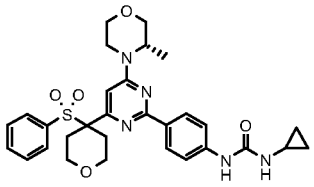
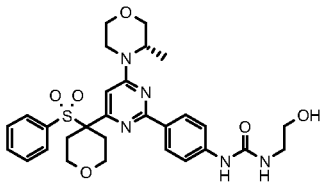
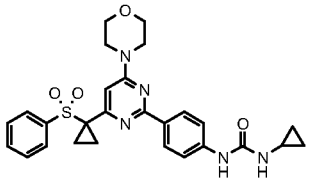
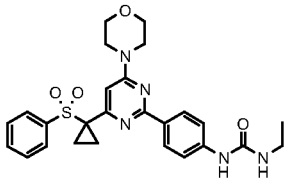
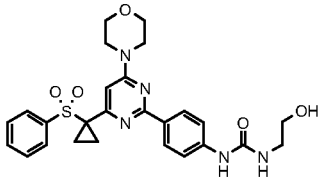
Example	Structure	NAME	LCMS MH+	Retention time (min)
36bx		1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	566	2.30
36by		1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	580	2.31
36bz		1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea	575	2.55
36ca***		1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	534	1.56
36cb***		1-ethyl-3-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.67
36cc***		3-cyclopropyl-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	560	1.71

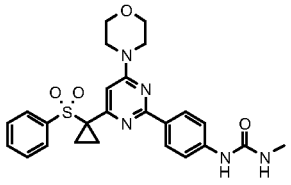
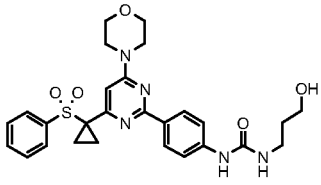
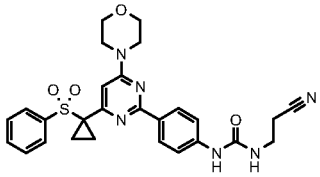
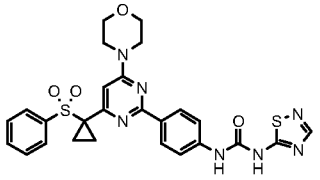
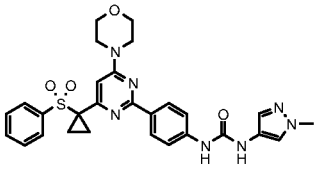
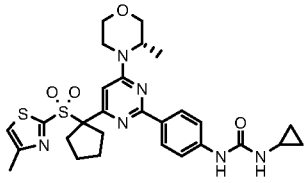
Example	Structure	NAME	LCMS MH+	Retention time (min)
36cd***		3-cyclobutyl-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	574	1.89
36ce***		3-(2-cyanoethyl)-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	573	1.62
36cf***		3-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea	562	1.83
36cg***		3-(2-hydroxyethyl)-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	564	1.46
36ch***		1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	600	1.62
36ci***		1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea	603	1.87

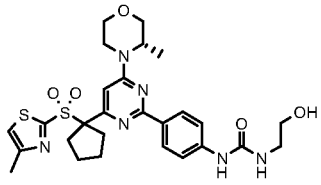
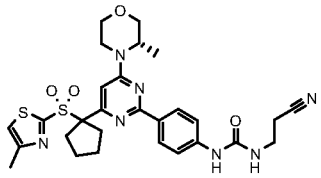
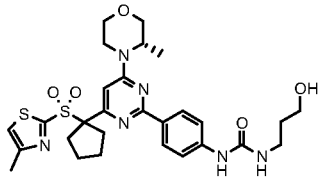
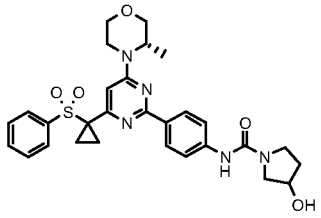
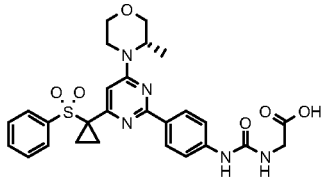
Example	Structure	NAME	LCMS MH+	Retention time (min)
36cj***		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea	559	1.94
36ck***		1-cyclopropyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-methylurea	530	1.96
36cl***		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylcyclopropyl)urea	530	1.88
36cm***		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	540	1.85
36cn***		3-tert-butyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	532	2.10
36co***		3-cyano-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	501	1.12

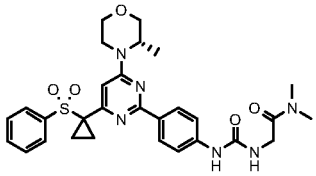
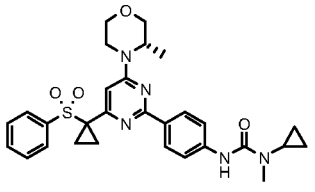
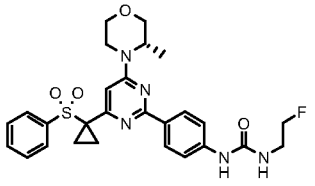
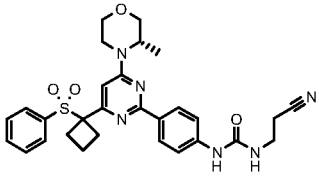
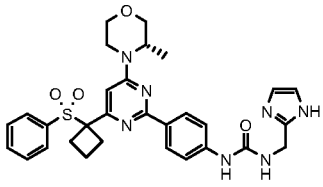
Example	Structure	NAME	LCMS MH+	Retention time (min)
36cp***		3-hydroxy-N-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]pyrrolidine-1-carboxamide	546	1.52
36cq***		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylsulfonylethyl)urea	582	1.61
36cr***		3-(1,1-dioxothiolan-3-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	594	1.66
36cs***		2-[[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamoylamino]-N,N-dimethylacetamide	561	1.59
36ct		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	579	1.37

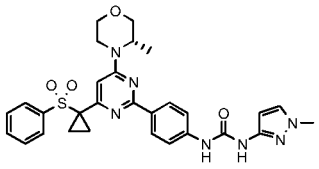
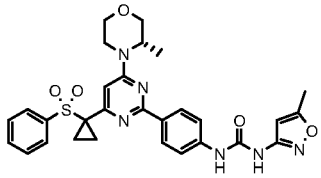
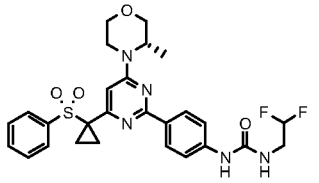
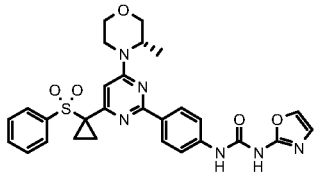
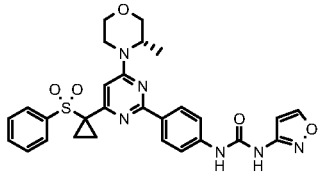
Example	Structure	NAME	LCMS MH+	Retention time (min)
36cu		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	575	1.76
36cv		3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	565	1.77
36cw		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	576	1.77
36cx		3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	566	1.78
36cy		1-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	553	2.14

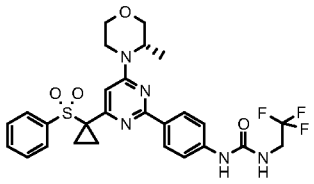
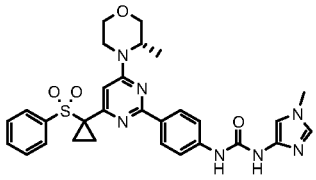
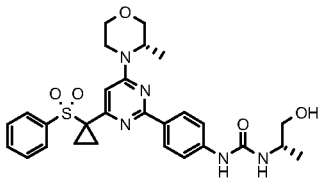
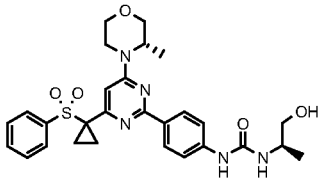
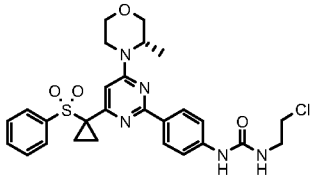
Example	Structure	NAME	LCMS MH+	Retention time (min)
36cz		3-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	567	2.29
36da		1-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	579	2.29
36db		1-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	583	1.93
36dc		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-cyclopropylurea	520	2.24
36dd		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-ethylurea	508	2.24
36de		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	524	1.89

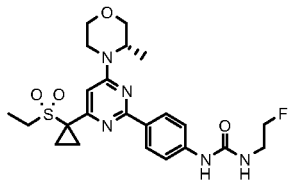
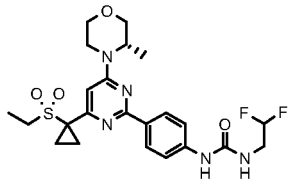
Example	Structure	NAME	LCMS MH+	Retention time (min)
36df		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-methylurea	494	2.08
36dg		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	538	1.95
36dh		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea	533	2.16
36di		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	564	1.41
36dj		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-(1-methylpyrazol-4-yl)urea	560	2.11
36dk****		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea	583	2.62

Example	Structure	NAME	LCMS MH+	Retention time (min)
36dl**		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea	588	2.24
36dm**		3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea	596	2.50
36dn**		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea	601	2.28
36do		N-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-hydroxypyrrolidine-1-carboxamide	564	2.02
36dp		2-[[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamoylamino]acetic acid	552	1.21

Example	Structure	NAME	LCMS MH+	Retention time (min)
36dq		2-[[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamoylamino]-N,N-dimethylacetamide	579	2.11
36dr		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-cyclopropyl-1-methylurea	548	2.61
36ds		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	540	2.33
36dt		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea	561	2.41
36du		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	588	2.31

Example	Structure	NAME	LCMS MH+	Retention time (min)
36dv		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-3-yl)urea	574	2.76
36dw		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-(5-methyl-1,2-oxazol-3-yl)urea	575	2.97
36dx		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	558	2.81
36dy		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-oxazol-2-yl)urea	561	2.51
36dz		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	561	2.85

Example	Structure	NAME	LCMS MH+	Retention time (min)
36ea		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2,2-trifluoroethyl)urea	576	2.94
36eb		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylimidazol-4-yl)urea	574	2.61
36ec		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea	552	2.47
36ed		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea	552	2.47
36ee		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-chloroethyl)urea	590	2.84

Example	Structure	NAME	LCMS MH+	Retention time (min)
36ef**		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	493	2.46
36eg**		3-(2,2-difluoroethyl)-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	511	2.60

* Following the initial reaction conditions the mixture was placed in a sealed tube and heated at 100°C in a microwave reactor for 10 minutes.

** The material was purified by trituration with diethyl ether

*** Following the initial reaction conditions the mixture was allowed to cool, tetrabutylammonium fluoride (1 equivalent) added and the reaction stirred at RT for 1 hour. The reaction was purified by prep HPLC.

**** The mixture was stirred at RT for 16 hours

Example 36a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.63 - 0.68 (2H, m), 0.68 - 0.73 (2H, m), 1.23 (3H, d), 1.53 - 1.58 (2H, m), 1.60 - 1.66 (2H, m), 1.88 - 1.98 (2H, m), 3.16 - 3.25 (1H, m), 3.28 - 3.35 (4H, m), 3.47 - 3.54 (3H, m), 3.63 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.23 (1H, d), 4.56 (1H, s), 4.69 (1H, t), 6.57 (1H, s), 6.77 (1H, s), 7.47 (2H, d), 8.21 (2H, d), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.142μM

Example 36b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.60 (2H, m), 1.62 - 1.68 (2H, m), 1.92 - 1.99 (2H, m), 3.23 - 3.31 (3H, m), 3.47 - 3.58 (3H, m), 3.64 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.21 (1H, d), 4.57 (1H, s), 4.71 (1H, t), 6.80 (1H, s), 7.64 (2H, d), 8.30 (2H, d), 9.46 (1H, s).

mTOR Kinase Assay (Echo): 0.00179μM

Example 36c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.52 - 1.58 (2H, m), 1.62 - 1.65 (2H, m), 1.89 - 1.97 (2H, m), 3.22 - 3.34 (3H, m), 3.44 - 3.56 (3H, m), 3.63 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.16 - 4.24 (1H, m), 4.35 (2H, d), 4.55 (1H, s), 4.69 (1H, s), 6.67 (1H, t), 6.77 (1H, s), 6.99 (2H, s), 7.52 (2H, d), 8.21 (2H, d), 8.99 (1H, s).

mTOR Kinase Assay (Echo): 0.114μM

Example 36d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70 - 0.78 (2H, m), 0.81 - 0.88 (2H, m), 1.23 (3H, d), 1.88 - 1.96 (1H, m), 2.01 - 2.14 (1H, m), 2.67 (3H, d), 2.81 - 2.99 (4H, m), 3.15 - 3.26 (2H, m), 3.50 (1H, dd), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.21 (1H, d), 4.55 (1H, s), 6.06 (1H, t), 6.70 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00317μM

Example 36e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39 - 0.44 (2H, m), 0.61 - 0.68 (2H, m), 0.72 - 0.78 (2H, m), 0.82 - 0.88 (2H, m), 1.23 (3H, d), 1.84 - 1.96 (1H, m), 2.02 - 2.12 (1H, m), 2.50 - 2.59 (2H, m), 2.81 - 3.01 (4H, m), 3.17 - 3.24 (1H, m), 3.50 (1H, dd), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.55 (1H, s), 6.42 (1H, t), 6.71 (1H, s), 7.48 (2H, d), 8.24 (2H, d), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.00667μM

Example 36f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.68 - 0.80 (2H, m), 0.81 - 0.89 (2H, m), 1.23 (3H, d), 1.84 - 1.95 (1H, m), 2.02 - 2.13 (1H, m), 2.76 - 3.00 (4H, m), 3.11 - 3.27 (3H, m), 3.43 - 3.56 (3H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.21 (1H, d), 4.54 (1H, s), 4.72 (1H, t), 6.24 (1H, t), 6.70 (1H, s), 7.48 (2H, d), 8.24 (2H, d), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.00278μM

Example 36g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.69 - 0.79 (2H, m), 0.81 - 0.89 (2H, m), 1.23 (3H, d), 1.84 - 1.96 (1H, m), 2.02 - 2.12 (1H, m), 2.63 - 2.73 (2H, m), 2.83 - 3.03 (4H, m), 3.14 - 3.23 (1H, m), 3.33 - 3.43 (2H, m), 3.51 (1H, dd), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.55 (1H, s), 6.51 (1H, t), 6.71 (1H, s), 7.51 (2H, d), 8.25 (2H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.00841μM

Example 36h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70 - 0.80 (2H, m), 0.82 - 0.91 (2H, m), 1.23 (3H, d), 1.86 - 1.97 (1H, m), 2.02 - 2.12 (1H, m), 2.77 - 3.03 (4H, m), 3.15 - 3.29 (5H, m), 3.51 (1H, d), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.55 (1H, s), 6.72 (1H, s), 7.38 (1H, s), 7.54 (2H, d), 7.76 (1H, s), 8.27 (2H, d), 8.37 (1H, s), 8.83 (1H, s).

mTOR Kinase Assay (Echo): 0.00314μM

Example 36i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.74 - 0.84 (2H, m), 0.87 - 0.94 (2H, m), 1.28 (3H, d), 1.91 - 2.01 (1H, m), 2.08 - 2.19 (1H, m), 2.84 - 3.09 (4H, m), 3.25 - 3.32 (2H, m), 3.56 (1H, d), 3.71 (1H, d), 3.82 (1H, d), 4.03 (1H, d), 4.27 (1H, d), 4.38 (2H, d), 4.61 (1H, s), 6.68 (1H, t), 6.76 (1H, s), 7.00 (1H, s), 7.56 (2H, d), 8.31 (2H, d), 8.98 (1H, s).

mTOR Kinase Assay (Echo): 0.0518μM

Example 36j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 0.68 - 0.75 (2H, m), 0.80 - 0.87 (2H, m), 1.22 (3H, d), 1.52 - 1.61 (2H, m), 1.76 - 1.86 (2H, m), 2.50 - 2.61 (4H, m), 2.74 - 2.90 (2H, m), 3.14 - 3.24 (1H, m), 3.50 (2H, dd), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.54 (1H, s), 6.42 (1H, s), 6.81 (1H, s), 7.50 (2H, d), 8.24 (2H, d), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.018μM

Example 36k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.66 - 0.77 (2H, m), 0.80 - 0.89 (2H, m), 1.22 (3H, d), 1.52 - 1.61 (2H, m), 1.76 - 1.86 (2H, m), 2.43 - 2.61 (3H, m), 2.75 - 2.89 (2H, m), 3.16 - 3.22 (3H, m), 3.43 - 3.55 (3H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.54 (1H, s), 4.73 (1H, t), 6.25 (1H, t), 6.81 (1H, s), 7.49 (2H, d), 8.24 (2H, d), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.0131μM

Example 36l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.66 - 0.76 (2H, m), 0.82 - 0.87 (2H, m), 1.22 (3H, d), 1.53 - 1.60 (2H, m), 1.74 - 1.85 (2H, m), 2.49 - 2.61 (3H, m), 2.65 - 2.72 (2H, m), 2.74 - 2.88 (2H, m), 3.16 - 3.25 (1H, m), 3.33 - 3.40 (2H, m), 3.50 (1H, d), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.23 (1H, d), 4.55 (1H, s), 6.52 (1H, t), 6.81 (1H, s), 7.51 (2H, d), 8.26 (2H, d), 8.91 (1H, s).

mTOR Kinase Assay (Echo): 0.0428μM

Example 36m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.67 - 0.77 (2H, m), 0.81 - 0.89 (2H, m), 1.22 (3H, d), 1.52 - 1.64 (4H, m), 1.78 - 1.85 (2H, m), 2.41 - 2.56 (3H, m), 2.74 - 2.93 (2H, m), 3.13 - 3.25 (3H, m), 3.42 - 3.56 (3H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.16 - 4.26 (1H, m), 4.47 (1H, t), 4.54 (1H, s), 6.19 (1H, t), 6.81 (1H, s), 7.49 (2H, d), 8.24 (2H, d), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.0347μM

Example 36n: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.76 - 1.80 (2H, m), 1.93 - 1.97 (2H, m), 2.48 (3H, s), 3.14 - 3.21 (1H, m), 3.47 (1H, t), 3.62 (1H, d), 3.76 (1H, d), 3.97

(1H, d), 4.14 - 4.17 (1H, m), 4.32 (2H, d), 4.42 - 4.49 (1H, m), 6.61 (1H, t), 6.78 (1H, s), 6.93 (2H, bs), 7.43 (2H, d), 7.84 (1H, s), 7.90 (2H, d), 8.90 (1H, s), 11.85 (1H, s).

mTOR Kinase Assay (Echo): 0.0248μM

Example 36o: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.77 - 1.79 (2H, m), 1.94 - 1.97 (2H, m), 2.48 (3H, s), 2.70 (2H, t), 3.14 - 3.22 (1H, m), 3.35 - 3.39 (2H, m), 3.44 - 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.15 - 4.18 (1H, m), 4.42 - 4.48 (1H, m), 6.51 (1H, t), 6.78 (1H, s), 7.43 (2H, d), 7.84 (1H, s), 7.90 (2H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.00358μM

Example 36p: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.77 - 1.81 (2H, m), 1.95 - 1.99 (2H, m), 2.51 (3H, s), 3.16 - 3.24 (1H, m), 3.45 - 3.51 (1H, m), 3.61 - 3.65 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.16 - 4.20 (1H, m), 4.43 - 4.49 (1H, m), 6.82 (1H, s), 7.55 (2H, d), 7.87 (1H, s), 8.00 (2H, d), 8.37 (1H, s), 9.45 (1H, s), 11.32 (1H, s).

mTOR Kinase Assay (Echo): 0.00161μM

Example 36q: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.63 - 0.66 (2H, m), 0.69 - 0.73 (2H, m), 1.21 (3H, d), 1.77 - 1.80 (2H, m), 1.94 - 1.97 (2H, m), 2.48 (3H, s), 3.14 - 3.21 (1H, m), 3.44 (2H, d), 3.47 - 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.98 (1H, m), 4.14 - 4.17 (1H, m), 4.42 - 4.48 (1H, m), 4.83 (1H, s), 6.54 (1H, s), 6.77 (1H, s), 7.40 (2H, d), 7.84 (1H, s), 7.89 (2H, d), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.0889μM

Example 36r: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.54 - 1.57 (2H, m), 1.65 - 1.68 (2H, m), 2.70 (2H, t), 3.27 (3H, s), 3.35 - 3.40 (2H, m), 3.72 (8H, s), 6.53 (1H, t), 6.81 (1H, s), 7.50 - 7.54 (2H, m), 8.20 - 8.24 (2H, m), 8.93 (1H, s).

mTOR Kinase Assay (Echo): 0.00733μM

Example 36s: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.55 - 1.59 (2H, m), 1.67 - 1.70 (2H, m), 3.27 (3H, s), 3.73 (8H, s), 6.86 (1H, s), 7.61 - 7.65 (2H, m), 8.30 - 8.33 (2H, m), 8.37 (1H, s), 9.44 (1H, s), 11.40 (1H, s).

mTOR Kinase Assay (Echo): 0.00475μM

Example 36t: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.54 - 1.57 (2H, m), 1.65 - 1.68 (2H, m), 3.27 (3H, s), 3.72 (8H, s), 4.32 (2H, d), 6.62 (1H, t), 6.81 - 6.83 (2H, m), 7.03 (1H, s), 7.50 - 7.54 (2H, m), 8.20 - 8.23 (2H, m), 8.94 (1H, s), 11.83 (1H, s).

mTOR Kinase Assay (Echo): 0.194μM

Example 36u: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.53 - 1.56 (2H, m), 1.62 - 1.65 (2H, m), 2.70 (2H, t), 3.17 - 3.24 (1H, m), 3.35 - 3.52 (5H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.24 (1H, m), 4.52 - 4.58 (1H, m), 6.53 (1H, t), 6.78 (1H, s), 7.50 - 7.54 (2H, m), 8.18 - 8.22 (2H, m), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.00922μM

Example 36v: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.63 - 0.67 (2H, m), 0.69 - 0.73 (2H, m), 1.23 (3H, d), 1.32 (3H, t), 1.53 - 1.58 (2H, m), 1.60 - 1.65 (2H, m), 3.17 - 3.24 (1H, m), 3.40 - 3.52 (5H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.24 (1H, m), 4.52 - 4.58 (1H, m), 4.81 - 4.86 (1H, m), 6.57 (1H, s), 6.78 (1H, s), 7.46 - 7.50 (2H, m), 8.17 - 8.21 (2H, m), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.467μM

Example 36w: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.53 - 1.56 (2H, m), 1.62 - 1.65 (2H, m), 3.17 - 3.24 (1H, m), 3.40 - 3.52 (3H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.18 - 4.24 (1H, m), 4.32 (2H, d), 4.53 - 4.58 (1H, m), 6.63 (1H, t), 6.78 (1H, s), 6.84 (1H, s), 7.03 (1H, s), 7.50 - 7.54 (2H, m), 8.18 - 8.22 (2H, m), 8.93 (1H, s), 11.84 (1H, s).

mTOR Kinase Assay (Echo): 0.11μM

Example 36x: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.63 - 0.66 (2H, m), 1.18 (2H, d), 1.59 - 1.62 (3H, m), 1.88 - 1.90 (2H, m), 2.09 (2H, s), 3.15 (1H, dt), 3.30 (2H, s), 3.44 - 3.49 (1H, m), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.41 (1H, s), 4.83 (1H, s), 6.53 (1H, s), 6.65 (1H, s), 7.36 - 7.44 (4H, m), 7.80 - 7.86 (4H, m), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.182μM

Example 36y: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.59 - 1.62 (2H, m), 1.88 - 1.91 (2H, m), 2.70 (2H, t), 3.13 - 3.18 (1H, m), 3.33 - 3.39 (2H, m), 3.46 (1H, t), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.14 (1H, d), 4.43 (1H, s), 6.49 (1H, t), 6.65 (1H, s), 7.40 - 7.44 (4H, m), 7.81 - 7.86 (4H, m), 8.89 (1H, s).

mTOR Kinase Assay (Echo): 0.00131μM

Example 36z: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.62 - 1.64 (2H, m), 1.90 - 1.94 (2H, m), 3.17 - 3.18 (1H, m), 3.42 - 3.51 (1H, m), 3.62 (1H, d), 3.76 (1H, d), 3.94 - 3.98 (1H, m), 4.16 (1H, d), 4.44 (1H, s), 6.69 (1H, s), 7.43 (2H, t), 7.52 (2H, d), 7.83 - 7.87 (2H, m), 7.92 (2H, d), 8.37 (1H, s), 9.39 (1H, s), 11.34 (1H, s).

mTOR Kinase Assay (Echo): 0.00208μM

Example 36aa: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.59 - 1.62 (2H, m), 1.88 - 1.91 (2H, m), 3.12 - 3.19 (1H, m), 3.43 - 3.49 (1H, m), 3.59 - 3.63 (1H, m), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.32 (2H, d), 4.42 (1H, s), 6.60 (1H, t), 6.65 (1H, s), 6.94 (2H, s), 7.42 (4H, t), 7.81 - 7.86 (4H, m), 8.91 (1H, s), 11.89 (1H, s).

mTOR Kinase Assay (Echo): 0.0749μM

Example 36ab: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.19 (3H, d), 1.51 - 1.60 (2H, m), 1.80 - 1.89 (2H, m), 2.53 - 2.58 (1H, m), 2.70 - 2.80 (4H, m), 3.12 (1H, dt), 3.47 (1H, dt), 3.63 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.10 (1H, d), 4.46 (1H, d), 6.41 (1H, d), 6.59 (1H, s), 7.37 (2H, d), 7.54 - 7.56 (1H, m), 7.57 - 7.59 (1H, m), 7.76 (2H, d), 7.85 (1H, dt), 8.48 (1H, s), 8.73 - 8.75 (1H, m).

mTOR Kinase Assay (Echo): 0.011μM

Example 36ac: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.52 - 1.58 (2H, m), 1.81 - 1.89 (2H, m), 2.68 - 2.80 (4H, m), 3.08 - 3.15 (2H, m), 3.27 (1H, s), 3.44 - 3.50 (3H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.10 (1H, d), 4.47 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.59 (1H, s), 7.36 (2H, d), 7.54 - 7.59 (2H, m), 7.76 (2H, d), 7.85 (1H, dt), 8.73 - 8.75 (2H, m).

mTOR Kinase Assay (Echo): 0.00441μM

Example 36ad: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 8.87 (1H, s), 8.74 (1H, d), 7.85 (1H, td), 7.77 (2H, d), 7.54 - 7.59 (2H, m), 7.38 (2H, d), 6.60 (1H, s), 6.51 (1H, t), 4.48 (1H, s), 4.10 (1H, d), 3.96 (1H, dd), 3.75 (1H, d), 3.63 (1H, dd), 3.47 (1H, td), 3.37 (2H, q), 3.12 (1H, td), 2.72 - 2.81 (4H, m), 2.70 (2H, t), 1.80 - 1.89 (2H, m), 1.55 - 1.58 (2H, m), 1.19 (3H, d).

mTOR Kinase Assay (Echo): 0.0323μM

Example 36ae: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.55 - 1.63 (4H, m), 1.81 - 1.89 (2H, m), 2.68 - 2.80 (4H, m), 3.08 - 3.19 (3H, m), 3.45 - 3.49 (3H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.10 (1H, d), 4.48 (2H, t), 6.18 (1H, t), 6.59 (1H, s), 7.36 (2H, d), 7.53 - 7.59 (2H, m), 7.75 (2H, d), 7.85 (1H, dt), 8.65 (1H, s), 8.74 (1H, d).

mTOR Kinase Assay (Echo): 0.0151μM

Example 36af: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.18 (3H, d), 1.88 - 1.95 (1H, m), 2.11 - 2.17 (1H, m), 2.53 - 2.57 (2H, m), 2.79 - 2.87 (2H, m), 3.12 (1H, dt), 3.23 - 3.28 (3H, m), 3.46 (1H, dt), 3.62 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.09 (1H, d), 4.44 (1H, s), 6.40 (1H, d), 6.48 (1H, s), 7.37 (2H, d), 7.58 - 7.61 (2H, m), 7.87 (1H, ddt), 8.48 (1H, s), 8.74 - 8.75 (1H, m).

mTOR Kinase Assay (Echo): 0.00275μM

Example 36ag: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.86 - 1.97 (1H, m), 2.09 - 2.18 (1H, m), 2.65 (3H, s), 2.79 - 2.87 (2H, m), 3.12 (1H, dt), 3.22 - 3.28 (2H, m), 3.46 (1H, dt), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.08 (1H, d), 4.44 (1H, s), 6.04 - 6.07 (1H, m), 6.48 (1H, s), 7.37 (2H, d), 7.58 - 7.61 (2H, m), 7.74 (2H, d), 7.87 (1H, dt), 8.68 (1H, s), 8.75 (1H, d).

mTOR Kinase Assay (Echo): 0.0013μM

Example 36ah: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.88 - 1.95 (1H, m), 2.10 - 2.17 (1H, m), 2.81 - 2.87 (2H, m), 3.08 - 3.19 (2H, m), 3.22 - 3.27 (3H, m), 3.44 - 3.50 (3H, m), 3.62 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.08 (1H, d), 4.45 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.48 (1H, s), 7.35 (2H, d), 7.60 (2H, t), 7.74 (2H, d), 7.87 (1H, t), 8.75 (2H, s).

mTOR Kinase Assay (Echo): 0.00247μM

Example 36ai: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.88 - 1.95 (1H, m), 2.09 - 2.16 (1H, m), 2.69 (2H, t), 2.78 - 2.87 (2H, m), 3.10 - 3.16 (1H, m), 3.23 - 3.25 (3H, m), 3.35 - 3.39 (2H, m), 3.47 (1H, t), 3.62 (1H, dd), 3.74 (1H, d), 3.95 (1H, d), 4.09 (1H, d), 4.45 (1H, s), 6.49 (1H, s), 7.38 (2H, d), 7.58 - 7.61 (2H, m), 7.76 (2H, d), 7.87 (1H, dt), 8.74 - 8.75 (1H, m), 8.86 (1H, s).

mTOR Kinase Assay (Echo): 0.00561μM

Example 36aj: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.89 - 1.97 (1H, m), 2.11 - 2.18 (1H, m), 2.79 - 2.87 (2H, m), 3.13 (1H, dt), 3.23 - 3.29 (2H, m), 3.47 (1H, dt), 3.62 (1H, dd), 3.75 (1H, d), 3.79 (3H, s), 3.96 (1H, dd), 4.10 (1H, d), 4.45 (1H, s), 6.50 (1H, s), 7.38 (1H, s), 7.41 (2H, d), 7.59 - 7.62 (1H, m), 7.76 (1H, s), 7.77 (2H, d), 7.86 - 7.90 (1H, m), 7.88 (1H, dt), 8.38 (1H, s), 8.75 - 8.76 (1H, m), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00258μM

Example 36ak: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.89 - 1.98 (1H, m), 2.10 - 2.19 (1H, m), 2.79 - 2.87 (2H, m), 3.13 (1H, dt), 3.23 - 3.28 (2H, m), 3.47 (1H, dt), 3.62 (1H, dd), 3.74 (2H, s), 3.75 (1H, d), 3.96 (1H, dd), 4.10 (1H, d), 4.45 (1H, s), 6.25 (1H, d), 6.51 (1H, s), 7.43 (2H, d), 7.54 (1H, d), 7.59 - 7.63 (1H, m), 7.60 (1H, d), 7.79 (2H, d), 7.88 (1H, dt), 8.75 - 8.76 (1H, m), 8.91 (1H, s), 9.11 (1H, s).

mTOR Kinase Assay (Echo): 0.00245μM

Example 36al: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.41 (2H, m), 0.63 - 0.66 (2H, m), 1.59 (2H, m), 1.88 (2H, m), 2.57 - 2.61 (1H, m), 3.66 (4H, s), 3.68 (4H, s), 6.39 (1H, s), 6.71 (1H, s), 7.38 - 7.43 (4H, m), 7.78 (2H, d), 7.85 (2H, t), 8.52 (1H, s).

mTOR Kinase Assay (Echo): 0.0187μM

Example 36am: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.58 - 1.61 (2H, m), 1.87 - 1.90 (2H, m), 2.70 (2H, t), 3.37 (2H, q), 3.67 (4H, s), 3.69 (4H, s), 6.49 (1H, t), 6.72 (1H, s), 7.39 - 7.44 (4H, m), 7.79 - 7.86 (4H, m), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.0277μM

Example 36an: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.59 - 1.62 (2H, m), 1.89 - 1.92 (2H, m), 3.68 (4H, s), 3.70 (4H, s), 6.76 (1H, s), 7.43 (2H, t), 7.51 (2H, d), 7.83 - 7.96 (4H, m), 8.37 (1H, s), 9.39 (1H, s), 11.33 (1H, s).

mTOR Kinase Assay (Echo): 0.0104μM

Example 36ao: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.57 - 1.61 (2H, m), 1.87 - 1.90 (2H, m), 3.09 - 3.16 (2H, m), 3.65 - 3.66 (4H, m), 3.69 - 3.70 (4H, m), 6.12 (1H, t), 6.71 (1H, s), 7.37 - 7.44 (4H, m), 7.78 (2H, d), 7.82 - 7.86 (2H, m), 8.64 (1H, s)

Example 36ap: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.57 - 1.61 (2H, m), 1.87 - 1.90 (2H, m), 2.66 (3H, d), 3.66 (4H, s), 3.69 - 3.70 (4H, m), 6.01 - 6.05 (1H, m), 6.71 (1H, s), 7.38 - 7.43 (4H, m), 7.78 (2H, d), 7.82 - 7.86 (2H, m), 8.72 (1H, s)

Example 36aq: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.58 - 1.61 (2H, m), 1.88 - 1.91 (2H, m), 3.63 - 3.67 (4H, m), 3.69 - 3.73 (4H, m), 3.79 (3H, s), 6.73 (1H, s), 7.38 - 7.45 (5H, m), 7.77 - 7.86 (5H, m), 8.34 (1H, s), 8.82 (1H, s)

Example 36ar: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.66 - 1.69 (2H, m), 1.95 - 1.98 (2H, m), 3.15 - 3.19 (2H, m), 3.44 - 3.48 (2H, m), 3.69 (8H, s), 4.72 (1H, t), 6.22 (1H, t), 6.73 (1H, s), 7.34 (2H, d), 7.63 (2H, d), 7.77 (2H, d), 8.77 (1H, s), 8.86 (2H, d)

Example 36as: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.66 - 1.70 (2H, m), 1.96 - 1.99 (2H, m), 3.69 (8H, s), 3.79 (3H, s), 6.74 (1H, s), 7.40 (3H, d), 7.66 (2H, d), 7.77 - 7.78 (3H, m), 8.35 (1H, s), 8.80 (1H, s), 8.87 (2H, d).

mTOR Kinase Assay (Echo): 0.00911μM

Example 36at: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.66 - 1.69 (2H, m), 1.95 - 1.99 (2H, m), 2.66 (3H, d), 3.69 (8H, s), 6.02 - 6.04 (1H, m), 6.73 (1H, s), 7.35 (2H, d), 7.63 (2H, d), 7.77 (2H, d), 8.71 (1H, s), 8.86 (2H, d)

Example 36au: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.66 - 1.69 (2H, m), 1.95 - 1.98 (2H, m), 3.09 - 3.16 (2H, m), 3.69 (8H, s), 6.13 (1H, t), 6.73 (1H, s), 7.35 (2H, d), 7.63 (2H, d), 7.77 (2H, d), 8.63 (1H, s), 8.86 (2H, d)

Example 36av: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.66 - 1.69 (2H, m), 1.95 - 1.98 (2H, m), 2.53 - 2.57 (1H, m), 3.69 (8H, s), 6.40 (1H, d), 6.73 (1H, s), 7.36 (2H, d), 7.64 (2H, d), 7.77 (2H, d), 8.50 (1H, s), 8.86 (2H, d).

mTOR Kinase Assay (Echo): 0.00995μM

Example 36aw: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.66 - 1.69 (2H, m), 1.95 - 1.98 (2H, m), 2.70 (2H, t), 3.36 (2H, q), 3.69 (8H, s), 6.49 (1H, t), 6.73 (1H, s), 7.37 (2H, d), 7.64 (2H, d), 7.77 (2H, d), 8.86 (2H, d), 8.89 (1H, s)

Example 36ax: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.56 - 1.63 (2H, m), 1.66 - 1.69 (3H, m), 1.95 - 1.98 (2H, m), 3.16 (2H, q), 3.47 (2H, q), 3.69 (8H, s), 4.47 (1H, t), 6.17 (1H, t), 6.73 (1H, s), 7.34 (2H, d), 7.63 (2H, d), 7.77 (2H, d), 8.86 (2H, d)

Example 36ay: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.19-3.26 (1H, td), 3.30 (3H, s), 3.46-3.53 (1H, td), 3.63-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.00 (1H, dd), 4.22-4.25 (1H, bd), 4.58 (1H, bs), 6.81 (1H, s), 7.14 (1H, s), 7.39-7.40 (1H, d), 7.59-7.62 (2H, d), 8.28-8.30 (2H, d), 9.21 (1H, s), 10.50 (1H, s).

mTOR Kinase Assay (Echo): 0.00117μM

Example 36az: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 2.44 (3H, s), 3.19-3.26 (1H, td), 3.31 (3H, s), 3.46-3.52 (1H, td), 3.63-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.98-4.00 (1H, dd), 4.22-4.25 (1H, bd), 4.59 (1H, bs), 6.81 (1H, s), 7.61-7.63 (2H, d), 8.21-8.22 (1H, d), 8.28-8.30 (2H, d), 8.99-9.00 (1H, d), 9.41 (1H, s), 9.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00149μM

Example 36ba: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.19-3.25 (1H, td), 3.30 (3H, s), 3.47-3.52 (1H, td), 3.63-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.00 (1H, dd), 4.22-4.25 (1H, d), 4.59 (1H, bs), 6.81 (1H, s), 7.16 (1H, s), 7.63-7.66 (2H, d), 7.84 (1H, bs), 8.28-8.30 (2H, d), 10.45 (1H, bs), 10.88 (1H, bs).

mTOR Kinase Assay (Echo): 0.00312μM

Example 36bb: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.24 (3H, d), 1.54-1.58 (2H, q), 1.59-1.63 (2H, m), 1.66-1.69 (2H, q), 3.15-3.25 (3H, m), 3.30 (3H, s), 3.45-3.52 (3H, m), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.46-4.49 (1H,

t), 4.58 (1H, bs), 6.19-6.22 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.0205μM

Example 36bc: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.67 (2H, m), 1.16-1.18 (3H, d), 1.60-1.68 (2H, m), 1.89-1.92 (2H, m), 3.10-3.18 (1H, td), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.08-4.12 (1H, d), 4.38 (1H, bs), 5.76 (1H, s), 6.40-6.41 (1H, d), 6.63 (1H, s), 7.38-7.40 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, t), 7.78-7.85 (4H, m), 8.49 (1H, s).

mTOR Kinase Assay (Echo): 0.00205μM

Example 36bd: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.57-1.67 (4H, m), 1.81-1.92 (4H, m), 2.18-2.25 (2H, m), 3.10-3.18 (1H, td), 3.42-3.49 (1H, td), 3.59-3.62 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.08-4.19 (2H, m), 4.38 (1H, bs), 6.42-6.44 (1H, d), 6.62 (1H, s), 7.35-7.37 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.85 (4H, m), 8.52 (1H, s).

mTOR Kinase Assay (Echo): 0.00258μM

Example 36be: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.89-1.92 (2H, m), 3.10-3.20 (1H, td), 3.30 (2H, m (under water peak)) 3.42-3.55 (2H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.07-4.11 (1H, d), 4.38 (1H, bs), 6.35-6.38 (1H, t), 6.47-6.49 (1H, d), 6.63 (1H, s), 7.38-7.40 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.81 (2H, d), 7.84-7.86 (2H, d), 8.89 (1H, s).

mTOR Kinase Assay (Echo): 0.00376μM

Example 36bf: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10-1.12 (6H, d), 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.59-1.92 (2H, m), 3.10-3.19 (1H, td), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.81 (2H, m), 3.94-3.97 (1H, dd), 4.09-4.12 (1H, d), 4.38 (1H, bs), 6.02-6.04 (1H, d), 6.62 (1H, s), 7.35-7.38 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.85 (4H, m), 8.49 (1H, s).

mTOR Kinase Assay (Echo): 0.00457μM

Example 36bg: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.89-1.90 (2H, m), 3.09-3.16 (3H, m), 3.42-3.49 (1H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.95-3.97 (1H, dd), 4.09-4.12 (1H, d), 4.38 (1H, bs), 6.12-6.15 (1H, t), 6.62 (1H, s), 7.37-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, t), 7.78-7.85 (4H, m), 8.62 (1H, s).

mTOR Kinase Assay (Echo): 0.000922μM

Example 36bh: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.89-1.92 (2H, m), 3.10-3.15 (1H, td), 3.17-3.19 (2H, m), 3.42-3.49 (3H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.08-4.11 (1H, d), 4.38 (1H, bs), 4.71-4.74 (1H, t), 6.22-6.24 (1H, t), 6.62 (1H, s), 7.36-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.85 (4H, m), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.00121μM

Example 36bi: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87-0.91 (3H, t), 1.16-1.18 (3H, d), 1.41-1.50 (2H, m), 1.60-1.67 (2H, m), 1.89-1.92 (2H, m), 3.04-3.09 (2H, q), 3.10-3.17 (1H, td), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.08-4.12 (1H, d), 4.39 (1H, bs), 6.16-6.19 (1H, t), 6.62 (1H, s), 7.37-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.85 (4H, m), 8.61 (1H, s).

mTOR Kinase Assay (Echo): 0.00231μM

Example 36bj: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.60-1.68 (2H, m), 1.89-1.92 (2H, m), 2.65-2.66 (3H, d), 3.10-3.17 (1H, td), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.09-4.12 (1H, d), 4.38 (1H, bs), 6.03-6.06 (1H, q), 6.62 (1H, s), 7.38-7.40 (2H, d), 7.57-7.61 (2H, t), 7.70-7.73 (1H, tt), 7.74-7.85 (4H, m), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.000621μM

Example 36bk: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.24 (6H, s), 1.60-1.67 (2H, m), 1.88-1.91 (2H, m), 3.10-3.17 (1H, td), 3.38-3.40 (2H, d), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.08-4.12 (1H, d), 4.38 (1H, bs), 4.93-4.96 (1H, t), 5.98 (1H, s), 6.62 (1H, s), 7.33-7.35 (2H, d), 7.58-7.61 (2H, t), 7.70-7.74 (1H, m), 7.78-7.84 (4H, m), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00433μM

Example 36bl: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.56-1.67 (4H, m), 1.89-1.92 (2H, m), 3.10-3.17 (3H, m), 3.42-3.49 (3H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.08-4.12 (1H, d), 4.38 (1H, bs), 4.46-4.49 (1H, t), 6.16-6.19 (1H, t), 6.62 (1H, s), 7.37-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.85 (4H, m), 8.67 (1H, s).

mTOR Kinase Assay (Echo): 0.00208μM

Example 36bm: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.18 (3H, d), 1.60-1.68 (2H, m), 1.89-1.92 (2H, m), 2.68-2.72 (2H, t), 3.11-3.18 (1H, td), 3.34-3.39 (2H, q), 3.43-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.09-4.12 (1H, d), 4.38 (1H, bs), 6.49-6.52 (1H, t), 6.63 (1H, s), 7.39-7.41 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.86 (4H, m), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.00193μM

Example 36bn: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.60-1.68 (2H, m), 1.88-1.93 (2H, m), 3.10-3.17 (1H, td), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.08-4.12 (1H, d), 4.31-4.33 (2H, d), 4.38 (1H, bs), 6.59-6.63 (2H, m), 6.94 (2H, bs), 7.39-7.41 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, t), 7.78-7.81 (2H, d), 7.84-7.87 (2H, d), 8.88 (1H, s), 11.84 (1H, bs).

mTOR Kinase Assay (Echo): 0.00637μM

Example 36bo: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.63-0.66 (2H, q), 0.69-0.73 (2H, q), 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.89-1.92 (2H, m), 3.10-3.17 (1H, td), 3.42-3.49 (3H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.09-4.12 (1H, d), 4.38 (1H, bs), 4.83 (1H, bs), 6.54 (1H, s), 6.63 (1H, s), 7.35-7.37 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.74-7.85 (4H, m), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.0176μM

Example 36bp: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.89-1.90 (2H, m), 3.10-3.17 (1H, td), 3.42-3.49 (1H, td), 3.59-3.62 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.08-4.12 (1H, d), 4.38 (1H, bs), 4.43-4.46 (2H, t), 4.72-4.81 (3H, m), 6.63 (1H, s), 6.91-6.93 (1H, d), 7.37-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.86 (4H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00198μM

Example 36bq: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.19 (3H, d), 1.61-1.66 (2H, m), 1.91-1.92 (2H, m), 3.12-3.18 (1H, td), 3.44-3.50 (1H, td), 3.61-3.64 (1H, dd), 3.74-3.77 (1H, d), 3.95-3.99 (1H, dd), 4.10-4.14 (1H, d), 4.40 (1H, bs), 6.66 (1H, s), 7.52-7.54 (2H, d), 7.59-7.62 (2H, t), 7.72-7.76 (1H, t), 7.79-7.81 (3H, d), 7.90-7.92 (2H, d), 8.28 (1H, s), 9.39 (1H, s).

mTOR Kinase Assay (Echo): 0.00131μM

Example 36br: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.18 (3H, d), 1.61-1.68 (2H, m), 1.90-1.91 (2H, m), 3.11-3.17 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.74-3.76 (1H, d), 3.79 (3H, s), 3.94-3.98 (1H, dd), 4.09-4.13 (1H, d), 4.39 (1H, bs), 6.64 (1H, s), 7.38 (1H,

s), 7.42-7.44 (2H, d), 7.58-7.62 (2H, t), 7.71-7.73 (1H, t), 7.77-7.81 (3H, m), 7.86-7.88 (2H, d), 8.36 (1H, s), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00188μM

Example 36bs: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39-0.43 (2H, m), 0.62-0.67 (2H, m), 1.19-1.20 (3H, d), 1.82-1.93 (1H, m), 2.03-2.14 (1H, m), 2.54 (1H, m), 2.75-2.82 (2H, m), 3.01-3.09 (2H, m), 3.10-3.17 (1H, td), 3.44-3.51 (1H, td), 3.61-3.65 (1H, dd), 3.74-3.77 (1H, d), 3.94-3.98 (1H, dd), 4.06-4.09 (1H, d), 4.44 (1H, bs), 6.40-6.41 (1H, d), 6.46 (1H, s), 7.36-7.39 (2H, d), 7.43-7.51 (4H, m), 7.58-7.62 (1H, m), 7.78-7.80 (2H, d), 8.48 (1H, s).

mTOR Kinase Assay (Echo): 0.00161μM

Example 36bt: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21 (3H, d), 1.82-1.93 (1H, m), 2.03-2.14 (1H, m), 2.74-2.82 (2H, m), 3.02-3.10 (2H, m), 3.13-3.19 (3H, m), 3.44-3.51 (3H, m), 3.62-3.65 (1H, dd), 3.74-3.77 (1H, d), 3.94-3.98 (1H, dd), 4.07-4.10 (1H, d), 4.45 (1H, bs), 4.71-4.74 (1H, t), 6.22-6.25 (1H, t), 6.47 (1H, s), 7.35-7.37 (2H, d), 7.44-7.51 (4H, m), 7.58-7.62 (1H, m), 7.78-7.81 (2H, d), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.00105μM

Example 36bu: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21 (3H, d), 1.82-1.93 (1H, m), 2.04-2.14 (1H, m), 2.65-2.66 (3H, d), 2.75-2.82 (2H, m), 3.02-3.11 (2H, m), 3.13-3.19 (1H, td), 3.45-3.51 (1H, td), 3.62-3.65 (1H, dd), 3.74-3.77 (1H, d), 3.94-3.98 (1H, dd), 4.06-4.10 (1H, d), 4.45 (1H, bs), 6.03-6.06 (1H, q), 6.46 (1H, s), 7.36-7.38 (2H, d), 7.44-7.51 (4H, m), 7.58-7.62 (1H, m), 7.78-7.80 (2H, d), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.00118μM

Example 36bv: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20-1.21 (3H, d), 1.83-1.94 (1H, m), 2.04-2.15 (1H, m), 2.76-2.83 (2H, m), 3.02-3.10 (2H, m), 3.11-3.18 (1H, td), 3.45-3.52 (1H, td), 3.62-3.66 (1H, dd), 3.75-3.77 (1H, d), 3.79 (3H, s), 3.95-3.98 (1H, dd), 4.07-4.10 (1H, d), 4.46 (1H, bs), 6.48 (1H, s), 7.38-7.51 (7H, m), 7.59-7.76 (1H, m), 7.76 (1H, s), 7.82-7.84 (2H, d), 8.36 (1H, s), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00264μM

Example 36bw: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.67 (2H, m), 1.20-1.22 (3H, d), 1.49-1.58 (2H, m), 1.80-1.87 (2H, m), 2.53 (2H, m), 2.67-2.73 (2H, m), 3.12-3.18 (1H, td), 3.46-3.53 (1H, td), 3.63-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.95-3.99 (1H, dd), 4.09-4.12 (1H, d), 4.48-4.49 (1H, bs), 6.40-6.41 (1H, d), 6.62 (1H, s), 7.37-7.39 (2H, d), 7.42-7.48 (4H, m), 7.57-7.61 (1H, m), 7.80-7.82 (2H, d), 8.48 (1H, s).

mTOR Kinase Assay (Echo): 0.00909μM

Example 36bx: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20-1.22 (3H, d), 1.50-1.59 (2H, m), 1.80-1.89 (2H, m), 2.52-2.61 (2H, m), 2.66-2.74 (2H, m), 3.11-3.19 (3H, m), 3.44-3.52 (3H, m), 3.63-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.95-3.99 (1H, dd), 4.08-4.12 (1H, d), 4.48 (1H, bs), 4.71-4.74 (1H, t), 6.22-6.25 (1H, t), 6.62 (1H, s), 7.35-7.38 (2H, d), 7.42-7.48 (4H, m), 7.57-7.61 (1H, m), 7.80-7.82 (2H, d), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.00269μM

Example 36by: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20-1.22 (3H, d), 1.52-1.56 (2H, m), 1.57-1.63 (2H, m), 1.79-1.88 (2H, m), 2.54-2.61 (2H, m), 2.67-2.72 (2H, m), 3.11-3.17 (3H, m), 3.45-3.52 (3H, m), 3.63-3.66 (1H, dd), 3.75-3.78 (1H, d), 3.95-3.99 (1H, dd), 4.09-4.12 (1H, d), 4.46-4.49 (2H, m), 6.17-6.19 (1H, t), 6.62 (1H, s), 7.35-7.38 (2H, d), 7.42-7.48 (4H, m), 7.57-7.61 (1H, m), 7.79-7.82 (2H, d), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.012μM

Example 36bz: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21-1.22 (3H, d), 1.50-1.59 (2H, m), 1.81-1.88 (2H, m), 2.53-2.59 (2H, m), 2.67-2.72 (4H, m), 3.11-3.19 (1H, td), 3.34-3.39 (2H, m), 3.46-3.52 (1H, td), 3.63-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.95-3.99 (1H, dd), 4.09-4.13 (1H, d), 4.49 (1H, bs), 6.49-6.52 (1H, t), 6.63 (1H, s), 7.38-7.40 (2H, d), 7.42-7.48 (4H, m), 7.57-7.61 (1H, m), 7.81-7.83 (2H, d), 8.86 (1H, s).

mTOR Kinase Assay (Echo): 0.0143μM

Example 36ca: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.68-1.74 (2H, m), 2.20-2.27 (2H, td), 2.67-2.68 (3H, d), 2.82-2.87 (2H, t), 3.05-3.09 (2H, m), 3.18-3.22 (1H, m), 3.22-3.25 (2H, t), 3.37-3.40 (2H, t), 3.50-3.58 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.96 (2H, m), 3.98-4.01 (1H, dd), 4.39-4.32 (1H, d), 4.57 (1H, s), 6.10-6.13 (1H, q), 6.86 (1H, s), 7.50-7.53 (2H, d), 8.21-8.23 (2H, d), 8.79 (1H, s)

Example 36cb: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.68-1.75 (2H, m), 2.20-2.27 (2H, td), 2.54 (3H, d), 2.82-2.87 (2H, t), 3.06-3.11 (2H, m), 3.12-3.16 (1H, m), 3.18-3.24 (2H, m), 3.37-3.40 (2H, t), 3.50-3.57 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.91-3.95 (2H, m), 4.00-4.02 (1H, dd), 4.29-4.32 (1H, d), 4.58 (1H, s), 6.27-6.29 (1H, t), 6.86 (1H, s), 7.50-7.52v(2H, d), 8.21-8.23 (2H, d), 8.78 (1H, s)

Example 36cc: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (2H, d), 1.68-1.75 (2H, m), 2.20-2.27 (2H, td), 2.538-2.543 (3H, d), 2.82-2.87 (2H, t), 3.06-3.09 (2H, m), 3.16-3.21 (1H, m), 3.22-3.25 (2H, m), 3.37-3.40 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.96

(2H, m), 4.00-4.02 (1H, dd), 4.29-4.33 (1H, d), 4.58 (1H, s), 6.49-6.50 (1H, d), 6.86 (1H, s), 7.51-7.53 (2H, d), 8.22-8.24 (2H, d), 8.61 (1H, s)

Example 36cd: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.65 (2H, m), 1.67-1.74 (2H, m), 2.19-2.26 (4H, m), 2.537-2.541 (3H, d), 2.81-2.86 (2H, t), 3.05-3.09 (2H, m), 3.16-3.22 (2H, m), 3.24-3.26 (1H, m), 3.37-3.40 (2H, t), 3.49-3.56 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.79 (1H, d), 3.90-3.96 (2H, m), 3.98-4.01 (1H, dd), 4.11-4.21 (1H, sex), 4.29-4.32 (1H, d), 4.57 (1H, s), 6.52-6.54 (1H, d), 6.86 (1H, s), 7.48-7.50 (2H, d), 7.54-7.67(1H, m), 8.21-8.23 (2H, d), 8.63 (1H, s)

Example 36ce: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.35 (3H, d), 1.67-1.74 (2H, m), 2.20-2.27 (2H, td), 2.538-2.541 (3H, d), 2.70-3.73 (2H, t), 2.82-2.87 (2H, t), 3.05-3.09 (2H, m), 3.18-3.23 (2H, m), 3.25-3.26 (1H, m), 3.18-3.23 (2H, m), 2.25-2.26 (1H, m), 3.36-3.40 (4H, m), 3.50-3.56 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.96 (2H, qu), 3.98-4.02 (1H, dd), 4.30-4.33 (1H, d), 4.56-4.58 (1H, m), 6.54-6.57 (1H, t), 6.86 (1H, s), 7.52-7.54 (2H, d), 8.23-8.25 (2H, d), 8.95 (1H, s)

Example 36cf: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.68-1.75 (2H, m), 2.20-2.27 (2H, td), 2.82-2.87 (2H, t), 3.16-3.22 (2H, m), 3.25 (1H, m), 3.37-3.40 (2H, t), 3.50-3.56 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.96 (2H, m), 4.00-4.02 (1H, dd), 4.29-4.33 (1H, d), 4.58 (1H, s), 6.23-6.25 (1H, t), 6.86 (1H, t), 7.49-7.52 (2H, d), 8.21-8.23 (2H, d), 8.69 (1H, s)

Example 36cg: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.68-1.75 (2H, m), 2.20-2.27 (2H, td), 2.82-2.87 (2H, t), 3.06-3.09 (2H, m), 3.17-3.23 (4H, m), 3.25-3.26 (1H, m), 3.37-3.40(2H, t), 3.46-3.48 (2H, t), 3.50-3.56 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.96 (2H, qu), 3.98-4.02 (1H, dd) 4.29-4.33 (1H, d), 4.57 (1H, s), 6.30-6.33 (1H, t), 6.86 (1H, s), 7.49-7.51 (2H, d), 8.22-8.24 (2H, d), 8.87 (1H, s)

Example 36ch: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.68-1.75 (2H, m), 2.20-2.28 (2H, td), 2.82-2.87 (2H, t), 3.06-3.10 (2H, m), 3.18-3.22 (2H, m), 3.23-3.25 (1H, m), 3.38-3.41 (2H, t), 3.50-3.57 (1H, td), 3.67-3.70 (1H, dd), 3.77 (1H, s), 3.80 (3H, s), 3.91-3.96 (2H, qu), 3.98-4.02 (1H, dd), 4.30-4.33 (1H, d), 4.58 (1H, exchange), 6.87 (1H, s), 7.390-7.392 (1H, d), 7.55-7.57 (2H, d), 7.77 (1H, s), 8.25-8.27 (2H, d), 8.49 (1H, exchange), 8.93 (1H, exchange)

Example 36ci: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.68-1.75 (2H, m), 2.20-2.28 (2H, td), 2.82-2.86 (2H, t), 3.07-3.11 (2H, m), 3.16-3.20 (1H, m), 3.22-3.23 (1H, d),

3.38-3.41 (2H, t), 3.51-3.57 (2H, td), 3.68-3.69 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.96 (2H, t), 3.99-4.01 (1H, d), 4.29-4.33 (1H, d), 4.57-4.58 (1H, exchange), 6.84 (1H, s), 7.23 (1H, s), 7.57-7.59 (1H, m), 7.65-7.67 (2H, d), 8.20-8.22 (2H, d)

Example 36cj: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.63-1.66 (2H, m), 1.93-2.00 (2H, m), 3.15-3.20 (2H, m), 3.217-3.226 (1H, d), 3.47-3.51 (1H, dd), 3.53-3.57 (4H, m), 3.63-3.67 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.01 (1H, dd), 4.22-4.25 (1H, d), 4.57 (1H, exchange), 4.73 (1H, exchange), 6.77 (1H, s), 6.84-6.85 (1H, d), 7.33-7.34 (1H, d), 7.66-7.68 (2H, d), 8.23-8.25 (2H, d)

Example 36ck: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70-0.74 (2H, m), 0.91-0.93 (2H, dd), 1.24-1.26 (3H, d), 1.56-1.58 (2H, m), 1.64-1.66 (2H, m), 1.92-1.99 (2H, m), 2.72-2.77 (1H, sep), 2.89 (2H, s), 3.16-3.20 (2H, t), 3.22-3.23 (1H, d), 3.4703.50 (1H, dd), 3.51-3.56 (4H, m), 3.63-3.67 (1H, dd), 3.77-3.80 (1H, d), 3.97-4.01 (1H, dd), 4.22-4.25 (1H, d), 4.57 (1H, exchange), 6.79 (1H, s), 7.64-7.67 (2H, dd), 8.22-8.24 (2H, s), 8.41 (1H, exchange)

Example 36cl: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.56-0.59 (2H, t), 0.66-0.68 (2H, t), 1.24-1.26 (3H, d), 1.31-1.36 (3H, m), 1.56-1.60 (2H, m), 1.62-1.66 (2H, m), 1.92-2.00 (2H, m), 3.16-3.21 (2H, t), 3.47-3.50 (1H, dd), 2.52-3.55 (4H, m), 3.63-3.67 (1H, dd), 3.52-3.55 (4H, m), 3.63-3.67 (1H, dd), 3.77-3.79 (1H, d), 4.00-4.01 (1H, dd), 4.21-4.24 (1H, d), 4.56 (1H, exchange), 6.78 (1H, s), 7.49-7.51 (2H, d), 8.21-8.23 (2H, d)

Example 36cm: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.58 (2H, m), 1.64-1.67 (2H, m), 1.92-1.99 (2H, m), 3.19-3.26 (1H, dd), 3.51-3.55 (6H, m), 3.63-3.67 (1H, dd), 3.77-3.79 (1H, d), 3.97-4.01 (1H, dd), 4.21-4.24 (1H, d), 4.57 (1H, s), 4.71 (1H, s), 5.94-6.24 (1H, tt), 6.55-6.58 (1H, t), 6.80 (1H, s), 7.51-7.54 (2H, d), 8.23-8.26 (2H, d), 8.96 (1H, s)

Example 36cn: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.32 (9H, s), 1.54-1.60 (2H, m), 1.61-1.67 (2H, m), 1.92-1.99 (2H, m), 3.18-3.26 (1H, m), 3.47-3.50 (1H, dd), 3.52-3.56 (4H, m), 3.63-3.67 (1H, dd), 3.77-3.80 (1H, d), 3.97-4.01 (1H, dd), 4.21-4.24 (1H, d), 4.57 (1H, s), 4.72 (1H, exchange), 6.09 (1H, s), 6.78 (1H, s), 7.45-7.48 (2H, d), 8.20-8.23 (2H, d), 8.52 (1H, s)

Example 36co: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.59 (2H, m), 1.60-1.64 (2H, m), 1.91-1.98 (2H, m), 3.46-3.50 (1H, dd), 3.50-3.54 (4H, m), 3.62-3.66 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.08 (1H, s), 4.19-4.22 (1H, d), 4.55 (exchange), 4.70 (exchange), 6.73 (1H, s), 7.59-7.61 (2H, d), 8.10-8.12 (2H, d), 8.38 (1H, exchange)

Example 36cp: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.55-1.59 (2H, m), 1.62-1.66 (2H, m), 1.77-1.84 (2H, m), 1.91-1.99 (2H, m), 3.16-3.20 (2H, m), 3.21-3.25 (1H, dd), 3.46-3.47 (1H, d), 3.49-3.55 (6H, m), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.25 (1H, d), 4.31-4.32 (1H, m), 4.56 (exchange), 6.78 (1H, s), 7.64-7.66 (2H, d), 8.20-8.22 (2H, d), 8.34 (exchange)

Example 36cq: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.59 (2H, m), 1.62-1.65 (2H, m), 1.91-1.98 (2H, m), 3.05 (3H, s), 3.16-3.25 (2H, m), 3.33-3.34 (2H, d), 3.46-3.50 (1H, dd), 3.50-3.58 (6H, m), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.20-4.23 (1H, d), 4.56 (exchange), 4.70 (exchange), 6.45-6.48 (1H, t), 6.78 (1H, s), 7.51-7.53 (2H, d), 8.21-8.24 (2H, d), 9.05 (exchange)

Example 36cr: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.60 (2H, m), 1.62-1.66 (2H, m), 1.92-1.99 (2H, m), 3.00-3.05 (1H, dd), 3.16-3.22 (6H, m), 3.42-3.47 (2H, dd), 3.51-3.55 (4H, m), 3.63-3.67 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.45-4.48 (exchange, t), 4.56 (exchange), 6.79 (1H, s), 7.11 (exchange), 7.52-7.54 (2H, d), 8.22-8.24 (2H, d), 9.21 (exchange)

Example 36cs: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.58 (2H, m), 1.62-1.66 (2H, m), 1.91-1.98 (2H, m), 2.89 (3H, s), 2.98 (3H, s), 3.16-3.22 (2H, m), 3.46-3.50 (1H, dd), 3.50-2.54 (4H, m), 3.63-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-3.97 (1H, d), 3.99-4.00 (2H, d), 4.20-4.24 (1H, d), 4.57 (1H, exchange), 6.43-6.45 (t, exchange), 6.79 (1H, s), 7.50-7.52 (2H, d), 8.22-8.24 (2H, d), 9.19 (exchange)

Example 36ct: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15-1.20 (3H, d), 1.70-1.79 (2H, q), 1.95-2.05 (2H, q), 3.10-3.20 (1H, td), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.10-4.20 (1H, d), 4.45 (1H, bs), 6.70 (1H, s), 7.45-7.52 (2H, d), 7.75-7.80 (1H, dd), 7.80-7.82 (2H, d), 8.00-8.05 (1H, d), 8.10-8.15 (1H, td), 8.40 (1H, s), 8.85 (1H, d), 9.40 (1H, s), 11.40 (1H, br s).

mTOR Kinase Assay (Echo): 0.00157μM

Example 36cu: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10-1.15 (3H, d), 1.70-1.79 (2H, q), 1.95-2.00 (2H, q), 3.10-3.20 (1H, td), 3.45-3.50 (1H, td), 3.60-3.62 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.10-4.20 (1H, d), 4.30 (2H, d), 4.45 (1H, bs), 6.60 (1H, t), 6.70 (1H, s), 6.90-7.00 (2H, br d), 7.40 (2H, d), 7.75-7.80 (3H, m), 8.00-8.05 (1H, d), 8.10-8.15 (1H, td), 8.80 (1H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.0686μM

Example 36cv: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.55-0.65 (2H, q), 0.65-0.75 (2H, q), 1.10-1.15 (3H, d), 1.70-1.79 (2H, q), 1.95-2.00 (2H, q), 3.10-3.20 (1H, td), 3.40-3.50 (2H, m), 3.60-3.62 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.10-4.20 (1H, d), 4.45 (1H, bs), 4.80 (1H, bs), 6.55 (1H, t), 6.65 (1H, s), 7.30 (2H, d), 7.70-7.80 (3H, m), 7.95-8.00 (1H, d), 8.05-8.10 (1H, td), 8.60 (1H, s), 8.80 (1H, d).

mTOR Kinase Assay (Echo): 0.259μM

Example 36cw: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15-1.20 (3H, d), 1.65-1.70 (2H, q), 1.95-2.00 (2H, q), 3.10-3.20 (1H, td), 3.40-3.50 (1H, td), 3.60-3.64 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.10-4.20 (1H, d), 4.35 (2H, d), 4.45 (1H, bs), 6.60 (1H, t), 6.70 (1H, s), 6.80-7.10 (2H, m), 7.40 (2H, d), 7.70 (2H, d), 7.80 (2H, dd), 8.85 (2H, dd), 8.90 (1H, s), 11.85 (1H, s).

Example 36cx: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.55-0.65 (2H, q), 0.65-0.75 (2H, q), 1.15-1.20 (3H, d), 1.70-1.75 (2H, q), 1.95-2.00 (2H, q), 3.10-3.20 (1H, td), 3.45 (2H, d), 3.50 (1H, td), 3.60-3.63 (1H, dd), 3.74-3.78 (1H, d), 3.94-3.99 (1H, dd), 4.10-4.20 (1H, d), 4.45 (1H, bs), 4.80-4.90 (1H, t), 6.55 (1H, s), 6.65 (1H, s), 7.30 (2H, d), 7.65 (2H, d), 7.80 (2H, dd), 8.70 (1H, s), 8.85 (2H, dd)

Example 36cy: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, m), 2.22-2.30 (2H, td), 2.65 (3H, d), 2.75 (2H, t), 3.13 (3H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.75 (1H, d), 3.90-3.95 (2H, d), 3.98 (1H, dd), 4.15 (1H, d), 4.50 (1H, br s), 6.05 (1H, q), 6.68 (1H, s), 7.37 (2H, d), 7.44 (2H, d), 7.46 (2H, d), 7.61 (1H, tt), 7.76 (2H, d), 8.68 (1H, s)

Example 36cz: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.21 (3H, d), 2.26-2.31 (2H, td), 2.74 (2H, t), 3.12 (5H, dt), 3.50 (1H, td), 3.65 (1H, dd), 3.76 (1H, d), 3.90 (2H, d), 3.97 (1H, dd), 4.14 (1H, d), 4.52 (1H, m), 6.14 (1H, t), 6.68 (1H, s), 7.36 (2H, d), 7.44 (4H, q), 7.60 (1H, m), 7.76 (2H, d), 8.60 (1H, s)

Example 36da: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.41 (2H, q), 0.65 (2H, q), 1.21 (3H, d), 2.23-2.32 (2H, td), 2.55 (1H, dd), 2.75 (2H, m), 3.15 (3H, m), 3.50 (1H, td), 3.66 (1H, dd), 3.76 (1H, d), 3.91 (2H, d), 3.97 (1H, dd), 4.14 (1H, d), 4.51 (1H, br s), 6.41 (1H, d), 6.69 (1H, s), 7.37 (2H, d), 7.44 (4H, dd), 7.61 (1H, t), 7.77 (2H, d), 8.48 (1H, s)

Example 36db: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 2.26-2.31 (2H, td), 2.74-2.78 (2H, t), 3.11-3.17 (5H, m), 3.46 (2H, q), 3.56 (1H, dd), 3.66 (1H, dd), 3.76 (1H, d), 3.90 (2H, d), 3.97 (1H, dd), 4.15 (1H, d), 4.50 (1H, br s), 4.72 (1H, t), 6.24 (1H, t), 6.68 (1H, s), 7.36 (2H, d), 7.44 (4H, q), 7.60 (1H, m), 7.77 (2H, d), 8.75 (1H, s)

Example 36dc: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.67 (2H, m), 1.60-1.64 (2H, q), 1.88-1.91 (2H, q), 2.54-2.57 (1H, m), 3.63-3.64 (4H, m), 3.68-3.70 (4H, m), 6.40-6.41 (1H, d), 6.68 (1H, s), 7.37-7.40 (2H, d), 7.57-7.61 (2H, t), 7.71-7.74 (1H, tt), 7.78-7.83 (4H, t), 8.50 (1H, s)

Example 36dd: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.60-1.64 (2H, q), 1.88-1.91 (2H, q), 3.09-3.16 (2H, m), 3.63-3.64 (4H, m), 3.68-3.70 (4H, m), 6.12-6.15 (1H, t), 6.68 (1H, s), 7.36-7.38 (2H, d), 7.57-7.61 (2H, t), 7.71-7.74 (1H, tt), 7.78-7.82 (4H, m), 8.62 (1H, s).

mTOR Kinase Assay (Echo): 0.00291μM

Example 36de: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.60-1.64 (2H, q), 1.88-1.91 (2H, q), 3.15-3.19 (2H, m), 3.44-3.48 (2H, q), 3.63-3.64 (4H, m), 3.68-3.70 (4H, m), 4.71-4.74 (1H, t), 6.21-6.24 (1H, t), 6.68 (1H, s), 7.36-7.38 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.83 (4H, m), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.00389μM

Example 36df: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.60-1.64 (2H, q), 1.88-1.91 (2H, q), 2.65-2.66 (3H, d), 3.63-3.64 (4H, m), 3.68-3.69 (4H, m), 6.02-6.06 (1H, m), 6.68 (1H, s), 7.37-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.82 (4H, m), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00712μM

Example 36dg: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.56-1.64 (4H, m), 1.88-1.91 (2H, q), 3.14-3.19 (2H, q), 3.45-3.49 (2H, q), 3.63-3.64 (4H, m), 3.68-3.70 (4H, m), 4.46-4.49 (1H, t), 6.16-6.19 (1H, t), 6.68 (1H, s), 7.36-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.82 (4H, m), 8.67 (1H, s).

mTOR Kinase Assay (Echo): 0.0164μM

Example 36dh: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.60-1.64 (2H, q), 1.88-1.91 (2H, q), 2.68-2.72 (2H, t), 3.34-3.39 (2H, q), 3.63-3.64 (4H, m), 3.68-3.69 (4H, m), 6.49-6.52 (1H, m), 6.68 (1H, s), 7.38-7.41 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.84 (4H, m), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.0034μM

Example 36di: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.61-1.65 (2H, q), 1.89-1.92 (2H, q), 3.63-3.66 (4H, m), 3.69-3.71 (4H, m), 6.73 (1H, m), 6.95 (1H, s), 7.08 (1H, s), 7.21 (1H, s), 7.49-7.52 (2H, d), 7.59-7.63 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.91 (2H, d), 7.92-7.94 (2H, d), 8.38 (1H, s), 9.40 (1H, s), 11.39 (1H, s). (ammonium salt)

Example 36dj: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.61-1.64 (2H, q), 1.89-1.92 (2H, q), 3.63-3.65 (4H, m), 3.69-3.70 (4H, m), 3.79 (3H, s), 6.69 (1H, s), 7.38-7.39 (1H, d), 7.41-7.44 (2H, d), 7.58-7.62 (2H, t), 7.71-7.75 (1H, tt), 7.77 (1H, s), 7.79-7.81 (2H, dd), 7.83-7.86 (2H, d), 8.36 (1H, s), 8.80 (1H, s)

Example 36dk: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.21 (3H, d), 1.58 - 1.64 (2H, m), 1.86 - 1.88 (2H, m), 2.39 (3H, s), 2.54 - 2.58 (1H, m), 2.75 - 2.78 (4H, m), 3.11 - 3.18 (1H, m), 3.46 - 3.51 (1H, m), 3.62 - 3.66 (1H, m), 3.76 (1H, d), 3.95 - 3.98 (1H, m), 4.13 - 4.16 (1H, m), 4.48 - 4.54 (1H, m), 6.40 (1H, s), 6.66 (1H, s), 7.43 (2H, d), 7.64 (1H, s), 7.89 (2H, d), 8.51 (1H, s).

mTOR Kinase Assay (Echo): 0.00905μM

Example 36dl: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.57 - 1.63 (2H, m), 1.84 - 1.89 (2H, m), 2.39 (3H, s), 2.74 - 2.79 (4H, m), 3.12 - 3.20 (3H, m), 3.44 - 3.51 (3H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.12 - 4.16 (1H, m), 4.48 - 4.53 (1H, m), 4.72 (1H, t), 6.24 (1H, t), 6.66 (1H, s), 7.41 (2H, d), 7.64 (1H, s), 7.89 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00399μM

Example 36dm: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.57 - 1.64 (2H, m), 1.84 - 1.90 (2H, m), 2.39 (3H, s), 2.70 (2H, t), 2.74 - 2.79 (4H, m), 3.12 - 3.18 (1H, m), 3.35 - 3.39 (2H, m), 3.46 - 3.51 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.15 (1H, d), 4.48 - 4.54 (1H, m), 6.51 (1H, t), 6.67 (1H, s), 7.44 (2H, d), 7.64 (1H, s), 7.90 (2H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.0298μM

Example 36dn: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.57 - 1.61 (4H, m), 1.85 - 1.90 (2H, m), 2.39 (3H, s), 2.74 - 2.79 (4H, m), 3.12 - 3.19 (3H, m), 3.45 - 3.51 (3H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.14 (1H, d), 4.47 - 4.54 (1H, m), 4.47 (1H, t), 6.18 (1H, t), 6.66 (1H, s), 7.41 (2H, d), 7.64 (1H, s), 7.89 (2H, d), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.0138μM

Example 36do: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.19(3H, d), 1.61-1.68(2H, m), 1.78-1.86(1H, m), 1.88-1.98(3H, m), 3.10-3.18(1H, td), 3.31-3.33(1H, d), 3.43-3.49(4H, m), 3.59-3.63(1H, dd), 3.73-3.76(1H, d), 3.94-3.98(1H, dd), 4.10-4.13(1H, d), 4.31(1H, bs), 4.38(1H, bs), 4.94-4.95(1H, d), 6.63(1H, s), 7.52-7.55(2H, d), 7.58-7.61(2H, t), 7.70-7.74(1H, tt), 7.79-7.84(4H, m), 8.28(1H, s).

Example 36dp: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.18(3H, d), 1.60-1.68(2H, m), 1.87-1.93(2H, m), 3.10-3.17(1H, td), 3.43-3.49(1H, td), 3.53-3.54(2H, m), 3.59-3.63(1H, dd),

3.73-3.76(1H, d), 3.94-3.97(1H, dd), 4.09-4.12(1H, d), 4.38(1H, bs), 6.47(1H, t), 6.63(1H, s), 7.39-7.41(2H, d), 7.57-7.61(2H, t), 7.70-7.74(1H, tt), 7.78-7.83(4H, m), 9.27(1H, s). (H from OH group barried under water peak).

Example 36dq: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18(3H, d), 1.61-1.68(2H, m), 1.87-1.92(2H, m), 2.88(3H, s), 2.97(3H, s), 3.10-3.18(1H, td), 3.42-3.49(1H, td), 3.59-3.63(1H, dd), 3.73-3.76(1H, d), 3.94-3.98(3H, m), 4.09-4.12(1H, d), 4.39(1H, bs), 6.37-6.40(1H, t), 6.63(1H, s), 7.38-7.40(2H, d), 7.57-7.61(2H, t), 7.69-7.74(1H, tt), 7.78-7.80(2H, dd), 7.84-7.86(2H, d), 9.12(1H, s).

Example 36dr: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.68-0.72(2H, m), 0.88-0.93(2H, m), 1.17-1.19(3H, d), 1.61-1.68(2H, m), 1.89-1.92(2H, m), 2.69-2.75(1H, m), 2.87(3H, s), 3.11-3.18(1H, td), 3.43-3.50(1H, td), 3.59-3.63(1H, dd), 3.74-3.76(1H, d), 3.94-3.98(1H, dd), 4.09-4.14(1H, d), 4.39(1H, bs), 6.64(1H, s), 7.52-7.54(2H, d), 7.58-7.62(2H, t), 7.70-7.74(1H, tt), 7.79-7.85(4H, m), 8.34(1H, s).

Example 36ds: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18(3H, d), 1.60-1.68(2H, m), 1.87-1.93(2H, m), 3.10-3.18(1H, td), 3.36-3.40(1H, q), 3.42-3.49(2H, m), 3.59-3.63(1H, dd), 3.73-3.76(1H, d), 3.94-3.98(1H, dd), 4.09-4.12(1H, d), 4.39(1H, bs), 4.40-4.43(1H, t), 4.52-4.55(1H, t), 6.40-6.43(1H, t), 6.63(1H, s), 7.38-7.40(2H, d), 7.57-7.61(2H, t), 7.70-7.74(1H, tt), 7.78-7.80(2H, dd), 7.84-7.86(2H, d), 8.77(1H, s).

Example 36dt: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21(3H, d), 1.85-1.93(1H, m), 2.04-2.14(1H, m), 2.68-2.72(2H, t), 2.76-2.83(2H, m), 3.02-3.10(2H, m), 3.13-3.19(1H, td), 3.34-3.39(2H, q), 3.45-3.52(1H, td), 3.62-3.65(1H, dd), 3.74-3.77(1H, d), 3.94-3.98(1H, dd), 4.07-4.10(1H, d), 4.45(1H, bs), 6.47(1H, s), 6.49-6.52(1H, t), 7.38-7.40(2H, d), 7.44-7.51(4H, m), 7.58-7.62(1H, tt), 7.80-7.82(2H, d), 8.86(1H, s).

Example 36du: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21(3H, d), 1.82-1.93(1H, m), 2.05-2.13(1H, m), 2.76-2.83(2H, m), 3.02-3.19(4H, m), 3.45-3.51(1H, td), 3.62-3.65(1H, dd), 3.74-3.77(1H, d), 3.94-3.98(1H, dd), 4.06-4.10(1H, d), 4.31-4.33(2H, d), 4.45-4.46(1H, bs), 6.47(1H, s), 6.59-6.62(1H, t), 6.94(2H, bs), 7.38-7.40(2H, d), 7.44-7.51(4H, m), 7.58-7.62(1H, tt), 7.80-7.82(2H, d), 8.87(1H, s).

Example 36dv: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.64 (2H, m), 1.90 (2H, m), 3.15 (1H, m), 3.47 (1H, m), 3.61 (1H, m), 3.76 (4H, m), 3.95 (1H, m), 4.14 (1H, m), 4.39 (1H, m), 6.26 (1H, m), 6.65 (1H, s), 7.44 (2H, m), 7.59 (3H, m), 7.74 (1H, m), 7.80 (2H, m), 7.88 (2H, m), 8.94 (1H, s), 9.12 (1H, s)

Example 36dw: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.64 (2H, m), 1.91 (2H, m), 3.15 (1H, m), 3.34 (3H, s), 3.46 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.12 (1H, m), 4.40 (1H, m), 6.58 (1H, m), 6.66 (1H, m), 7.45 (2H, m), 7.60 (2H, m), 7.77 (3H, m), 7.90 (2H, m), 9.03 (1H, s), 9.49 (1H, s)

Example 36dx: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.64 (2H, m), 1.90 (2H, m), 3.14 (1H, m), 3.52 (4H, m), 3.75 (1H, m), 3.96 (1H, m), 4.11 (1H, m), 4.38 (1H, m), 6.08 (1H, m), 6.53 (1H, m), 6.63 (1H, s), 7.40 (2H, m), 7.60 (2H, m), 7.72 (1H, m), 7.82 (4H, m), 8.92 (1H, s)

Example 36dy: Spectrum not recorded.

Example 36dz: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.64 (2H, m), 1.90 (2H, m), 3.15 (1H, m), 3.47 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.13 (1H, m), 4.40 (1H, m), 6.66 (1H, s), 6.88 (1H, m), 7.46 (2H, m), 7.61 (2H, m), 7.77 (3H, m), 7.90 (2H, m), 8.77 (1H, m), 9.05 (1H, s), 9.64 (1H, s)

Example 36ea: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.64 (2H, m), 1.91 (2H, m), 3.14 (1H, m), 3.46 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.94 (3H, m), 4.12 (1H, m), 4.39 (1H, m), 6.64 (1H, s), 6.79 (1H, m), 7.40 (2H, m), 7.59 (2H, m), 7.79 (5H, m), 8.99 (1H, s)

Example 36eb: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.65 (2H, m), 1.91 (2H, m), 3.15 (1H, m), 3.46 (1H, m), 3.61 (4H, m), 3.75 (1H, m), 3.97 (1H, m), 4.12 (1H, m), 4.40 (1H, m), 6.64 (1H, s), 6.97 (1H, s), 7.41 (3H, m), 7.61 (2H, m), 7.80 (5H, m), 8.70 (1H, s), 9.07 (1H, s)

Example 36ec: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.17 (3H, d), 1.64 (2H, m), 1.90 (2H, m), 3.13 (1H, m), 3.40 (3H, m), 3.67 (3H, m), 3.96 (1H, m), 4.10 (1H, m), 4.37 (1H, m), 4.83 (1H, t), 6.10 (1H, m), 6.63 (1H, s), 7.36 (2H, m), 7.60 (2H, m), 7.78 (5H, m), 8.70 (1H, s)

Example 36ed: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.17 (3H, d), 1.64 (2H, m), 1.91 (2H, m), 3.14 (1H, m), 3.42 (3H, m), 3.67 (3H, m), 3.96 (1H, m), 4.11 (1H, m), 4.39 (1H, m), 4.83 (1H, t), 6.10 (1H, m), 6.62 (1H, s), 7.36 (2H, m), 7.59 (2H, m), 7.77 (5H, m), 8.71 (1H, s)

Example 36ee: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.63 (2H, m), 1.90 (2H, m), 3.13 (1H, m), 3.45 (3H, m), 3.67 (4H, m), 3.95 (1H, m), 4.12 (1H, m), 4.39 (1H, m), 6.47 (1H, m), 6.63 (1H, s), 7.39 (2H, m), 7.60 (2H, m), 7.79 (5H, m), 8.91 (1H, s)

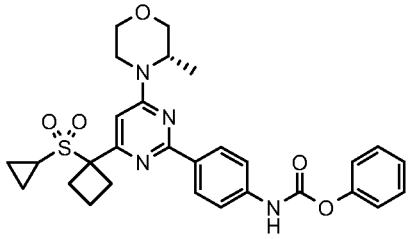
Example 36ef: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.23 (d, 3H), 1.33 (t, 3H), 1.52 - 1.58 (m, 2H), 1.60 - 1.66 (m, 2H), 3.20 (td, 1H), 3.37 - 3.53 (m, 5H), 3.63 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.14 - 4.28 (m, 1H), 4.42 (t, 1H), 4.50 - 4.62 (m, 1H), 4.54 (t, 1H), 6.47 (t, 1H), 6.79 (s, 1H), 7.51 (d, 2H), 8.20 (d, 2H), 8.85 (s, 1H)

Example 36eg: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.23 (d, 3H), 1.33 (t, 3H), 1.53 - 1.58 (m, 2H), 1.60 - 1.66 (m, 2H), 3.20 (td, 1H), 3.44 (q, 2H), 3.48 - 3.65 (m, 4H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.16 - 4.26 (m, 1H), 4.51 - 4.64 (m, 1H), 6.07 (tt, 1H), 6.56 (t, 1H), 6.79 (s, 1H), 7.52 (d, 2H), 8.21 (d, 2H), 8.97 (s, 1H)

The preparation of the phenyl carbamates required for **Examples 36a – 36eg** are either described below or have been described previously.

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



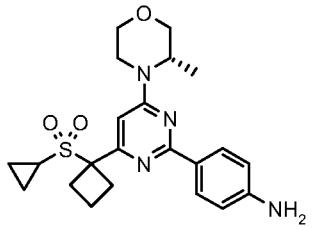
Sodium hydrogen carbonate (259 mg, 3.08 mmol) was added to 4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (880 mg, 2.05 mmol) in dioxane (20 mL) at 5°C under an atmosphere of nitrogen. Phenyl chloroformate (0.387 mL, 3.08 mmol) was then added and the resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with DCM (50 mL), the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid which was collected by filtration and dried under vacuum (1.06 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.69 - 0.80 (2H, m), 0.81 - 0.90 (2H, m), 1.23 (3H, d), 1.86 - 1.98 (1H, m), 2.02 - 2.12 (1H, m), 2.80 - 3.04 (5H, m), 3.15 - 3.28

(1H, m), 3.46 - 3.59 (1H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.23 (1H, d), 4.57 (1H, s), 6.74 (1H, s), 7.22 - 7.31 (3H, m), 7.41 - 7.49 (2H, m), 7.62 (2H, d), 8.33 (2H, d), 10.42 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 549; HPLC tR = 3.05 min.

4-[4-(1-Cyclopropylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

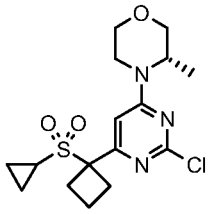


Bis(triphenylphosphine)palladium(II) chloride (0.164 g, 0.23 mmol) was added to 2-chloro-4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.3 g, 3.50 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.149 g, 5.24 mmol) and an aqueous solution of sodium carbonate (1 mL, 2.00 mmol) in a solvent mixture of DMF (5 mL), DME (12 mL), water (1 mL) and ethanol (1 mL) at RT . The resulting mixture was stirred at 90°C for 5 hours under an atmosphere of nitrogen. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, and the crude product further purified by ion exchange chromatography using an SCX column, eluting with 7N ammonia in methanol, to give the desired material as a beige solid (0.88 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70 - 0.89 (4H, m), 1.21 (3H, d), 1.84 - 1.93 (1H, m), 2.02 - 2.10 (1H, m), 2.76 - 2.98 (5H, m), 3.10 - 3.24 (1H, m), 3.45 - 3.55 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.18 (1H, d), 4.50 (1H, s), 5.52 (2H, d), 6.60 (2H, d), 8.07 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 429; HPLC tR = 2.41 min.

2-Chloro-4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



1,3-Dibromopropane (2.95 mL, 28.93 mmol) was added to 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.2 g, 9.64 mmol), tetrabutylammonium bromide (0.311 g, 0.96 mmol) and an aqueous solution of sodium hydroxide (2.89 mL, 28.93 mmol) in toluene (24.11 mL). The reaction was stirred at RT for 1 hour then water added and the layers separated. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in isohexane, to give the desired material as a colourless gum (1.3 g).

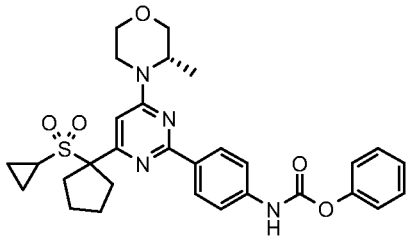
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.69 - 0.78 (2H, m), 0.88 - 0.93 (2H, m), 1.20 (3H, d), 1.83 - 1.95 (1H, m), 2.02 - 2.12 (1H, m), 2.50 - 2.60 (1H, m), 2.67 - 2.80 (2H, m), 2.83 - 2.96 (2H, m), 3.13 - 3.25 (1H, m), 3.40 - 3.49 (1H, m), 3.61 (1H, d), 3.72 (1H, d), 3.93 (1H, d), 4.06 (1H, s), 4.40 (1H, s), 6.82 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 372; HPLC tR = 2.04 min.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

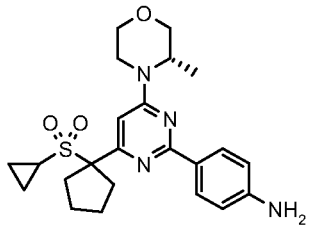


Sodium hydrogen carbonate (228 mg, 2.71 mmol) was added to 4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (800 mg, 1.81 mmol) in dioxane (20 mL) at 5°C under an atmosphere of nitrogen. Phenyl chloroformate (0.341 mL, 2.71 mmol) was then added. The resulting mixture was stirred at RT for 2 hours then diluted with ethyl acetate (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid which was collected by filtration and dried under vacuum (700 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.57 - 0.78 (2H, m), 0.79 - 0.90 (2H, m), 1.23 (3H, d), 1.53 - 1.62 (2H, m), 1.77 - 1.87 (2H, m), 2.41 - 2.50 (2H, m), 2.55 - 2.62 (1H, m), 2.76 - 2.91 (2H, m), 3.16 - 3.26 (1H, m), 3.45 - 3.56 (1H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.55 (1H, s), 6.84 (1H, s), 7.20 - 7.34 (3H, m), 7.41 - 7.51 (2H, m), 7.62 (2H, d), 8.34 (2H, d), 10.42 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 563; HPLC tR = 3.15 min.

4-[4-(1-Cyclopropylsulfonylcyclopentyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



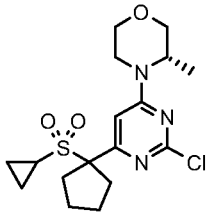
Bis(triphenylphosphine)palladium(II) chloride (0.122 g, 0.17 mmol) was added to 2-chloro-4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1 g, 2.59 mmol), and an aqueous solution of sodium carbonate (1 mL, 2.00 mmol) in a solvent mixture

of DMF (5 mL), DME (12 mL), water (1 mL) and ethanol (1 mL). The resulting mixture was stirred at 90°C for 5 hours under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, followed by ion exchange chromatography using an SCX column, eluting with 7N ammonia in methanol, to give the desired material as a beige solid (0.80 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.67 - 0.79 (2H, m), 0.81 - 0.89 (2H, m), 1.22 (3H, d), 1.50 - 1.59 (2H, m), 1.75 - 1.85 (2H, m), 2.41 - 2.51 (2H, m), 2.72 - 2.90 (3H, m), 3.11 - 3.23 (1H, m), 3.45 - 3.56 (1H, m), 3.58 - 3.66 (1H, m), 3.76 (1H, d), 3.97 (1H, d), 4.18 (1H, d), 4.51 (1H, s), 5.52 (1H, d), 6.61 (2H, d), 6.71 (1H, s), 8.07 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 443; HPLC tR = 2.51 min.

2-Chloro-4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



1,4-Dibromobutane (0.322 mL, 2.71 mmol) was added to 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (900 mg, 2.71 mmol), tetrabutylammonium bromide (87 mg, 0.27 mmol) and an aqueous solution of sodium hydroxide (0.814 mL, 8.14 mmol) in toluene (20 mL). The reaction was stirred at RT for 1 hour then water added and the organic layer separated, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in isohexane, to give the desired material as a yellow gum (1043 mg).

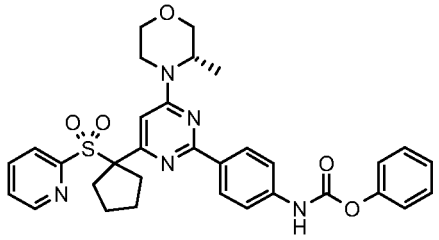
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.66 - 0.75 (2H, m), 0.88 - 0.94 (2H, m), 1.20 (3H, d), 1.50 - 1.57 (2H, m), 1.74 - 1.83 (2H, m), 2.36 - 2.46 (2H, m), 2.54 - 2.69 (3H, m), 3.13 - 3.25 (1H, m), 3.40 - 3.50 (1H, m), 3.59 (1H, d), 3.72 (1H, d), 3.93 (1H, d), 4.04 (1H, d), 4.41 (1H, s), 6.92 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 386; HPLC tR = 2.47 min.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]carbamate

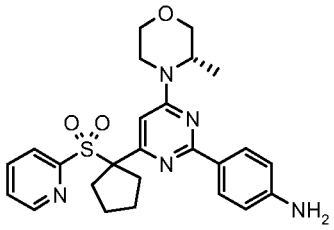


Sodium bicarbonate (139 mg, 1.66 mmol) and phenyl chloroformate (0.14 mL, 1.11 mmol) were added to a solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]aniline (530 mg, 1.11 mmol), in 1,4-dioxane (5.6 mL) and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (10 mL), washed with water (10 mL), the organic layer dried ($MgSO_4$), filtered and evaporated. The crude product was triturated with diethyl ether to give the desired material as a cream solid (620 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.51 - 1.62 (2H, m), 1.80 - 1.90 (2H, m), 2.68 - 2.82 (4H, m), 3.10 - 3.17 (1H, m), 3.44 - 3.50 (1H, m), 3.61 - 3.64 (1H, m), 3.75 (1H, d), 3.94 - 3.97 (1H, m), 4.12 (1H, d), 4.49 (1H, s), 6.64 (1H, s), 7.24 - 7.30 (3H, m), 7.45 (2H, t), 7.50 (2H, d), 7.55 - 7.59 (2H, m), 7.84 - 7.86 (3H, m), 8.74 (1H, d), 10.37 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 600; HPLC tR = 3.05 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]aniline

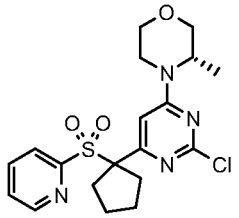


4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (418 mg, 1.91 mmol), an aqueous solution of sodium carbonate (2.2 mL, 4.40 mmol), and dichlorobis(triphenylphosphine)palladium(II) (51.4 mg, 0.07 mmol) were added to a solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidine (620 mg, 1.47 mmol) in a solvent mixture of DMF (0.24 mL), DME (9.33 mL), water (4.0 mL) and ethanol (2.67 mL). The resultant mixture was heated at 90°C for 4 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate (10 mL) and washed with water (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give the desired material as a cream solid (530 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.51 - 1.58 (2H, m), 1.80 - 1.88 (2H, m), 2.68 - 2.79 (4H, m), 3.09 (1H, dt), 3.46 (1H, dt), 3.61 (1H, dd), 3.74 (1H, d), 3.94 (1H, dd), 4.01 - 4.06 (1H, m), 4.43 (1H, d), 6.46 - 6.49 (3H, m), 7.54 (1H, d), 7.57 - 7.60 (1H, m), 7.60 (2H, d), 7.85 (1H, dt), 8.74 (1H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 480; HPLC tR = 2.37 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidine



1,4-dibromobutane (0.77 mL, 6.51 mmol) was added to 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine (600 mg, 1.63 mmol) in toluene (4 mL) followed by tetrabutylammonium bromide (52.4 mg, 0.16 mmol) and an aqueous solution of sodium hydroxide (0.976 mL, 9.76 mmol). The reaction was stirred at 60°C overnight then

the toluene removed under reduced pressure and the reaction redissolved in DCM and washed with water. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a white solid (620 mg).

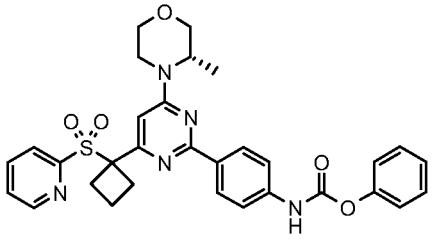
NMR Spectrum: ^1H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.50 - 1.58 (2H, m), 1.75 - 1.85 (2H, m), 2.53 - 2.57 (2H, m), 2.63 - 2.71 (3H, m), 3.11 (1H, dt), 3.41 (1H, dt), 3.56 (1H, dd), 3.70 (1H, d), 3.91 (1H, dd), 4.32 (1H, s), 6.67 (1H, s), 7.65 (1H, d), 7.70 - 7.73 (1H, m), 8.03 (1H, dt), 8.74 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 423, HPLC tR = 2.26 min

The preparation of 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate



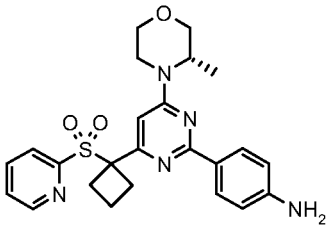
Sodium bicarbonate (154 mg, 1.84 mmol) and phenyl chloroformate (0.154 mL, 1.22 mmol) were added to a solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline (570 mg, 1.22 mmol), in 1,4-dioxane (6.0 mL) and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (10 mL), washed with water (10 mL), the organic layer dried ($MgSO_4$), filtered and evaporated. The crude product was triturated with diethyl ether to give the desired material as a cream solid (600 mg).

NMR Spectrum: ^1H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.86 - 1.98 (1H, m), 2.07 - 2.19 (1H, m), 2.80 - 2.87 (2H, m), 3.10 - 3.17 (1H, m), 3.23 - 3.30 (2H, m), 3.47 (1H,

dt), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.10 - 4.18 (1H, m), 4.46 (1H, s), 6.52 (1H, s), 6.74 - 6.78 (1H, m), 7.15 (1H, t), 7.23 - 7.30 (3H, m), 7.45 (1H, t), 7.51 (1H, d), 7.60 - 7.62 (2H, m), 7.83 - 7.90 (3H, m), 8.74 (1H, d), 10.39 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 586; HPLC tR = 3.04 min.

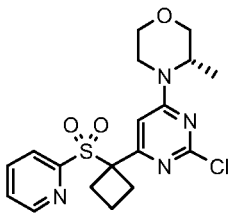
4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline



4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (460 mg, 2.10 mmol), an aqueous solution of sodium carbonate (2.42 mL, 4.84 mmol) and dichlorobis(triphenylphosphine)palladium(II) (56.6 mg, 0.08 mmol) were added to a solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidine (660 mg, 1.61 mmol) in a solvent mixture of DMF (0.24 mL), DME (9.33 mL), water (4.0 mL) and ethanol (2.67 mL) and the suspension heated at 90°C for 4 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate (10 mL) and washed with water (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give the desired material as a cream solid (570 mg).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 466; HPLC tR = 2.27 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidine



1,3-Dibromopropane (1.565 mLl, 15.35 mmol) was added to 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine (2.83 g, 7.67 mmol), in toluene (20 mL) followed by tetrabutylammonium bromide (0.247 g, 0.77 mmol) and an

aqueous solution of sodium hydroxide (2.3 mL, 23.02 mmol). The reaction was stirred at 60°C overnight. The toluene was removed under reduced pressure and the reaction redissolved in DCM and the organics washed with water then dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a cream solid (0.66 g).

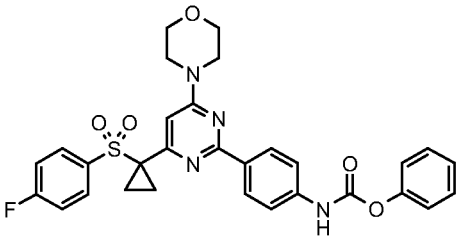
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.86 - 1.95 (1H, m), 2.05 - 2.13 (1H, m), 2.68 - 2.76 (2H, m), 3.07 - 3.18 (3H, m), 3.37 - 3.43 (1H, m), 3.55 (1H, dd), 3.69 (1H, d), 3.90 (2H, dd), 4.28 (1H, s), 6.52 (1H, s), 7.68 - 7.73 (2H, m), 8.03 (1H, dt), 8.74 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 409, HPLC tR = 2.03 min

The preparation of 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate



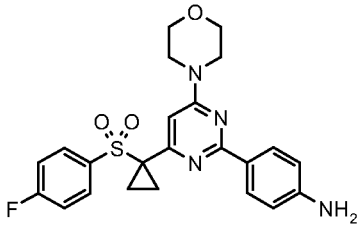
Sodium bicarbonate (0.776 g, 9.24 mmol) was added to 4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline (2.8 g, 6.16 mmol), in 1,4-dioxane (30.8 mL) at RT, followed by the dropwise addition of phenyl chloroformate (0.775 ml, 6.16 mmol) over 2 minutes and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (20 mL), and washed with water (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to

afford a solid which was triturated with diethyl ether to give the desired material as a cream solid (3.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.59 - 1.62 (2H, m), 1.88 - 1.91 (2H, m), 3.57 (4H, s), 3.69 (4H, s), 6.75 (1H, s), 7.24 - 7.30 (3H, m), 7.40 - 7.47 (4H, m), 7.53 (2H, d), 7.83 - 7.89 (4H, m), 10.40 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 575; HPLC tR = 3.03 min.

4-[4-[1-(4-Fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline

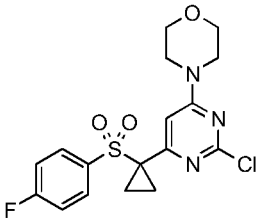


Bis(triphenylphosphine)palladium(II) chloride (0.285 g, 0.41 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.312 g, 10.55 mmol) and 2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidine (3.23 g, 8.12 mmol) and an aqueous solution of sodium carbonate (12.18 mL, 24.36 mmol) in a solvent mixture of DME (20 mL), ethanol (10 mL) and water (10 mL) at RT under an atmosphere of nitrogen. The resulting mixture was stirred at 95°C for 4 hours. The reaction mixture was allowed to cool, diluted with ethyl acetate (20 mL), and washed with water (2 x 20mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give the desired material as a cream solid (2.8 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.55 - 1.58 (2H, m), 1.85 - 1.88 (2H, m), 3.62 (4H, d), 3.67 - 3.70 (4H, m), 6.49 (2H, d), 6.61 (1H, s), 7.41 (2H, t), 7.62 (2H, d), 7.82 - 7.85 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 455; HPLC tR = 2.42 min.

2-Chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidine

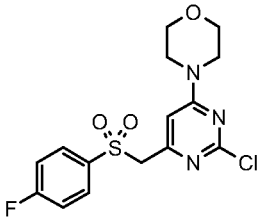


1,2-Dibromoethane (0.695 mL, 8.07 mmol) was added to 2-chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-morpholin-4-ylpyrimidine (3 g, 8.07 mmol), tetrabutylammonium bromide (0.260 g, 0.81 mmol) and an aqueous solution of sodium hydroxide (2.42 mL, 24.21 mmol) in toluene (20.17 mL). The reaction was stirred at RT for 4 hours, the toluene removed under reduced pressure and the residue redissolved in DCM. The organics were washed with water, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was triturated with diethyl ether to give the desired material as a cream solid (3.23 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.52 - 1.55 (2H, m), 1.81 - 1.84 (2H, m), 3.56 (4H, s), 3.63 - 3.65 (4H, m), 6.77 (1H, s), 7.80 - 7.84 (2H, m), 7.82 (2H, t)

LCMS Spectrum: m/z (ESI+)(M+H)+ 398, HPLC tR = 2.26 min

2-Chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-morpholin-4-ylpyrimidine



4-Fluorobenzenesulfinic acid sodium salt (3.30 g, 18.11 mmol) was added to 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine (5.00 g, 14.72 mmol) in acetonitrile (150 mL) at RT under an atmosphere of nitrogen. The resulting solution was stirred at 80°C for 20 hours. The solvent was removed and the residue redissolved in DCM. The organics were washed twice with water, dried ($MgSO_4$) and filtered. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material as a white solid (3.98 g).

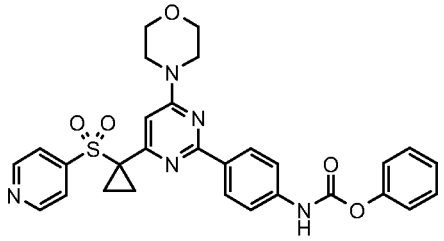
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.55-3.67 (8H, m), 4.65 (2H, s), 6.78 (1H, s), 7.47-7.52 (2H, m), 7.84-7.87 (2H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 372; HPLC tR = 1.99 min.

The preparation of 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate

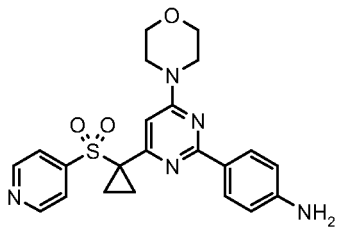


Sodium bicarbonate (0.677 g, 8.06 mmol) was added to 4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (2.35 g, 5.37 mmol), in 1,4-dioxane (26.9 mL) at RT, followed by the dropwise addition of phenyl chloroformate (0.676 mL, 5.37 mmol) over 2 minutes and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (20 mL), and washed with water (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford a solid which was triturated with diethyl ether to give the desired material as a cream solid (3.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.67 - 1.70 (2H, m), 1.94 - 1.99 (2H, m), 3.57 (4H, s), 3.69 (4H, s), 6.74 - 6.77 (2H, m), 7.24 - 7.26 (2H, m), 7.43 - 7.50 (3H, m), 7.73 (2H, d), 7.78 (2H, d), 8.86 (2H, d), 9.29 (1H, s), 10.39 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 558; HPLC tR = 2.71 min.

4-[4-Morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline



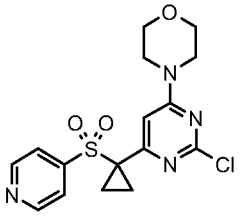
Bis(triphenylphosphine)palladium(II) chloride (0.309 g, 0.44 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.505 g, 11.43 mmol) and 2-chloro-4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidine (3.35 g, 8.80 mmol) and an aqueous

solution of sodium carbonate (13.19 mL, 26.39 mmol) in a solvent mixture of DME (20 mL), ethanol (10 mL) and water (10 mL) at RT under an atmosphere of nitrogen. The resulting mixture was stirred at 95°C for 4 hours. The reaction mixture was diluted with ethyl acetate (20 mL), and washed with water (2 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give the desired material as a brown solid (2.37 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.63 - 1.67 (2H, m), 1.93 - 1.96 (2H, m), 3.64 (4H, d), 3.67 - 3.69 (4H, m), 5.52 (2H, s), 6.45 (2H, d), 6.62 (1H, s), 7.47 (2H, d), 7.76 (2H, dd), 8.85 (2H, dd)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 438; HPLC tR = 1.94 min.

2-Chloro-4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidine

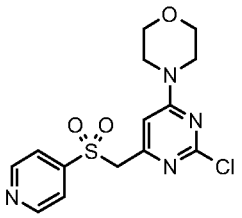


1,2-Dibromoethane (0.510 mL, 22.55 mmol) was added to 2-chloro-4-morpholin-4-yl-6-(pyridin-4-ylsulfonylmethyl)pyrimidine (4 g, 11.27 mmol) in toluene (56.4 mL) followed by tetrabutylammonium bromide (0.363 g, 1.13 mmol) and an aqueous solution of sodium hydroxide (5.64 mL, 56.37 mmol). The reaction was stirred at 60°C for 7 hours then the toluene removed under reduced pressure and the residue redissolved in DCM. The organics were washed with water, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was triturated with diethyl ether to give the desired material as a brown solid (3.35 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.60 - 1.63 (2H, m), 1.89 - 1.92 (2H, m), 3.58 (4H, d), 3.63 - 3.65 (4H, m), 6.81 (1H, s), 7.74 (2H, d), 8.88 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 381, HPLC tR = 1.70 min

2-Chloro-4-morpholin-4-yl-6-(pyridin-4-ylsulfonylmethyl)pyrimidine

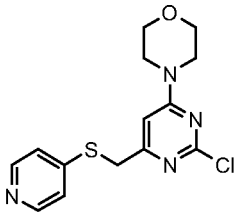


2-Chloro-4-morpholin-4-yl-6-(pyridin-4-ylsulfanylmethyl)pyrimidine (3.28 g, 10.16 mmol) was dissolved in dioxane (45 mL) and 2N sulfuric acid (0.11 mL) was added. The solution was heated to 55°C. A solution of sodium tungstate dihydrate (0.067 g, 0.20 mmol) in water (1.08 mL) was added to the solution and allowed to stir for 10 minutes. Hydrogen peroxide (6.28 mL, 203.2 mmol) was then added dropwise over several minutes. The solution was heated at 55°C for 3 hours. Water was added and the reaction was allowed to cool. The aqueous solution was extracted with DCM and the organics separated, dried ($MgSO_4$), filtered and evaporated. The crude product was triturated with diethyl ether to give the desired material as a cream solid (3.20 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.56 (4H, s), 3.65 - 3.68 (4H, m), 4.77 (2H, s), 6.84 (1H, s), 7.78 (2H, d), 8.92 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 355, HPLC tR = 1.53 min

2-Chloro-4-morpholin-4-yl-6-(pyridin-4-ylsulfanylmethyl)pyrimidine



2-Chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine (5 g, 14.72 mmol) was added portionwise to 4-mercaptopyridine (1.8 g, 16.20 mmol) and DBU (2.344 mL, 16.20 mmol) in acetonitrile (73.6 mL) at RT. The resulting suspension was stirred at RT for 30 minutes. The reaction mixture was evaporated to dryness, redissolved in DCM (50 mL) and the organics washed with water (50 mL), dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% ethyl acetate in DCM, to give the desired material as a beige solid (3.3 g).

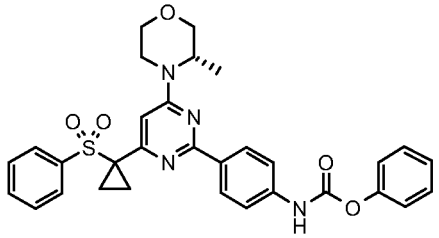
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.58 (4H, s), 3.64 - 3.67 (4H, m), 4.24 (2H, s), 6.97 (1H, s), 7.35 (2H, d), 8.38 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 323, HPLC tR = 1.75 min

The preparation of 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

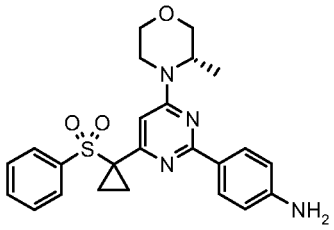


Phenyl chloroformate (0.471 mL, 3.75 mmol) was added dropwise to 4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.690 g, 3.75 mmol) and sodium bicarbonate (0.473 g, 5.63 mmol) in dioxane and the resulting mixture stirred at RT for 18 hours. The solvent was removed, DCM added and the organics washed with water dried ($MgSO_4$), filtered and evaporated to give the desired material as a beige solid (2.44 g) which was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.17-1.19 (3H, d), 1.62-1.69 (2H, m), 1.90-1.93 (2H, m), 3.12-3.19 (1H, td), 3.41-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.10-4.14 (1H, d), 4.39 (1H, bs), 6.66 (1H, s), 7.24-7.30 (3H, m), 7.43-7.47 (2H, t), 7.51-7.53 (2H, d), 7.58-7.61 (2H, t), 7.70-7.74 (1H, t), 7.79-7.81 (2H, d), 7.92-7.94 (2H, d), 10.38 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+=571; HPLC tR=3.00 min.

4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

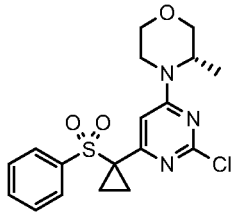


Bis(triphenylphosphine)palladium (II) chloride (0.246 g, 0.35 mmol) was added in one portion to 4-[1-(benzenesulfonyl)cyclopropyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.76 g, 7.01 mmol), 4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.535 g, 7.01 mmol) and an aqueous solution of sodium carbonate (17.52 mL, 35.04 mmol) in a solvent mixture of 18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol) and the resulting mixture stirred at 80°C for 3 hours under an atmosphere of nitrogen. The crude product was dissolved in ethyl acetate and washed with water. The organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give the desired material as a yellow solid (3.35 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.15-1.16 (3H, d), 1.58-1.66 (2H, m), 1.85-1.91 (2H, m), 3.07-3.14 (1H, td), 3.41-3.48 (1H, td), 3.58-3.61 (1H, dd), 3.72-3.75 (1H, d), 3.93-3.96 (1H, dd), 4.05-4.08 (1H, d), 4.33 (1H, bs), 5.50 (2H, s), 6.49-6.53 (3H, t), 7.57-7.61 (2H, t), 7.68-7.71 (3H, m), 7.78-7.81 (2H, d).

LCMS Spectrum: m/z (ES+) (M+H)+=451; HPLC tR=2.37 min.

4-[1-(Benzenesulfonyl)cyclopropyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

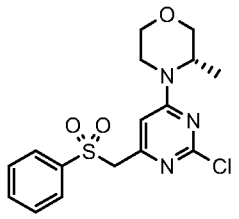


Sodium hydroxide (50% w/w aqueous solution, 299.03 mmol) was added to 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.0 g, 5.44 mmol), 1,2-dibromoethane (1.406 mL, 16.31 mmol) and tetrabutylammonium bromide (0.175 g, 0.54 mmol) in toluene (75 mL) and the resulting mixture stirred at 60°C for 4 hours. Water

was added and the mixture was extracted with toluene. The organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (2.76 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13-1.15 (3H, d), 1.55-1.57 (2H, m), 1.83-1.86 (2H, m), 3.09-3.16 (1H, td), 3.36-3.43 (1H, td), 3.52-3.56 (1H, dd), 3.68-3.71 (1H, d), 3.86-3.93 (2H, m), 4.20 (1H, bs), 6.67 (1H, s), 7.60-7.63 (2H, m), 7.72-7.77 (3H, m).
LCMS Spectrum: m/z (ES+) (M+H)+=394; HPLC tR=2.28 min.

4-(Benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

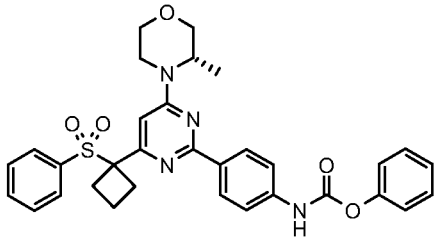


Benzenesulfinic acid, sodium salt (4.22 g, 25.74 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7.0 g, 19.80 mmol) in acetonitrile (200 mL) and the resulting mixture stirred under a nitrogen atmosphere at 80°C for 20 hours. The reaction was cooled and the solvent was removed. DCM was added and the solution was washed with water. The DCM was dried ($MgSO_4$), filtered and the solvent was removed. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material as a cream solid (6.21 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15-1.16 (3H, d), 3.11-3.18 (1H, td), 3.38-3.45 (1H, td), 3.55-3.58 (1H, dd), 3.70-3.73 (1H, d), 3.85-3.94 (2H, m), 4.15 (1H, bs), 4.64 (2H, s), 6.67 (1H, s), 7.63-7.66 (2H, m), 7.74-7.80 (3H, m).
LCMS Spectrum: m/z (ES+) (M+H)+=368; HPLC tR=2.05 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

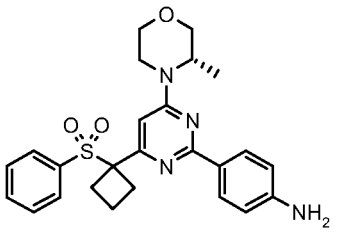


Phenyl chloroformate (0.083 mL, 0.66 mmol) was added to 4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.307 g, 0.66 mmol) and sodium hydrogen carbonate (0.083 g, 0.99 mmol) in dioxane and the resulting mixture was stirred at RT for 2 hours. The solvent was removed and the residue partitioned between DCM and water. The organics were washed with water, dried ($MgSO_4$), filtered and evaporated to give the desired material as a gum (0.386 g) which was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.31-1.33 (3H, d), 1.87-1.99 (1H, m), 2.20-2.31 (1H, m), 2.75-2.83 (2H, m), 3.17-3.32 (3H, m), 3.57-3.63 (1H, td), 3.73-3.77 (1H, dd), 3.80-3.83 (1H, d), 4.01-4.05 (1H, dd), 4.09-4.12 (1H, d), 4.44 (1H, bs), 6.55 (1H, s), 6.78-6.81 (1H, d), 7.16-7.28 (4H, m), 7.36-7.42 (5H, m), 7.49-7.51 (2H, d), 7.56 (1H, s), 7.89-7.92 (2H, d).

LCMS Spectrum: m/z (ES+) (M+H)+=585; HPLC tR=3.30 min.

4-[4-[1-(Benzenesulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



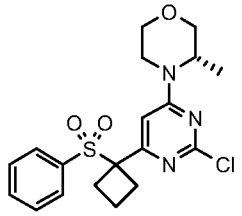
Bis(triphenylphosphine)palladium (II) chloride (0.023 g, 0.03 mmol) was added in one portion to 4-[1-(benzenesulfonyl)cyclobutyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.270 g, 0.66 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.145 g, 0.66 mmol) and an aqueous solution of sodium carbonate (1.653 mL, 3.31 mmol) in

a solvent mixture comprising 18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol and the resulting mixture was stirred at 80°C for 3 hours under an atmosphere of nitrogen. The crude product was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give a sample which was further purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired as a colourless gum (0.395 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.30-1.32 (3H, d), 1.87-1.98 (1H, m), 2.19-2.29 (1H, m), 2.74-2.83 (2H, m), 3.14-3.22 (2H, m), 3.24-3.31 (1H, td), 3.57-3.63 (1H, td), 3.73-3.85 (4H, m), 4.01-4.04 (1H, dd), 4.08-4.12 (1H, d), 4.43-4.45 (1H, m), 6.48 (1H, s), 6.55-6.57 (2H, d), 7.26-7.31 (2H, t), 7.39-7.43 (1H, t), 7.48-7.51 (2H, dd), 7.74-7.76 (2H, d).

LCMS Spectrum: m/z (ES+) (M+H)+=465; HPLC tR=2.49 min.

4-[1-(Benzenesulfonyl)cyclobutyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Sodium hydroxide (50% w/w aqueous solution, 120.21 mmol) was added to 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.804 g, 2.19 mmol), 1,3-dibromopropane (0.666 mL, 6.56 mmol) and tetrabutylammonium bromide (0.070 g, 0.22 mmol) in toluene (50 mL) and the resulting mixture was stirred at 45°C for 1 hour. Water was added, the organics separated, washed with water, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (0.27 g).

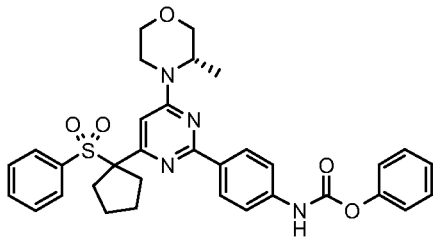
NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.29-1.31 (3H, d), 1.89-1.96 (1H, m), 2.17-2.28 (1H, m), 2.63-2.67 (2H, m), 3.07-3.16 (2H, m), 3.22-3.29 (1H, td), 3.50-3.57 (1H, td), 3.67-3.70 (1H, dd), 3.76-3.79 (1H, d), 3.95-4.01 (2H, m), 4.28 (1H, bs), 6.52 (1H, s), 7.41-7.44 (2H, t), 7.48-7.50 (2H, m), 7.57-7.61 (1H, m).

LCMS Spectrum: m/z (ES+) (M+H)+=408; HPLC tR=2.35 min.

The preparation of 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

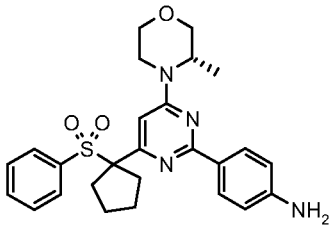


Phenyl chloroformate (0.244 mL, 1.94 mmol) was added to 4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.930 g, 1.94 mmol) and sodium hydrogen carbonate (0.245 g, 2.91 mmol) in dioxane and the resultant mixture stirred at RT for 2 hours. The solvent was removed and the residue partitioned between DCM and water. The organics were washed with water, dried ($MgSO_4$), filtered and evaporated to give the desired material as a beige solid (1.19 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21-1.23 (3H, d), 1.52-1.56 (2H, m), 1.80-1.88 (2H, m), 2.55-2.60 (2H, m), 2.67-2.69 (2H, m), 3.12-3.19 (1H, td), 3.46-3.52 (1H, td), 3.63-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.95-3.99 (1H, dd), 4.12-4.16 (1H, d), 4.50 (1H, bs), 6.66 (1H, s), 7.23-7.30 (3H, m), 7.42-7.51 (8H, m), 7.56-7.60 (1H, m), 7.88-7.90 (2H, d), 10.37 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+=599; HPLC tR=3.44 min.

4-[4-[1-(Benzenesulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

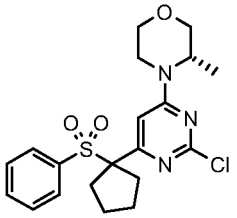


Bis(triphenylphosphine)palladium (II) chloride (0.072 g, 0.10 mmol) was added in one portion to 4-[1-(benzenesulfonyl)cyclopentyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.863 g, 2.05 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.448 g, 2.05 mmol) and an aqueous solution of sodium carbonate (5.11 mL, 10.23 mmol) in a solvent mixture comprising 18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol and the resultant mixture stirred at 80°C for 3 hours. The crude product was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give the desired material as a beige solid (0.93 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.20 (3H, d), 1.52-1.55 (2H, m), 1.81-1.85 (2H, m), 2.50 (2H, m), 2.67-2.70 (2H, m), 3.07-3.15 (1H, td), 3.45-3.51 (1H, td), 3.62-3.65 (1H, dd), 3.74-3.77 (1H, d), 3.94-3.97 (1H, dd), 4.04-4.08 (1H, d), 4.43-4.45 (1H, bs), 5.47 (2H, s), 6.48-6.51 (3H, m), 7.42-7.48 (4H, m), 7.57-7.62 (1H, m), 7.65-7.67 (2H, d).

LCMS Spectrum: m/z (ES+) (M+H)+=479; HPLC tR=2.67 min.

4-[1-(Benzenesulfonyl)cyclopentyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Sodium hydroxide (50% w/w aqueous solution, 112.53 mmol) was added to 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.753 g, 2.05 mmol), 1,4-dibromobutane (0.733 mL, 6.14 mmol) and tetrabutylammonium bromide (0.066 g, 0.20 mmol) in toluene (50 mL) and the resulting suspension stirred at 60°C for 4 hours. Water was added, the organic layer separated and washed twice with water. The organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica

chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a colourless gum (0.904 g).

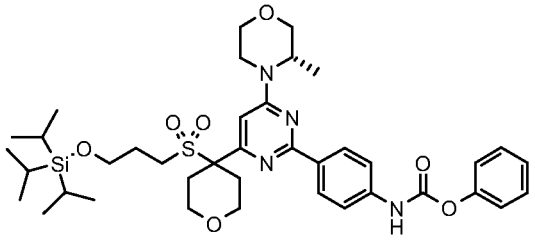
NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.28-1.30 (3H, d), 1.52-1.63 (2H, m), 1.83-1.93 (2H, m), 2.41-2.49 (2H, m), 2.56-2.66 (2H, m), 3.20-3.28 (1H, td), 3.49-3.56 (1H, td), 3.65-3.69 (1H, dd), 3.74-3.77 (1H, d), 3.95-3.99 (2H, m), 4.27 (1H, bs), 6.69 (1H, s), 7.38-7.46 (4H, m), 7.54-7.58 (1H, m).

LCMS Spectrum: m/z (ES+) (M+H)+=422; HPLC tR=2.61 min.

The preparation of 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[4-[3-tri(propan-2-yl)silyloxypropylsulfonyl]oxan-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[4-[3-tri(propan-2-yl)silyloxypropylsulfonyl]oxan-4-yl]pyrimidin-2-yl]phenyl]carbamate



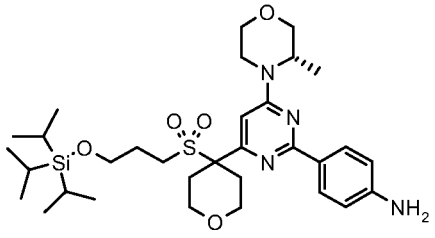
Sodium bicarbonate (0.380 g, 4.53 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[4-[3-tri(propan-2-yl)silyloxypropylsulfonyl]oxan-4-yl]pyrimidin-2-yl]aniline (1.910 g, 3.02 mmol), in 1,4-dioxane (15.09 mL) at RT. Phenyl chloroformate (0.380 mL, 3.02 mmol) was added dropwise over 2 minutes and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (40 mL), and washed with water (40 mL), The organic layer was dried ($MgSO_4$), filtered and evaporated to afford a solid which was triturated with diethyl ether to give the desired material as an amber solid (2.25 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87-0.88 (18H, d), 1.09-1.13 (1H, t), 1.23-1.25 (3H, d), 1.31 (1H, s), 1.74-1.81 (2H, qu), 2.20-2.27 (2H, td), 2.83-2.88 (2H, t), 3.00-3.04 (2H, td), 3.18-3.29 (3H, m), 3.49-3.51 (2H, m), 3.63-3.66 (2H, t), 3.78-3.80 (1H, d), 3.91-3.97 (2H, qu), 3.99-4.03 (1H, dd), 4.30-4.33 (1H, d), 4.58 (1H, exchange), 6.90 (1H, s),

7.25-7.27 (2H, dd), 7.29-7.31 (1H, dd), 7.44-7.47 (2H, d), 7.62-7.64 (2H, d), 8.30-8.32 (2H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 753.4; HPLC tR = 3.97 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[4-[3-tri(propan-2-yl)silyloxypropylsulfonyl]oxan-4-yl]pyrimidin-2-yl]aniline

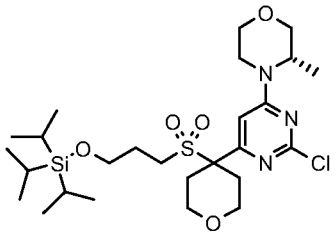


Dichlorobis(triphenylphosphine)palladium (II) (0.118 g, 0.17 mmol) was added to 3-[4-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]oxan-4-yl]sulfonylpropoxy-tri(propan-2-yl)silane (1.94 g, 3.37 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.959 g, 4.38 mmol) and 2M aqueous sodium carbonate (6.06 mL, 12.12 mmol) in water (9.35 mL), ethanol (3.74 mL) and DME (3.74 mL) and the resulting solution stirred at 80°C for 3 hours under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in DCM, to give the desired material as an amber solid (1.91 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90-0.91 (18H, d), 1.21-1.23 (3H, d), 1.73-1.80 (2H, qu), 2.17-2.25 (2H, td), 2.79-2.84 (2H, t), 2.98-3.02 (2H, td), 3.28 (2H, s), 3.31 (2H, s), 3.47-3.53 (1H, td), 3.63-3.67 (3H, m), 3.76-3.79 (1H, d), 3.90-3.96 (2H, qu), 3.97-4.01 (1H, dd), 4.25-4.29 (1H, d), 4.53-4.54 (1H, m), 5.53-5.55 (1H, d), 6.59-6.61 (2H, d), 6.76 (1H, s), 8.02-8.05 (2H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 633.34; HPLC tR = 3.67 min.

3-[4-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]oxan-4-yl]sulfonylpropoxy-tri(propan-2-yl)silane



Sodium tert-butoxide (1.519 g, 15.80 mmol) was added portionwise to 3-[[2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane (2 g, 3.95 mmol) and bis(2-bromoethyl) ether (1.987 mL, 15.80 mmol) in DMF (19.76 mL) at RT over a period of 5 minutes under a nitrogen atmosphere. The resulting solution was stirred at RT for 16 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (0.5 mL), concentrated and diluted with ethyl acetate (200 mL). The organics were separated, washed sequentially with water (2 x 200 mL) and saturated brine (100 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 40 to 60% ethyl acetate in isohexane, to give the desired material as an off white solid (1.94 g).

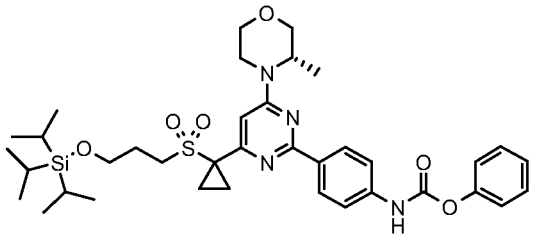
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.98-1.02 (18H, m), 1.20-1.22 (4H, q), 1.78-1.85 (2H, qu), 2.13-2.20 (2H, t), 2.65-2.69 (2H, m), 2.95-3.03 (2H, m), 3.15-3.24 (3H, q), 3.28-3.31 (3H, d), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.72-3.76 (2H, q), 3.87-3.92 (2H, qu), 3.94-3.98 (1H, dd), 4.11-4.14 (1H, d), 4.45 (1H, exchange), 6.99 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ 576.31; HPLC tR = 4.06 min

The preparation of 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane was described earlier.

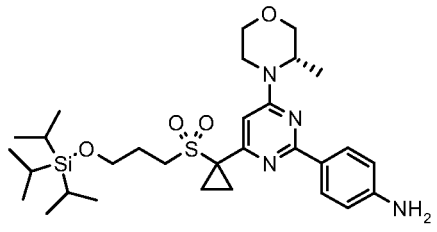
The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate



Sodium bicarbonate (0.749 g, 8.92 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclopropyl]pyrimidin-2-yl]aniline (3.5 g, 5.94 mmol), in 1,4-dioxane (29.7 mL) at RT. Phenyl chloroformate (0.748 mL, 5.94 mmol) was added dropwise over 2 minutes and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM (100 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford a solid, which was triturated with diethyl to give the desired material as a light yellow solid (4.13 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.95-0.96 (18H, d), 1.24-1.26 (3H, d), 1.30 (2H, s), 1.58-1.60 (2H, m), 1.54-1.67 (2H, m), 1.95-2.02 (2H, sex), 3.18-3.26 (1H, td), 3.38-3.43 (2H, m), 3.46-3.49 (3H, m), 3.62-3.66 (1H, dd), 3.75-3.78 (2H, t), 3.97-4.01 (1H, dd), 4.21-4.24 (1H, d), 4.57 (1H, exchange), 6.86 (1H, s), 7.25-7.27 (2H, d), 7.29-7.31 (1H, d), 7.44-7.46 (2H, d), 7.63-7.65 (2H, d), 8.27-8.30 (2H, d), 10.45 (1H, exchange)
LCMS Spectrum: m/z (ESI+)(M+H)+ 709.41; HPLC tR = 3.82 min

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclopropyl]pyrimidin-2-yl]aniline



Dichlorobis(triphenylphosphine)palladium (II) (0.214 g, 0.31 mmol) was added to 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropoxy-tri(propan-2-yl)silane (3.25 g, 6.11 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.739 g, 7.94 mmol) and 2M aqueous sodium carbonate (10.99 mL, 21.98 mmol)

in water (16.96 mL), ethanol (6.79 mL) and DME (6.79 mL) and the resulting solution stirred at 80°C for 3 hours under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in DCM, to give the desired material as an amber gum, which solidified on standing (3.50 g).

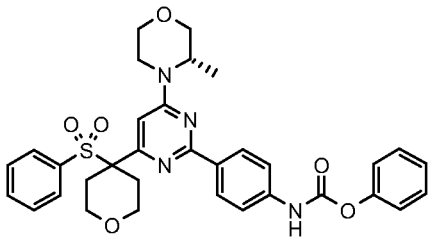
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.98-0.99 (18H, d), 1.53-1.58 (2H, m), 1.60-1.64 (2H, m), 1.96-2.03 (4H, m), 3.14-3.22 (1H, td), 3.29-3.31 (1H, d), 3.45-3.49 (3H, m), 3.61-3.64 (1H, dd), 3.75-3.78 (3H, t), 3.96-4.00 (1H, dd), 4.02-4.08 (1H, q), 4.15-4.19 (1H, d), 4.51 (1H, m), 5.55-5.57 (1H, d), 6.59-6.61 (2H, d), 6.71 (1H, s), 8.02-8.04 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 589.88; HPLC tR = 3.80 min

The preparation of 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropoxy-tri(propan-2-yl)silane was described earlier.

The preparation of phenyl *N*-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

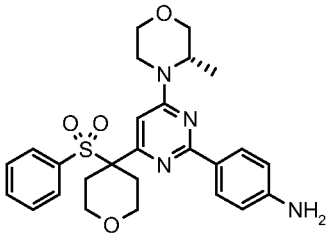


Phenyl chloroformate (0.098 mL, 0.78 mmol) was added dropwise to 4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.35 g, 0.71 mmol) and sodium bicarbonate (0.089 g, 1.06 mmol) in dioxane (25 mL) and the resulting suspension stirred at RT for 18 hours. The reaction mixture was diluted with DCM (20 mL), and washed with water (20 mL), the organic layer dried ($MgSO_4$), filtered and evaporated to give the desired material as an orange gum (0.45 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 2.20-2.30 (2H, td), 2.75 (2H, m), 3.23 (3H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.75 (1H, d), 3.85 (2H, dd), 3.97 (1H, dd), 4.20 (1H, d), 4.55 (1H, br s), 6.70-6.80 (3H, m), 7.15 (1H, t), 7.25 (2H, dd), 7.40-7.55 (7H, m), 7.85 (2H, d), 10.40 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 615; HPLC tR = 2.93 min.

4-[4-[4-(Benzenesulfonyl)oxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

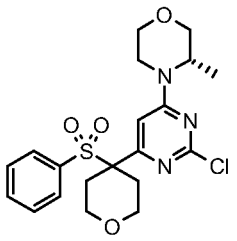


Bis(triphenylphosphine)palladium(II) chloride (0.067 g, 0.09 mmol) was added in one portion to 4-[4-(benzenesulfonyl)oxan-4-yl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.83 g, 1.90 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.498 g, 2.27 mmol) and an aqueous solution of sodium carbonate (4.74 mL, 9.48 mmol) in a DMF (3.60 mL), DME (9.56 mL), water (4.1 mL) and ethanol (2.72 mL) solution mixture. The resulting solution was stirred at 80°C for 3 hours under a nitrogen atmosphere. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (50 mL), and washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a beige solid (0.82 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 2.20-2.30 (2H, td), 2.75 (2H, m), 3.10-3.20 (3H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.75 (1H, d), 3.85 (2H, dd), 3.97 (1H, dd), 4.20 (1H, d), 4.50 (1H, d), 5.47 (2H, s), 6.45 (2H, d), 6.60 (1H, s), 7.40 (4H, m), 7.60 (3H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 495; HPLC tR = 2.37 min.

4-[4-(Benzenesulfonyl)oxan-4-yl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



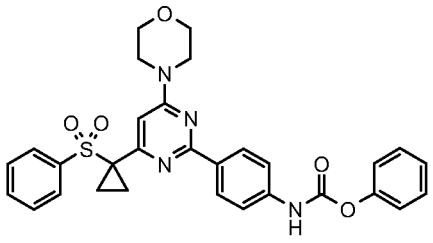
50% v/v aqueous sodium hydroxide (4.49 g, 112.14 mmol) was added to 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.75 g, 2.04 mmol), tetrabutylammonium bromide (0.066 g, 0.20 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (1.419 g, 6.12 mmol) in toluene (50 mL). The resulting mixture was stirred at 60°C for 6 hours. The reaction mixture was diluted with water (50 mL), and washed twice with more water (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a white solid (0.83 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 2.10-2.23 (2H, td), 2.60 (2H, td), 3.10-3.20 (3H, m), 3.25 (1H, d), 3.40 (1H, td), 3.60 (1H, dd), 3.70 (1H, dd), 3.80 (2H, dd), 3.90 (1H, dd), 4.40 (1H, d), 6.70 (1H, s), 7.40 (2H, d), 7.60 (2H, td), 7.75 (1H, td)
LCMS Spectrum: m/z (ESI+) (M+H)+ = 438; HPLC tR = 2.45 min.

The preparation of 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate

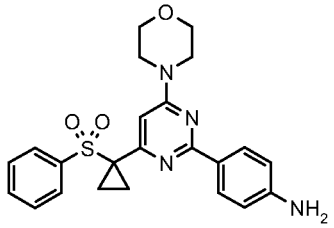


Phenyl chloroformate (0.307 mL, 2.45 mmol) was added to 4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline (1.069 g, 2.45 mmol) and sodium hydrogen carbonate (0.309 g, 3.67 mmol) in dioxane and the resulting suspension stirred at RT overnight. The solids were filtered and washed with dioxane and water and then dried in the vacuum oven at 50°C overnight. The filtrate was concentrated and the solids were filtered, rinsed with water and dried in the vacuum oven overnight. The two crops were combined to give the desired material as a beige solid (1.132 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.62-1.65 (2H, q), 1.89-1.92 (2H, q), 3.66-3.70 (8H, m), 6.71 (1H, s), 7.24-7.31 (3H, m), 7.43-7.47 (2H, t), 7.51-7.54 (2H, d), 7.58-7.62 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.81 (2H, d), 7.90-7.92 (2H, d), 10.40 (1H, bs).

LCMS Spectrum: m/z (ES+) (M+H)+=557; HPLC tR=3.03 min.

4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline

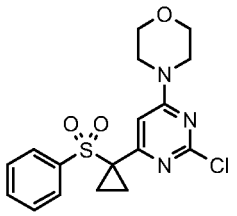


Bis(triphenylphosphine)palladium (II) chloride (0.088 g, 0.13 mmol) was added in one portion to 4-[1-(benzenesulfonyl)cyclopropyl]-2-chloro-6-morpholin-4-ylpyrimidine (0.956 g, 2.52 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.552 g, 2.52 mmol) and an aqueous solution of sodium carbonate (6.29 mL, 12.59 mmol) in a solvent mixture comprising 18% DMF and 82% of a 7:3:2 mixture of DME:water:Ethanol and the solution stirred at 80°C for 3 hours under a nitrogen atmosphere. The crude product was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol to give a sample that was further purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (1.07 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.58-1.62 (2H, q), 1.86-1.89 (2H, q), 3.59-3.60 (4H, m), 3.67-3.69 (4H, m), 5.50 (2H, s), 6.48-6.50 (2H, d), 6.58 (1H, s), 7.57-7.61 (2H, t), 7.66-7.68 (2H, d), 7.69-7.73 (1H, tt), 7.78-7.80 (2H, m).

LCMS Spectrum: m/z (ES+) (M+H)+=437; HPLC tR=2.19 min.

4-[1-(Benzenesulfonyl)cyclopropyl]-2-chloro-6-morpholin-4-ylpyrimidine

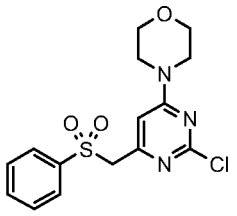


Sodium hydroxide (50% w/w aqueous solution, 248.52 mmol) was added 4-(benzenesulfonylmethyl)-2-chloro-6-morpholin-4-ylpyrimidine (1.599 g, 4.52 mmol), 1,2-dibromoethane (1.168 mL, 13.56 mmol) and tetrabutylammonium bromide (0.146 g, 0.45 mmol) in toluene (75 mL) and the resulting suspension stirred at 60°C for 18 hours. Water was added to the mixture, the organics separated, washed twice with water, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (0.956 g).

NMR Spectrum: ^1H NMR (400.132 MHz, DMSO-d_6) δ 1.53-1.56 (2H, q), 1.82-1.85 (2H, q), 3.53 (4H, bs), 3.63-3.65 (4H, t), 6.72 (1H, s), 7.59-7.63 (2H, m), 7.73-7.77 (3H, m).

LCMS Spectrum: m/z (ES+) (M+H)+=380; HPLC tR=2.02 min.

4-(Benzenesulfonylmethyl)-2-chloro-6-morpholin-4-ylpyrimidine



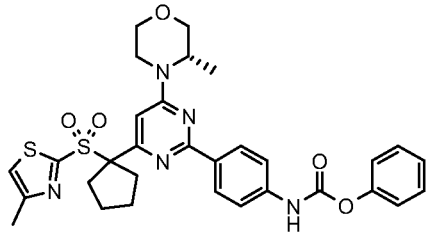
Sodium benzenesulfinate (4.31 g, 26.26 mmol) was added to 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine (6.86 g, 20.20 mmol) in acetonitrile (200 mL) at 22ºC under nitrogen. The resulting slurry was stirred at 80 °C for 3 hours. The reaction had gone to completion. The solvent was removed and DCM and water were added. The DCM was washed with water, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM. Pure fractions were evaporated to dryness to afford 4- (2-chloro-6-(phenylsulfonylmethyl)pyrimidin-4-yl)morpholine (4.96 g, 69.4 %) as a cream solid.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.53 (4H, bs), 3.64-3.67 (4H, t), 4.61 (2H, s), 6.71 (1H, s), 7.63-7.67 (2H, m), 7.75-7.81 (3H, m).
LCMS Spectrum: m/z (ES+) (M+H)+=354; HPLC tR=1.79 min.

The preparation of 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine was described earlier.

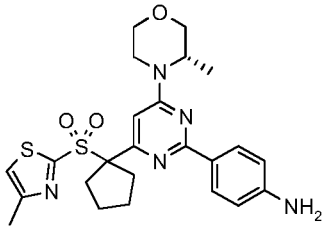
The preparation of phenyl N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]carbamate



Phenylchloroformate (0.232 mL, 1.85 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]aniline (840 mg, 1.68 mmol) and sodium bicarbonate (212 mg, 2.52 mmol) in dioxane (50 mL) at 10ºC under a nitrogen atmosphere. The resulting mixture was stirred at 10°C for 2 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford Phenyl N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]carbamate (1.24g) as a yellow dry film.
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.60 - 1.63 (2H, m), 1.83 - 1.92 (2H, m), 2.38 (3H, s), 2.76 - 2.80 (4H, m), 3.12 - 3.19 (1H, m), 3.49 - 3.55 (1H, m), 3.61 - 3.66 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.15 - 4.18 (1H, m), 4.49 - 4.56 (1H, m), 6.70 (1H, s), 7.24 - 7.26 (3H, m), 7.43 - 7.45 (2H, m), 7.56 (2H, d), 7.64 (1H, s), 7.99 (2H, d), 10.39 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 620; HPLC tR = 3.26min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]aniline

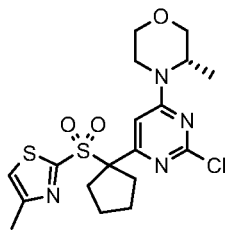


Bis(triphenylphosphine)palladium (II) chloride (0.162 g, 0.23 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidine (2.05g, 4.63 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.318 g, 6.02 mmol) and 2M aqueous sodium carbonate (8.33 mL, 16.66 mmol) in DME (10 mL), ethanol (10 mL) and water (25 mL) and the resulting mixture stirred at 80°C for 18 hours. The cooled reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in DCM, to give the desired material as a yellow gum (0.84 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.57 - 1.62 (2H, m), 1.83 - 1.89 (2H, m), 2.40 (3H, s), 2.73 - 2.78 (4H, m), 3.08 - 3.15 (1H, m), 3.44 - 3.50 (1H, m), 3.61 - 3.64 (1H, m), 3.75 (1H, d), 3.94 - 3.97 (1H, m), 4.10 (1H, d), 4.43 - 4.49 (1H, m), 5.50 (2H, s), 6.53 (2H, d), 6.54 (1H, s), 7.64 (1H, s), 7.73 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 500; HPLC tR = 2.66min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidine



1,4-Dibromobutane (0.627 mL, 5.30 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (2.06 g, 5.30 mmol), 40% aqueous sodium hydroxide solution (5.30 mL, 53 mmol) and tetrabutylammonium bromide (0.342 g, 1.06 mmol) in toluene (100 mL) and the resulting solution stirred at 60°C for 3 hours. The reaction mixture was concentrated and diluted with ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as an orange gum (2.55g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ δ 1.18 (3H, d), 1.57 - 1.62 (2H, m), 1.78 - 1.86 (2H, m), 2.45 (3H, s), 2.55 - 2.68 (4H, m), 3.10 - 3.17 (1H, m), 3.39 - 3.46 (1H, m), 3.55 - 3.59 (1H, m), 3.71 (1H, d), 3.90 - 3.99 (2H, m), 4.32 - 4.38 (1H, m), 6.72 (1H, s), 7.87 (1H, s)

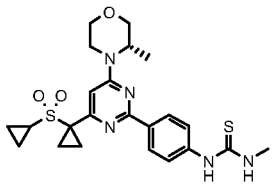
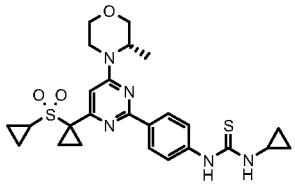
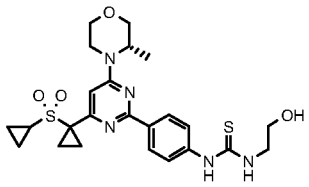
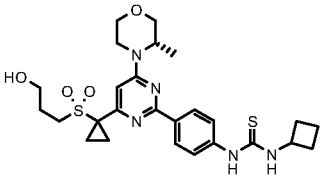
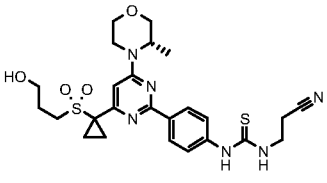
LCMS Spectrum: m/z (ESI+)(M+H)+ = 443; HPLC tR = 2.66min.

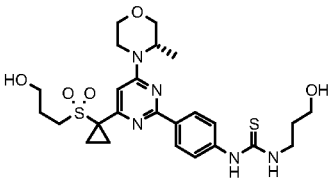
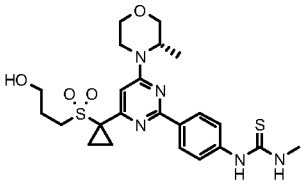
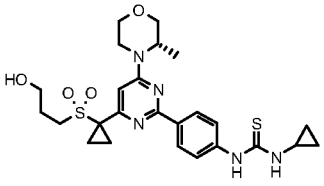
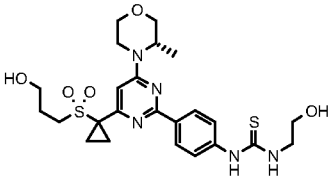
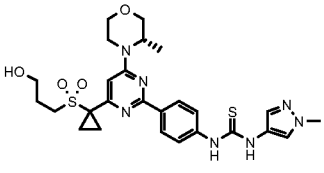
The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine was described earlier.

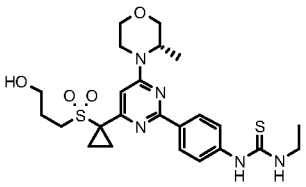
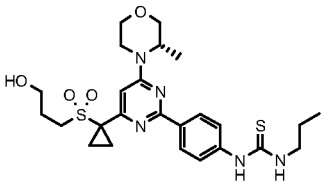
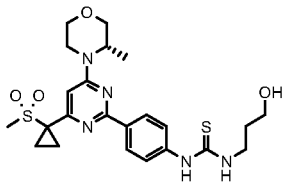
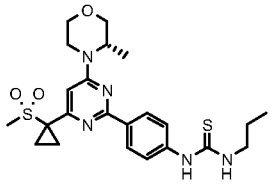
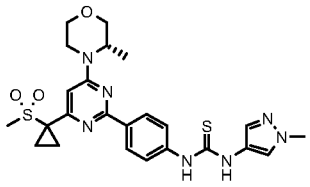
Example 37

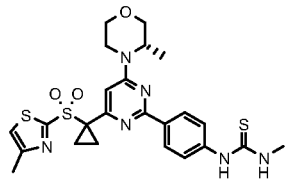
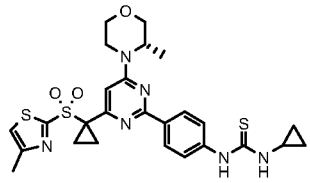
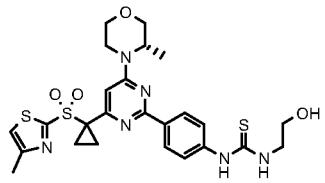
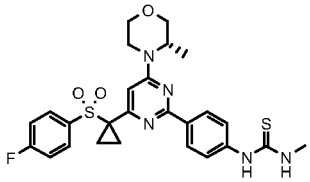
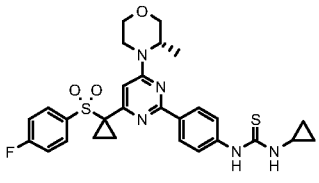
The following compounds were prepared according to the following general procedure.

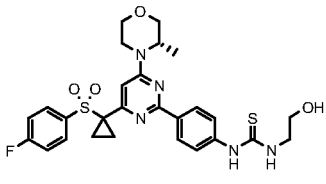
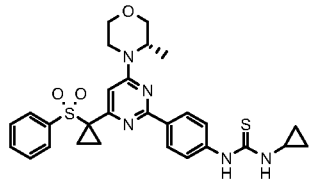
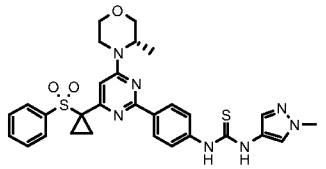
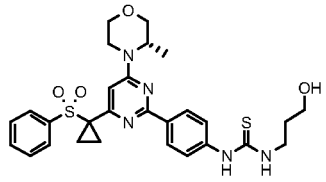
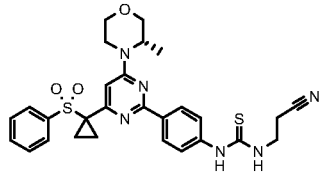
The appropriate aniline was treated with 1,1'-thiocarbonyldiimidazole in a solvent mixture of DCM and THF at RT for 2 - 16 hours. Triethylamine and the appropriate amine were added and the reactions stirred at RT for an additional 1 – 16 hours (unless otherwise stated). The mixtures were purified by prep HPLC.

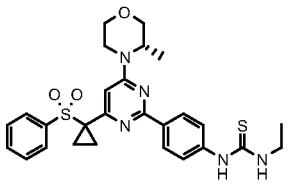
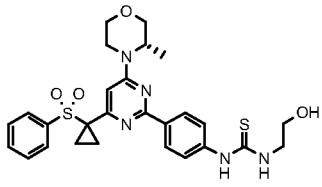
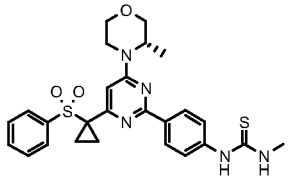
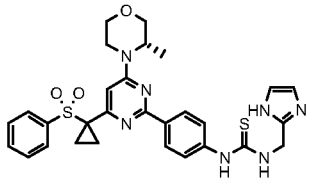
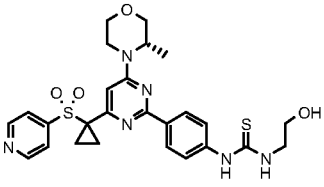
Example	Structure	NAME	LCMS MH+	Retention time (min)
37a		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea	488	2.14
37b		3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	514	2.28
37c		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea	518	1.95
37d		3-cyclobutyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	546	2.32
37e		3-(2-cyanoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	545	2.0

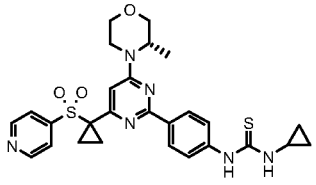
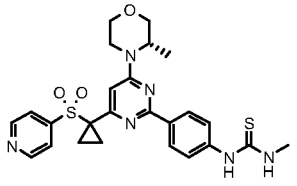
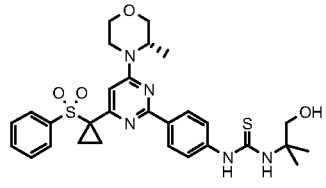
Example	Structure	NAME	LCMS MH+	Retention time (min)
37f		3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	572	1.78
37g		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea	506	1.75
37h		3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	532	1.87
37i		3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	536	1.60
37j		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)thiourea	572	1.72

Example	Structure	NAME	LCMS MH+	Retention time (min)
37k		1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	520	1.91
37l		3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylthiourea	534	2.07
37m		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	506.5	1.74
37n		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propylthiourea	490.5	2.24
37o		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)thiourea	528.5	1.84

Example	Structure	NAME	LCMS MH+	Retention time (min)
37p		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]thiourea	545	2.38
37q		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]thiourea	571	2.51
37r		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]thiourea	575	2.13
37s		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea	540	2.52
37t		3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	568	2.65

Example	Structure	NAME	LCMS MH+	Retention time (min)
37u		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea	572	2.27
37v		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylthiourea	550	2.59
37w		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)thiourea	589	2.30
37x		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)thiourea	568	2.20
37y		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)thiourea	563	2.49

Example	Structure	NAME	LCMS MH+	Retention time (min)
37z		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylthiourea	538	2.60
37aa		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea	554	2.18
37ab		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea	524	2.41
37ac		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea	590	2.40
37ad*		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	556	1.92

Example	Structure	NAME	LCMS MH+	Retention time (min)
37ae*		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	552	2.22
37af*		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	526	2.10
37ag		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)thiourea	582	2.50

* The appropriate aniline was treated with 1,1'-thiocarbonyldiimidazole in a solvent mixture of DCM and THF at RT for 16 hours. Triethylamine and the appropriate amine, dissolved in DMF, were added and the reactions stirred at 50°C for 1 hour. The mixture was purified by prep HPLC.

Example 37a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90 - 0.98 (2H, m), 0.99 - 1.08 (2H, m), 1.24 (3H, d), 1.55 - 1.62 (2H, m), 1.63 - 1.70 (2H, m), 2.91 - 3.05 (4H, m), 3.19 - 3.25 (1H, m), 3.44 - 3.55 (1H, m), 3.64 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.20 (1H, d), 4.56 (1H, s), 6.88 (1H, s), 7.55 (2H, d), 7.83 (1H, s), 8.27 (2H, d), 9.72 (1H, s).

mTOR Kinase Assay (Echo): 0.026μM

Example 37b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.57 - 0.63 (2H, m), 0.72 - 0.78 (2H, m), 0.90 - 0.96 (2H, m), 0.99 - 1.07 (2H, m), 1.24 (3H, d), 1.55 - 1.62 (2H, m), 1.63 - 1.68

(2H, m), 2.90 - 3.04 (2H, m), 3.17 - 3.27 (1H, m), 3.50 (1H, d), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.18 (1H, d), 4.56 (1H, s), 6.89 (1H, s), 7.62 (2H, d), 8.27 (2H, d), 9.50 (1H, s).

mTOR Kinase Assay (Echo): 0.0124μM

Example 37c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90 - 0.96 (2H, m), 1.00 - 1.07 (2H, m), 1.24 (3H, d), 1.55 - 1.61 (2H, m), 1.64 - 1.69 (2H, m), 2.95 - 3.05 (1H, m), 3.17 - 3.27 (3H, m), 3.44 - 3.56 (3H, m), 3.64 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.20 (1H, d), 4.55 (1H, s), 4.82 (1H, s), 6.88 (1H, s), 7.57 - 7.68 (2H, m), 7.86 (1H, s), 8.27 (2H, d), 9.81 (1H, s).

mTOR Kinase Assay (Echo): 0.00344μM

Example 37d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.60 (2H, m), 1.62 - 1.71 (3H, m), 1.89 - 1.98 (2H, m), 2.25 - 2.34 (2H, m), 2.42 - 2.52 (2H, m), 3.14 - 3.24 (3H, m), 3.41 - 3.55 (3H, m), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.20 (1H, d), 4.53 - 4.68 (2H, m), 6.81 (1H, s), 7.60 (2H, d), 8.11 (1H, s), 8.26 (2H, d), 9.58 (1H, s).

mTOR Kinase Assay (Echo): 0.00439μM

Example 37e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.60 (2H, m), 1.62 - 1.68 (2H, m), 1.91 - 1.98 (2H, m), 2.84 - 2.92 (2H, m), 3.13 - 3.24 (1H, m), 3.43 - 3.57 (5H, m), 3.64 (1H, d), 3.72 - 3.80 (3H, m), 3.97 (1H, d), 4.20 (1H, d), 4.57 (1H, s), 4.68 (1H, t), 6.83 (1H, s), 7.56 (2H, d), 8.16 (1H, s), 8.29 (2H, d), 9.98 (1H, s).

mTOR Kinase Assay (Echo): 0.0049μM

Example 37f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.59 (2H, m), 1.62 - 1.67 (2H, m), 1.93 - 1.98 (4H, m), 2.28 - 2.36 (2H, m), 2.65 - 2.70 (2H, m), 3.13 - 3.23 (1H, m), 3.44 - 3.56 (5H, m), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.20 (1H, d), 4.58 (1H, s), 4.71 (2H, s), 6.82 (1H, s), 7.00 (2H, s), 7.69 (2H, d), 8.21 (0H, s), 8.29 (2H, s).

mTOR Kinase Assay (Echo): 0.12μM

Example 37g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.59 (2H, m), 1.62 - 1.68 (2H, m), 1.89 - 1.99 (2H, m), 2.96 (3H, s), 3.14 - 3.28 (3H, m), 3.45 - 3.55 (3H, m), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.21 (1H, d), 4.58 (1H, s), 4.68 (1H, t), 6.82 (1H, s), 7.55 (2H, d), 7.84 (1H, s), 8.27 (2H, d), 9.73 (1H, s).

mTOR Kinase Assay (Echo): 0.0179μM

Example 37h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.56 - 0.66 (2H, m), 0.72 - 0.80 (2H, m), 1.24 (3H, d), 1.53 - 1.60 (2H, 1m), 1.62 - 1.68 (2H, m), 1.88 - 2.00 (2H, m), 2.92 (1H, s), 3.16 - 3.27 (1H, m), 3.44 - 3.58 (5H, m), 3.64 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H,

d), 4.57 (1H, s), 4.68 (1H, t), 6.82 (1H, s), 7.62 (2H, d), 8.14 (1H, s), 8.26 (2H, d), 9.50 (1H, s).

mTOR Kinase Assay (Echo): 0.0132μM

Example 37i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.59 (2H, m), 1.63 - 1.68 (2H, m), 1.89 - 1.97 (2H, m), 3.14 - 3.29 (5H, m), 3.46 - 3.60 (5H, m), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.21 (1H, d), 4.57 (1H, s), 4.68 (1H, t), 4.81 (1H, s), 6.82 (1H, s), 7.63 (2H, d), 7.96 (1H, s), 8.27 (2H, d), 9.81 (1H, s).

mTOR Kinase Assay (Echo): 0.00306μM

Example 37j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.60 (2H, m), 1.62 - 1.68 (2H, m), 1.89 - 1.99 (2H, m), 3.15 - 3.25 (1H, m), 3.41 - 3.56 (5H, m), 3.64 (1H, d), 3.82 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.58 (1H, s), 4.69 (1H, t), 6.82 (1H, s), 7.51 (1H, s), 7.62 (2H, d), 8.05 (1H, s), 8.28 (2H, d), 9.69 (1H, s).

mTOR Kinase Assay (Echo): 0.0309μM

Example 37k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, t), 1.24 (3H, d), 1.53 - 1.60 (2H, m), 1.62 - 1.67 (2H, m), 1.89 - 1.97 (2H, m), 3.14 - 3.28 (3H, m), 3.46 - 3.56 (5H, m), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.21 (1H, d), 4.58 (1H, s), 4.68 (1H, t), 6.82 (1H, s), 7.56 (2H, d), 7.88 (1H, s), 8.27 (2H, d), 9.62 (1H, s).

mTOR Kinase Assay (Echo): 0.0114μM

Example 37l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.91 (3H, t), 1.24 (3H, d), 1.53 - 1.60 (4H, m), 1.62 - 1.67 (2H, m), 1.90 - 1.97 (2H, m), 3.16 - 3.27 (3H, m), 3.42 - 3.53 (5H, m), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.21 (1H, d), 4.57 (1H, s), 4.68 (1H, t), 6.82 (1H, s), 7.58 (2H, d), 7.89 (1H, s), 8.26 (2H, d), 9.63 (1H, s).

mTOR Kinase Assay (Echo): 0.032μM

Example 37m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.67 - 1.75 (4H, m), 3.17 - 3.26 (1H, m), 3.28 (3H, s), 3.45 - 3.58 (5H, m), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.18 - 4.25 (1H, m), 4.52 - 4.63 (2H, m), 6.80 (1H, s), 7.57 - 7.60 (2H, m), 7.91 (1H, s), 8.24 - 8.27 (2H, m), 9.71 (1H, s).

mTOR Kinase Assay (Echo): 0.0506μM

Example 37n: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.91 (3H, t), 1.24 (3H, d), 1.53 - 1.62 (4H, m), 1.66 - 1.69 (2H, m), 3.22 (1H, td), 3.27 (3H, s), 3.43 - 3.52 (3H, m), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.18 - 4.25 (1H, m), 4.56 - 4.62 (1H, m), 6.80 (1H, s), 7.60 (2H, d), 7.91 (1H, s), 8.24 - 8.28 (2H, m), 9.65 (1H, s).

mTOR Kinase Assay (Echo): 0.0393μM

Example 37o: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.56 - 1.59 (2H, m), 1.67 - 1.70 (2H, m), 3.22 (1H, td), 3.27 (3H, s), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.81 (3H, s), 3.98 (1H, dd), 4.19 - 4.25 (1H, m), 4.57 - 4.63 (1H, m), 6.81 (1H, s), 7.51 (1H, s), 7.62 - 7.65 (2H, m), 8.05 (1H, s), 8.25 - 8.29 (2H, m), 9.67 - 9.76 (2H, m).

mTOR Kinase Assay (Echo): 0.033μM

Example 37p: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.78 - 1.81 (2H, m), 1.95 - 1.98 (2H, m), 2.48 (3H, s), 2.95 (3H, d), 3.16 - 3.23 (1H, m), 3.44 - 3.51 (1H, m), 3.62 (1H, d), 3.76 (1H, d), 3.96 - 3.99 (1H, m), 4.14 - 4.18 (1H, m), 4.44 - 4.50 (1H, m), 6.82 (1H, s), 7.47 (2H, d), 7.80 (1H, s), 7.84 (1H, s), 7.96 (2H, d), 9.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00534μM

Example 37q: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.58 - 0.62 (2H, m), 0.74 - 0.79 (2H, m), 1.22 (3H, d), 1.78 - 1.81 (2H, m), 1.95 - 1.98 (2H, m), 2.49 (3H, s), 2.87 - 2.97 (1H, m), 3.17 - 3.23 (1H, m), 3.44 - 3.51 (1H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.96 - 3.99 (1H, m), 4.15 - 4.18 (1H, m), 4.44 - 4.51 (1H, m), 6.83 (1H, s), 7.54 (2H, d), 7.84 (1H, s), 7.95 (2H, d), 8.15 (1H, s), 9.47 (1H, s).

mTOR Kinase Assay (Echo): 0.00294μM

Example 37r: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.78 - 1.81 (2H, m), 1.94 - 1.98 (2H, m), 2.48 (3H, s), 3.16 - 3.23 (1H, m), 3.44 - 3.50 (1H, m), 3.57 (4H, s), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.15 - 4.18 (1H, m), 4.43 - 4.52 (1H, m), 4.82 (1H, s), 6.82 (1H, s), 7.54 (2H, d), 7.84 (2H, s), 7.95 (2H, d), 9.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00162μM

Example 37s: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.59 - 1.65 (2H, m), 1.89 - 1.91 (2H, m), 2.94 (3H, d), 3.16 (1H, dt), 3.47 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.44 (1H, s), 6.69 (1H, s), 7.44 (4H, t), 7.80 - 7.90 (5H, m), 9.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00756μM

Example 37t: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.57 - 0.62 (2H, m), 0.74 - 0.79 (2H, m), 1.19 (3H, d), 1.61 - 1.63 (2H, m), 1.89 - 1.91 (2H, m), 2.90 - 2.94 (1H, m), 3.17 (1H, dt), 3.47 (1H, dt), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.45 (1H, s), 6.69 (1H, s), 7.42 (2H, t), 7.52 (2H, d), 7.83 - 7.89 (4H, m), 8.13 (1H, s), 9.47 (1H, s).

mTOR Kinase Assay (Echo): 0.00889μM

Example 37u: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (4H, d), 1.59 - 1.63 (3H, m), 1.89 - 1.91 (2H, m), 3.13 - 3.20 (1H, m), 3.43 - 3.50 (1H, m), 3.56 (4H, m), 3.60 - 3.63 (1H, m), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.44 (1H, s), 4.81 (1H, s), 6.68 (1H, s), 7.42 (2H, t), 7.53 (2H, d), 7.83 - 7.86 (1H, m), 7.88 (2H, d), 9.78 (1H, s).

mTOR Kinase Assay (Echo): 0.000395μM

Example 37v: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.58-0.62 (2H, m), 0.74-0.79 (2H, m), 1.17-1.19 (3H, d), 1.62-1.69 (2H, m), 1.88-1.93 (2H, m), 2.92 (1H, bs), 3.12-3.19 (1H, td), 3.43-3.50 (1H, td), 3.60-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.10-4.13 (1H, d), 4.41 (1H, bs), 6.67 (1H, s), 7.49-7.52 (2H, d), 7.58-7.62 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.81 (2H, d), 7.89-7.91 (2H, d), 8.10 (1H, bs), 9.47 (1H, bs).

mTOR Kinase Assay (Echo): 0.00549μM

Example 37w: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15-1.20 (3H, d), 1.60-1.70 (2H, m), 1.90-1.95 (2H, bs), 3.12-31.7 (1H, m), 3.25-3.30 (1H, m obscured by solvent peak), 3.45-3.50 (1H, m), 3.6 (1H, d), 3.7 (1H, d), 3.8 (3H, s), 4.0 (1H, m), 4.1 (1H, d), 4.40-4.45 (1H, bs), 6.7 (1H, s), 7.49-7.53 (3H, m), 7.68-7.73 (2H, m), 7.7 (1H, t), 7.8 (2H, d), 7.9 (2H, d), 8.0 (1H, bs), 9.7 (1H, bs).

mTOR Kinase Assay (Echo): 0.00137μM

Example 37x: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.19 (3H, d), 1.61-1.67 (2H, m), 1.68-1.75 (2H, m), 1.88-1.93 (2H, m), 3.11-3.17 (1H, td), 3.43-3.55 (5H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.09-4.12 (1H, d), 4.40 (1H, bs), 4.53-4.54 (1H, t), 6.66 (1H, s), 7.45-7.47 (2H, d), 7.58-7.62 (2H, t), 7.70-7.75 (1H, tt), 7.79-7.81 (2H, dd), 7.86 (1H, bs), 7.89-7.92 (2H, d), 9.64 (1H, bs).

mTOR Kinase Assay (Echo): 0.00944μM

Example 37y: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.19 (3H, d), 1.61-1.68 (2H, m), 1.89-1.92 (2H, m), 2.85-2.88 (2H, t), 3.11-3.19 (1H, td), 3.43-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.75 (3H, m), 3.94-3.98 (1H, dd), 4.09-4.12 (1H, d), 4.41 (1H, bs), 6.67 (1H, s), 7.42-7.45 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.81 (2H, dd), 7.90-7.93 (2H, d), 8.08-8.11 (1H, t), 9.91 (1H, s).

mTOR Kinase Assay (Echo): 0.00553μM

Example 37z: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.12-1.19 (6H, m), 1.61-1.69 (2H, m), 1.89-1.92 (2H, m), 3.11-3.19 (1H, td), 3.43-3.52 (3H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.09-4.12 (1H, d), 4.40 (1H, bs), 6.66 (1H, s), 7.44-7.46 (2H, d), 7.58-

7.62 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.81 (2H, d), 7.84 (1H, bs), 7.90-7.92 (2H, d), 9.58 (1H, bs).

mTOR Kinase Assay (Echo): 0.00481μM

Example 37aa: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.19 (3H, d), 1.61-1.69 (2H, m), 1.88-1.92 (2H, m), 3.11-3.19 (1H, td), 3.43-3.49 (1H, td), 3.51-3.63 (5H, m), 3.72-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.09-4.12 (1H, d), 4.40 (1H, bs), 4.82 (1H, bs), 6.66 (1H, s), 7.51-7.53 (2H, d), 7.58-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.81 (2H, d), 7.89-7.91 (3H, m), 9.83 (1H, bs).

mTOR Kinase Assay (Echo): 0.00567μM

Example 37ab: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.19 (3H, d), 1.61-1.68 (2H, m), 1.88-1.92 (2H, m), 2.94-2.95 (3H, d), 3.11-3.17 (1H, td), 3.44-3.49 (1H, td), 3.58-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.08-4.12 (1H, d), 4.41 (1H, bs), 6.67 (1H, s), 7.43-7.45 (2H, d), 7.58-7.62 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.81 (3H, m), 7.90-7.92 (2H, d), 9.70 (1H, bs).

mTOR Kinase Assay (Echo): 0.003μM

Example 37ac: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.19 (3H, d), 1.62-1.69 (2H, m), 1.90-1.93 (2H, m), 3.12-3.18 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.09-4.13 (1H, d), 4.41 (1H, bs), 4.71-4.72 (2H, d), 6.67 (1H, s), 7.00 (2H, bs), 7.56-7.62 (4H, m), 7.70-7.74 (1H, tt), 7.79-7.81 (2H, dd), 7.91-7.93 (2H, d), 8.17 (1H, bs), 9.98 (1H, bs), 11.98 (1H, bs).

mTOR Kinase Assay (Echo): 0.0298μM

Example 37ad: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.70 (2H, q), 1.98 (2H, q), 3.10-3.20 (1H, td), 3.40-3.50 (1H, td), 3.50-3.58 (4H, m), 3.58 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.50 (1H, br s), 4.80 (1H, br s), 6.70 (1H, s), 7.50 (2H, d), 7.74-7.77 (4H, m), 7.82 (1H, s), 8.87 (2H, dd), 9.75 (1H, s)

Example 37ae: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ δ 0.60 (2H, q), 0.77 (2H, q), 1.20 (3H, d), 1.70 (2H, q), 1.98 (2H, q), 2.85-2.95 (1H, m), 3.19 (1H, td), 3.47 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.17 (1H, d), 4.48 (1H, br s), 6.71 (1H, s), 7.49 (2H, d), 7.72 (2H, d), 7.78 (2H, dd), 8.15 (1H, br s), 8.87 (2H, dd), 9.46 (1H, br s)

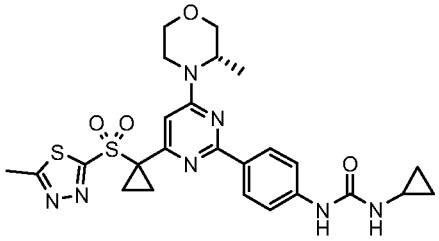
Example 37af: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.70 (2H, q), 1.98 (2H, q), 2.94 (3H, d), 3.17 (1H, td), 3.46 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.10-

4.20 (1H, d), 4.50 (1H, br s), 6.71 (1H, s), 7.43 (2H, d), 7.74-7.76 (2H, d), 7.77-7.79 (2H, dd), 7.82 (1H, m), 8.87 (2H, dd), 9.70 (1H, br s).

Example 37ag: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.45 (6H, s), 1.65 (2H, m), 1.90 (2H, m), 3.14 (1H, m), 3.46 (1H, m), 3.58 (3H, m), 3.75 (1H, m), 3.96 (1H, m), 4.11 (1H, m), 4.41 (1H, m), 6.67 (1H, s), 7.39 (1H, m), 7.50 (2H, m), 7.60 (2H, m), 7.75 (3H, m), 7.88 (2H, m)

The preparations of the anilines required for **Examples 37a – 37ag** have been described earlier.

Example 38: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea



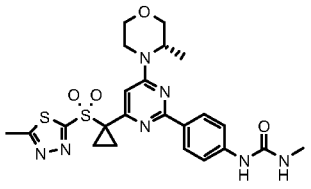
Cyclopropylamine (84 mg, 1.48 mmol) was added to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate (175 mg, 0.30 mmol) and triethylamine (0.205 mL, 1.48 mmol) in NMP (2 mL) at RT and the reaction was allowed to stir for 2 hours. The mixture was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a cream solid (112 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.37 - 0.45 (2H, m), 0.61 - 0.68 (2H, m), 1.21 (3H, d), 1.78 - 1.88 (2H, m), 1.97 - 2.05 (2H, m), 2.83 (3H, s), 3.12 - 3.23 (1H, m), 3.42 - 3.52 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.20 (1H, s), 4.52 (1H, s), 6.46 (1H, t), 6.77 (1H, s), 7.42 (2H, d), 7.74 (2H, d), 8.57 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 556; HPLC tR = 2.25 min.

mTOR Kinase Assay (Echo): 0.00131μM

The following compounds were made in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

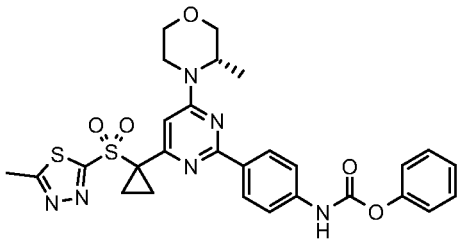
Example	Structure	NAME	LCMS MH+	Retention time (min)
38a		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	530	209

Example 38a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.82 - 1.85 (2H, m), 1.98 - 2.04 (2H, m), 2.66 (3H, s), 2.82 (3H, s), 3.13 - 3.25 (1H, m), 3.40 - 3.47 (1H, m), 3.61 (1H, d), 3.76 (1H, d), 3.96 (1H, d), 4.21 (1H, s), 6.08 (1H, t), 6.77 (1H, s), 7.42 (2H, d), 7.74 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.000918μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate



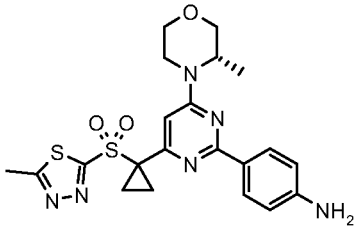
Phenyl chloroformate (0.398 mL, 3.17 mmol) was added slowly to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]aniline (1.25 g, 2.65 mmol) and sodium hydrogen carbonate (0.333 g, 3.97 mmol) in dioxane (30 mL) at 5°C under an atmosphere of nitrogen. The resulting mixture was stirred at

RT for 18 hours then the mixture diluted with ethyl actate (125 mL), and washed sequentially with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The crude material was triturated with diethyl ether and isohexane to give a solid which was collected by filtration and dried under vacuum to give the desired material as a cream solid (1.24 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.82 - 1.88 (2H, m), 2.00 - 2.05 (2H, m), 2.82 (3H, s), 3.20 (1H, dd), 3.42 - 3.50 (1H, m), 3.60 (1H, d), 3.76 (1H, d), 4.00 (1H, d), 4.23 (1H, s), 4.53 (1H, s), 6.81 (1H, s), 7.22 - 7.34 (3H, m), 7.40 - 7.50 (2H, m), 7.55 (2H, d), 7.84 (2H, d), 10.46 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 593; HPLC tR = 2.81 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]aniline



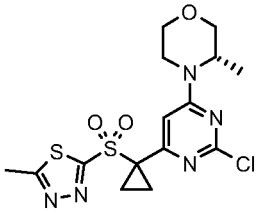
Bis(triphenylphosphine)palladium(II) chloride (0.164 g, 0.23 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidine (1.45 g, 3.49 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.146 g, 5.23 mmol) and aqueous sodium carbonate solution (3 mL, 6.00 mmol) in a solvent mixture of DMF (10 mL), DME (2 mL), water (2 mL) and ethanol (2 mL). The atmosphere was replaced with nitrogen and the reaction stirred at 90°C for 18 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with saturated brine (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 80% ethyl acetate in isohexane, to give the desired material as a beige solid (1.25 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.78 - 1.83 (2H, m), 1.98 - 2.01 (2H, m), 2.83 (3H, s), 3.10 - 3.21 (1H, m), 3.38 - 3.51 (1H, m), 3.60 (1H, d), 3.74

(1H, d), 3.95 (1H, d), 4.16 (1H, s), 4.48 (1H, s), 5.59 (2H, s), 6.51 (2H, d), 6.66 (1H, s), 7.57 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 473; HPLC tR = 2.14 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidine

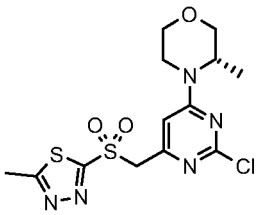


An aqueous solution of sodium hydroxide (20 mL, 532.5 mmol) was added to a stirred mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonylmethyl]pyrimidine (1.8 g, 4.62 mmol), 1,2-dibromoethane (1.99 ml, 23.08 mmol) and tetraethylammonium bromide (0.097 g, 0.46 mmol) in DCM (40 mL) at RT. The resulting mixture was stirred at RT for 24 hours then the mixture diluted with DCM (50 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was chromatographed on silica, elution gradient 10 to 60% ethyl acetate in isohexane, to give the desired material as a yellow gum (1.48 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.79 - 1.84 (2H, m), 1.94 - 2.01 (2H, m), 2.87 (3H, s), 3.17 - 3.23 (1H, m), 3.37 - 3.46 (1H, m), 3.55 (1H, dd), 3.71 (1H, d), 3.92 (1H, dd), 4.06 (1H, s), 4.33 (1H, s), 6.87 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 416; HPLC tR = 1.98 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonylmethyl]pyrimidine



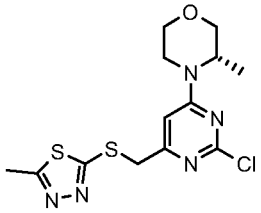
3-Chloroperoxybenzoic acid (4.77 g, 27.66 mmol) was added portionwise to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanylmethyl]pyrimidine (3.3

g, 9.22 mmol), in DCM (70 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at RT for 2 hours then diluted with ethyl acetate (250 mL), and washed sequentially with a 10% aqueous solution of sodium metabisulphite (100 mL) and 2M sodium carbonate (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 10 to 100% ethyl acetate in isohexane, to give the desired material as a white solid (2.22 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (4H, d), 2.87 (4H, s), 3.15 - 3.26 (1H, m), 3.44 (1H, td), 3.59 (1H, d), 3.73 (1H, d), 3.94 (2H, m), 4.22 (1H, s), 5.03 (2H, s), 6.92 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 390; HPLC tR = 1.83 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanylmethyl]pyrimidine

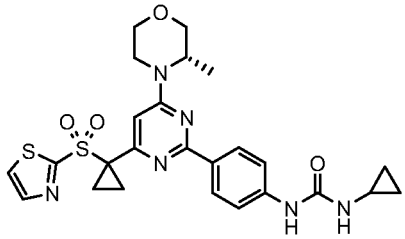


DIPEA (2.94 mL, 16.97 mmol) was added to 5-methyl-1,3,4-thiadiazole-2-thiol (1.645 g, 12.44 mmol), in acetonitrile (40 mL) at RT under an atmosphere of nitrogen. The resulting solution was stirred at RT for 20 minutes then 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4 g, 11.31 mmol) was added. The resulting mixture was stirred at RT for 1 hour then then mixture diluted with ethyl acetate (300 mL), and washed with water (150 mL).The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 0 to 2% methanol in ethyl acetate, to give the desired material as a white solid (3.30 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 6.90 (1H, s), 1.17 (3H, d), 2.68 (3H, s), 3.12 - 3.22 (1H, m), 3.42 (1H, td), 3.57 (1H, dd), 3.71 (1H, d), 3.86 - 4.04 (2H, m), 4.27 (1H, s), 4.42 (2H, s)

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

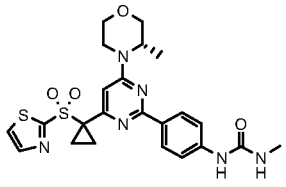
Example 39: 3-Cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea



Bis(triphenylphosphine)palladium(II) chloride (17.6 mg, 0.03 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidine (150 mg, 0.37 mmol), 1-cyclopropyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (170 mg, 0.56 mmol) and an aqueous solution of sodium carbonate (5 mL, 10.00 mmol) in a solvent mixture of DMF (2 mL), DME (16 mL), water (2 mL) and ethanol (2 mL). The atmosphere was replaced with nitrogen and the mixture stirred at 90°C for 18 hours. The mixture was allowed to cool and diluted with ethyl acetate (200 mL) and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 0 to 4% methanol in ethyl acetate. The crude material was further purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material (30 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.37 - 0.45 (2H, m), 0.60 - 0.67 (2H, m), 1.19 (3H, d), 1.76 - 1.82 (2H, m), 1.95 - 2.02 (2H, m), 3.12 - 3.21 (1H, m), 3.45 (1H, d), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.18 (1H, s), 4.44 (1H, s), 6.45 (1H, s), 6.73 (1H, s), 7.41 (2H, d), 7.83 (2H, d), 8.24 (1H, s), 8.28 (1H, s), 8.54 (1H, s)

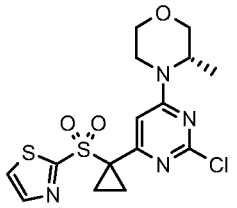
The following compound was made in an analogous fashion from 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidine and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
39a		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	515	2.05

Example 39a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.76 - 1.81 (2H, m), 1.96 - 2.01 (2H, m), 2.66 (3H, d), 3.11 - 3.22 (1H, m), 3.42 - 3.49 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.17 (1H, s), 4.44 (1H, s), 6.07 (1H, q), 6.73 (1H, s), 7.40 (2H, d), 7.82 (2H, d), 8.24 (1H, d), 8.28 (1H, d), 8.75 (1H, s)

The preparation of 2-chloro-4-[(*3S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidine is described below.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidine

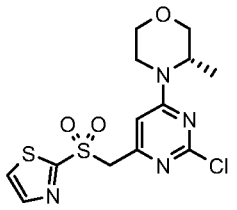


An aqueous solution of sodium hydroxide (0.235 mL, 6.27 mmol) was added to a stirred mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfonylmethyl)pyrimidine (2.35 g, 6.27 mmol), 1,2-dibromoethane (2.70 mL, 31.34 mmol) and tetraethylammonium bromide (0.132 g, 0.63 mmol) in toluene at RT. The resulting mixture was stirred at 70°C for 2 hours then was diluted with ethyl acetate (150 mL), and washed with water (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 60% ethyl acetate in isohexane, to give the desired material as a yellow solid (2.45 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (4H, d), 1.69 - 1.75 (2H, m), 1.91 - 1.96 (2H, m), 3.12 - 3.21 (1H, m), 3.40 (1H, d), 3.55 (1H, d), 3.70 (1H, d), 3.92 (1H, d), 4.00 (1H, s), 4.27 (1H, s), 6.84 (1H, s), 8.20 (1H, d), 8.33 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 401; HPLC tR = 2.04 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfonylmethyl)pyrimidine

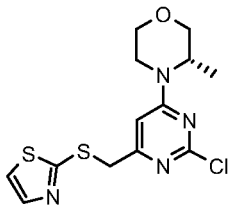


3-Chloroperoxybenzoic acid (6.04 g, 35.00 mmol) was added portionwise to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfanylmethyl)pyrimidine (4 g, 11.67 mmol), in DCM (10 mL) at RT under an atmosphere of nitrogen. The resulting solution was stirred at RT for 3 hours. The reaction mixture was diluted with ethyl acetate (250 mL), and washed with a 10% aqueous solution sodium metabisulphite (100 mL) and a saturated aqueous solution of sodium carbonate (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 100% ethyl acetate in isohexane, to give the desired material as a white solid (2.85 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 8.33 (1H, d), 1.18 (4H, d), 3.14 - 3.25 (1H, m), 3.43 (1H, dd), 3.58 (1H, d), 3.72 (1H, d), 3.88 - 4.01 (2H, m), 4.20 (1H, s), 4.87 (2H, s), 6.82 (1H, s), 8.24 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 375; HPLC tR = 1.86 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfanylmethyl)pyrimidine



DIPEA (2.94 mL, 16.97 mmol) was added to 2-mercaptothiazole (1.458 g, 12.44 mmol), in acetonitrile (40 mL) at RT under an atmosphere of nitrogen. The resulting solution was stirred

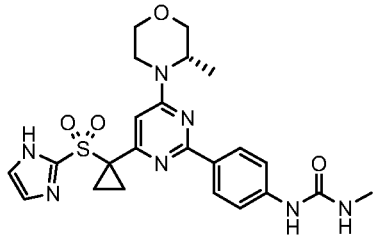
at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4 g, 11.31 mmol) was added and the mixture stirred for 1 hour. The reaction mixture was diluted with ethyl acetate (300 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 80% ethyl acetate in isohexane, to give the desired material as a colourless gum (3.77 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (5H, d), 3.15 (1H, td), 3.41 (2H, td), 3.56 (1H, dd), 3.70 (1H, d), 3.91 (2H, m), 4.25 (1H, s), 4.36 (2H, s), 6.84 (1H, s), 7.70 (1H, d), 7.76 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 343; HPLC tR = 2.07 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 40: 1-[4-[4-[1-(1*H*-Imidazol-2-ylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea



Anisole (0.159 mL, 1.46 mmol) was added to 1-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea (180 mg, 0.29 mmol) in TFA (8 mL) at RT under an atmosphere of nitrogen. The resulting solution was stirred at 60°C for 90 minutes then the solvent removed under reduced pressure and the residue chromatographed on an SCX column, eluting with 7M ammonia in methanol. The material was further purified by flash silica chromatography, elution gradient 10 to 90% ethyl acetate in isohexane, to give the desired material as a cream solid (122 mg).

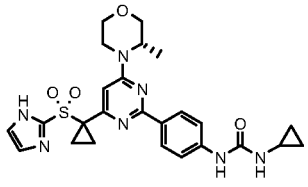
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.68 - 1.74 (2H, m), 1.91 - 1.98 (2H, m), 2.66 (3H, s), 3.09 - 3.19 (1H, m), 3.44 - 3.50 (1H, m), 3.61 (1H, d), 3.76

(1H, d), 3.97 (1H, d), 4.13 (1H, s), 4.40 (1H, s), 6.05 (1H, s), 6.64 (1H, s), 7.35 (2H, s), 7.43 (2H, d), 8.00 (2H, d), 8.71 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 493; HPLC tR = 1.33 min.

mTOR Kinase Assay (Echo): 0.00436μM

The following compound was made in an analogous fashion from 3-cyclopropyl-1-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea.

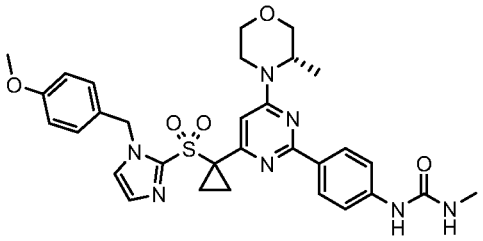
Example	Structure	NAME	LCMS MH+	Retention time (min)
40a		3-cyclopropyl-1-[4-[4-[1-(1H-imidazol-2-ylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	524	1.56

Example 40a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.38 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 1.19 (3H, d), 1.67 - 1.75 (2H, m), 1.89 - 1.99 (2H, m), 2.51 - 2.57 (1H, m), 3.11 - 3.22 (1H, m), 3.39 - 3.52 (1H, m), 3.61 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.11 (1H, d), 4.39 (1H, s), 6.41 (1H, s), 6.65 (1H, s), 7.36 (2H, s), 7.44 (2H, d), 8.00 (2H, d), 8.50 (1H, s) 13.5(1H,s).

mTOR Kinase Assay (Echo): 0.00649μM

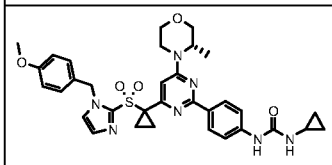
The preparation of 1-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylureais described below.

1-[4-[4-[1-[1-[(4-Methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea



Triethylamine (0.246 mL, 1.76 mmol) was added to phenyl *N*-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (240 mg, 0.35 mmol) and methylamine (0.705 mL, 1.41 mmol) in DMF (3 mL) at RT. The resulting solution was stirred at 40°C for 30 minutes then at RT overnight. The mixture was concentrated *in vacuo* and chromatographed on silica, elution gradient 100 % ethyl acetate, to give the desired material as a cream solid (190 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.68 - 1.72 (2H, m), 1.88 - 1.95 (2H, m), 2.67 (3H, d), 3.07 - 3.20 (1H, m), 3.36 - 3.51 (1H, m), 3.57 (1H, d), 3.68 - 3.79 (4H, m), 3.94 (1H, d), 4.06 (1H, s), 4.35 (1H, s), 5.21 (2H, s), 6.05 (1H, t), 6.55 (1H, s), 6.77 (2H, d), 7.05 (2H, d), 7.23 (1H, s), 7.41 - 7.48 (3H, m), 8.02 (2H, d), 8.72 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 618; HPLC tR = 2.17 min

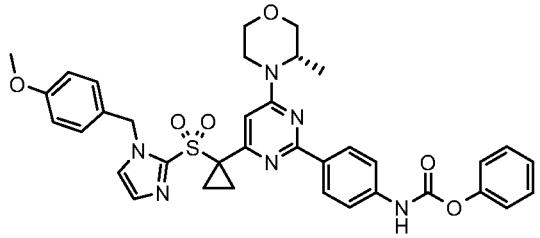
3-Cyclopropyl-1-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]ureawas made in an analogous fashion from phenyl *N*-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Structure	NAME	LCMS MH+	Retention time (min)
	3-cyclopropyl-1-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	644	2.32

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.38 - 0.45 (2H, m), 0.60 - 0.69 (2H, m), 1.14 (3H, d), 1.66 - 1.74 (2H, m), 1.88 - 1.94 (2H, m), 2.53 - 2.62 (1H, m), 3.09 - 3.18 (1H, m), 3.39 - 3.48 (1H, m), 3.57 (1H, d), 3.66 - 3.78 (4H, m), 3.95 (1H, d), 4.11 (1H, s), 4.35 (1H, s), 5.21 (2H, s), 6.43 (1H, s), 6.55 (1H, s), 6.77 (2H, d), 7.06 (2H, d), 7.23 (1H, s), 7.42 - 7.49 (3H, m), 8.02 (2H, d), 8.52 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

Phenyl N-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

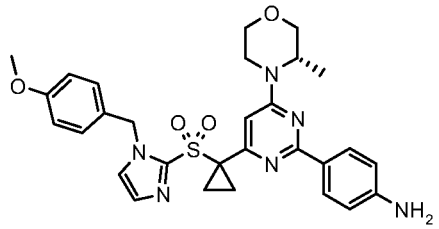


Phenyl chloroformate (0.202 mL, 1.61 mmol) was added to 4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (600 mg, 1.07 mmol) and sodium hydrogen carbonate (135 mg, 1.61 mmol) in dioxane (10 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 90 minutes. The reaction mixture was diluted with ethyl acetate (150 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid which was collected by filtration and dried under vacuum (570 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.67 - 1.74 (2H, m), 1.90 - 1.95 (2H, m), 3.03 - 3.21 (1H, m), 3.36 - 3.47 (1H, m), 3.53 - 3.62 (1H, m), 3.64 - 3.76 (4H, m), 3.95 (1H, d), 4.10 (1H, s), 4.37 (1H, s), 5.23 (2H, s), 6.60 (1H, s), 6.77 (2H, d), 7.06 (2H, d), 7.23 - 7.33 (4H, m), 7.42 - 7.50 (3H, m), 7.59 (2H, d), 8.11 (2H, d), 10.41 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 682; HPLC tR = 2.88 min

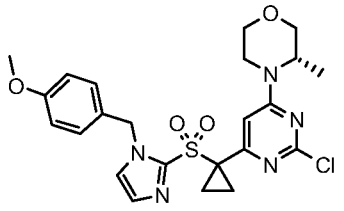
4-[4-[1-[1-[(4-Methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Bis(triphenylphosphine)palladium(II) chloride (42.5 mg, 0.06 mmol) was added to 2-chloro-4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (610 mg, 1.21 mmol), 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (530 mg, 2.42 mmol) and an aqueous solution of sodium carbonate (2 mL, 4.00 mmol) in a solvent mixture of DMF (2 mL), DME (4 mL), water (0.5 mL) and ethanol (0.5 mL) at RT. The atmosphere was replaced with nitrogen and the mixture stirred at 90°C for 5 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 100% ethyl acetate in isohexane, to give the desired material as a white solid (600 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (3H, d), 1.65 - 1.69 (2H, m), 1.88 - 1.92 (2H, m), 3.04 - 3.15 (1H, m), 3.41 (1H, td), 3.56 (1H, d), 3.67 - 3.75 (4H, m), 3.93 (1H, d), 4.06 (1H, s), 4.31 (1H, s), 5.16 (2H, s), 5.54 (2H, s), 6.44 (1H, s), 6.57 (2H, d), 6.79 (2H, d), 7.06 (2H, d), 7.22 (1H, s), 7.43 (1H, s), 7.87 (2H, d)

2-Chloro-4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



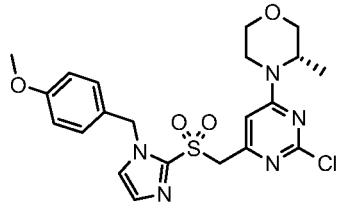
An aqueous solution of sodium hydroxide (10 mL, 186.4 mmol) was added to 2-chloro-4-[[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.1 g, 2.30 mmol), tetraethylammonium bromide (0.097 g, 0.46 mmol), and

1,2-dibromoethane (2.38 mL, 27.62 mmol) in DCM (20 mL) at RT under a nitrogen atmosphere. The reaction was stirred at RT for 4 hours. The reaction mixture was diluted with DCM (50 mL), the phases separated and the organic layer dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash silica chromatography, elution gradient 10 to 75% ethyl acetate in isohexane, to give the desired material as a white solid (0.77 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10 (4H, d), 1.64 (3H, m), 1.85 - 1.89 (2H, m), 3.03 - 3.15 (1H, m), 3.33 - 3.42 (1H, m), 3.50 (1H, d), 3.68 (1H, d), 3.74 (3H, s), 3.87 - 3.93 (2H, m), 4.06 (1H, s), 5.33 (2H, s), 6.57 (1H, s), 6.87 (2H, d), 7.17 (2H, d), 7.22 (1H, s), 7.59 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 504; HPLC tR = 2.35 min

2-Chloro-4-[[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylmethyl]-6-[(3I)-3-methylmorpholin-4-yl]pyrimidine

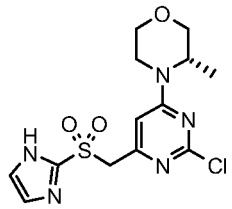


4-Methoxybenzyl chloride (0.470 mL, 3.46 mmol) was added to 2-chloro-4-(1*H*-imidazol-2-ylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.18 g, 3.30 mmol) and potassium carbonate (0.501 g, 3.63 mmol) in DMF (30 mL) at RT under a nitrogen atmosphere. The resulting mixture was stirred at 75°C for 1 hour then allowed to cool and diluted with ethyl acetate (100 mL). The mixture was washed with water (2 x 50 mL), the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give the desired material as a colourless gum (1.27 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 3.10 - 3.19 (1H, m), 3.35 - 3.45 (1H, m), 3.54 (1H, d), 3.70 (1H, d), 3.74 (3H, s), 3.87 - 3.96 (2H, m), 4.14 (1H, s), 4.68 (2H, s), 5.36 (2H, s), 6.55 (1H, s), 6.88 (2H, d), 7.15 - 7.28 (3H, m), 7.57 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 478; HPLC tR = 2.26 min

2-Chloro-4-(1*H*-imidazol-2-ylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

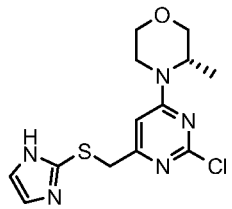


3-Chloroperoxybenzoic acid (2.62 g, 15.19 mmol) was added to 2-chloro-4-(1*H*-imidazol-2-ylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.25 g, 6.91 mmol) in DCM (100 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at RT for 2 hours. The reaction mixture was diluted with DCM (100 mL), and washed sequentially with an aqueous 10% solution of sodium metabisulphite (200 mL), and a saturated solution of sodium hydrogen carbonate (200 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid that was collected by filtration and dried under vacuum (1.8 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 3.06 - 3.21 (1H, m), 3.35 - 3.46 (1H, m), 3.55 (1H, d), 3.71 (1H, d), 3.83 - 3.97 (2H, m), 4.16 (1H, s), 4.66 (2H, s), 6.52 (1H, s), 7.35 (2H, s), 13.65(1H,s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 358; HPLC tR = 0.87 min

2-Chloro-4-(1*H*-imidazol-2-ylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



DIPEA (2.94 mL, 16.97 mmol) was added to 1*H*-imidazole-2-thiol (1.246 g, 12.44 mmol), in acetonitrile (50 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4 g, 11.31 mmol) was added and the mixture stirred for 1 hour. The reaction mixture was diluted with ethyl acetate (300 mL), and washed with water (150 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was

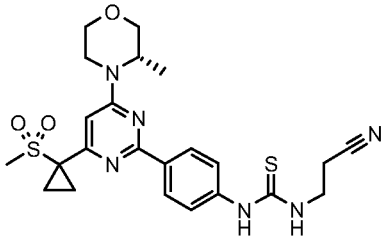
purified by flash silica chromatography, elution gradient 0 to 4% methanol in ethyl acetate, to give the desired material as a white solid (2.80 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 3.11 (1H, dd), 3.34 - 3.45 (1H, m), 3.54 (1H, dd), 3.69 (1H, d), 3.87 - 3.95 (2H, m), 4.06 (2H, s), 4.17 (1H, s), 6.52 (1H, s), 6.96 (1H, s), 7.17 (1H, s), 12.35 (1H,s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 326; HPLC tR = 1.41 min

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 41: 3-(2-Cyanoethyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea



A solution of 1,1'-thiocarbonyldiimidazole (50 mg, 0.28 mmol) in DCM (1 mL) was added to a suspension of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (75 mg, 0.19 mmol) in DCM (2 mL) and THF (1 mL). The reaction mixture was stirred at RT for 1 hour before addition of 3-aminopropionitrile (91 mg, 1.30 mmol) and triethylamine (0.026 mL, 0.19 mmol). Stirring was continued at RT overnight. The reaction was incomplete and significant insoluble material was observed so DMF (1 mL) was added and stirring continued for a further 1 hour. The reaction was still incomplete, so the reaction mixture was transferred to a microwave tube, sealed, heated to 100°C in the microwave reactor and held for 10 minutes. The reaction was still incomplete, so further 3-aminopropionitrile (91 mg, 1.30 mmol) was added and the reaction mixture stirred at RT for 2-3 hours. The reaction mixture was evaporated and residue purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (29 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.67 - 1.69 (2H, m), 2.87 (2H, t), 3.19 - 3.26 (1H, m), 3.27 (3H, s), 3.49 (1H, td), 3.64 (1H,

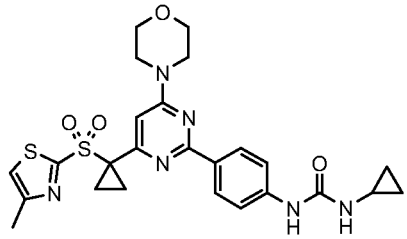
dd), 3.74 - 3.78 (3H, m), 3.98 (1H, dd), 4.18 - 4.25 (1H, m), 4.56 - 4.63 (1H, m), 6.82 (1H, s), 7.57 (2H, d), 8.16 (1H, s), 8.26 - 8.30 (2H, m), 9.98 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 501; HPLC tR = 1.99 min

mTOR Kinase Assay (Echo): 0.0308μM

The preparation of 4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline was described previously.

Example 42: 3-Cyclopropyl-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea



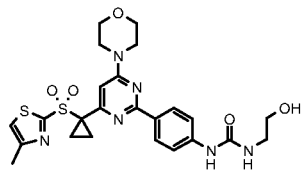
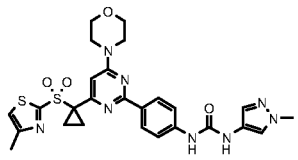
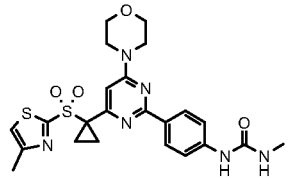
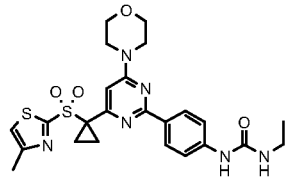
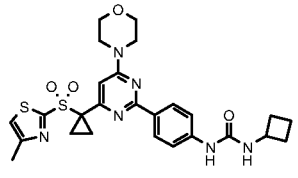
Triethylamine (0.119 mL, 0.85mmol) was added to a solution of phenyl *N*-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) and cyclopropylamine (0.059 mL, 0.85 mmol) in NMP (2 mL) and the resulting solution stirred at ambient temperature for 18 hours. The crude product was purified by preparative HPLC to give the desired material as a white solid (80 mg).

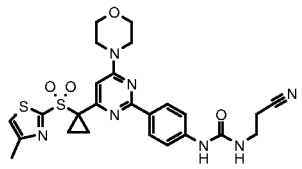
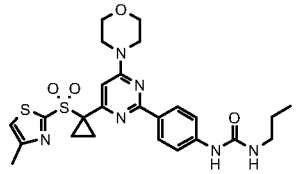
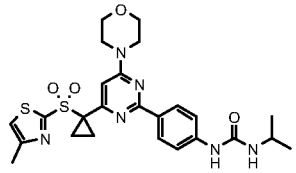
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.49 (3H, s), 2.54 - 2.58 (1H, m), 3.70 (8H, s), 6.40 (1H, s), 6.82 (1H, s), 7.42 (2H, d), 7.84 (1H, s), 7.87 (2H, d), 8.52 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 541; HPLC tR = 2.15min.

mTOR Kinase Assay (Echo): 0.000705μM

The compounds below were prepared in an analogous fashion using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
42a		3-(2-hydroxyethyl)-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	545	1.79
42b		3-(1-methylpyrazol-4-yl)-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	581	2.01
42c		3-methyl-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	515	1.96
42d		1-ethyl-3-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	529	2.14
42e		3-cyclobutyl-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	555	1.95

Example	Structure	NAME	LCMS MH+	Retention time (min)
42f		3-(2-cyanoethyl)-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	554	1.63
42g		3-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-propylurea	543	2.13
42h		1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-propan-2-ylurea	543	2.13

Example 42a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.48 (3H, s), 3.15 - 3.20 (2H, m), 3.44 - 3.48 (2H, m), 3.70 (8H, s), 4.72 (1H, t), 6.23 (1H, t), 6.82 (1H, s), 7.40 (2H, d), 7.84 (1H, s), 7.87 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00261μM

Example 42b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.75 - 1.79 (2H, m), 1.94 - 1.98 (2H, m), 2.50 (3H, s), 3.70 (8H, s), 3.79 (3H, s), 6.83 (1H, s), 7.38 (1H, s), 7.46 (2H, d), 7.77 (1H, s), 7.85 (1H, s), 7.90 (2H, d), 8.36 (1H, s), 8.82 (1H, s).

Example 42c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.49 (3H, s), 2.66 (3H, d), 3.70 (8H, s), 6.04 (1H, q), 6.82 (1H, s), 7.41 (2H, d), 7.84 (1H, s), 7.86 (2H, d), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.0036μM

Example 42d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.49 (3H, s), 3.09 - 3.16 (2H, m), 3.70 (8H, s), 6.14 (1H, t), 6.82 (1H, s), 7.41 (2H, d), 7.84 (1H, s), 7.86 (2H, d), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.000425μM

Example 42e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.57 - 1.66 (2H, m), 1.75 - 1.78 (2H, m), 1.81 - 1.91 (2H, m), 1.94 - 1.97 (2H, m), 2.18 - 2.25 (2H, m), 2.48 (3H, s), 3.70 (8H, s), 4.09 - 4.19 (1H, m), 6.43 (1H, d), 6.82 (1H, s), 7.39 (2H, d), 7.84 (1H, s), 7.86 (2H, d), 8.54 (1H, s).

mTOR Kinase Assay (Echo): 0.00257μM

Example 42f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.49 (3H, s), 2.70 (2H, t), 3.34 - 3.39 (2H, m), 3.70 (8H, s), 6.52 (1H, t), 6.83 (1H, s), 7.43 (2H, d), 7.84 (1H, s), 7.88 (2H, d), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.00264μM

Example 42g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.41 - 1.50 (2H, m), 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.49 (3H, s), 3.04 - 3.09 (2H, m), 3.70 (8H, s), 6.18 (1H, t), 6.82 (1H, s), 7.40 (2H, d), 7.84 (1H, s), 7.86 (2H, d), 8.63 (1H, s).

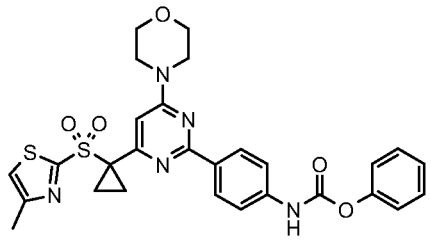
mTOR Kinase Assay (Echo): 0.00401μM

Example 42h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.48 (3H, s), 3.70 (8H, s), 3.73 - 3.81 (1H, m), 6.03 (1H, d), 6.82 (1H, s), 7.39 (2H, d), 7.84 (1H, s), 7.86 (2H, d), 8.51 (1H, s).

mTOR Kinase Assay (Echo): 0.00412μM

The preparation of phenyl *N*-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate



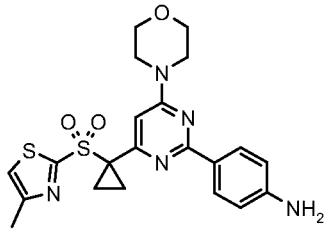
Phenyl chloroformate (0.664 mL, 5.29 mmol) was added to 4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline (2.2 g, 4.81 mmol) and sodium hydrogen carbonate (0.606 g, 7.21 mmol) in dioxane (100 mL) at 10°C under a

nitrogen atmosphere. The resulting mixture was stirred at 10°C for 2 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product as a gum (2.83 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.76 - 1.80 (2H, m), 1.94 - 1.97 (2H, m), 2.48 (3H, s), 3.70 (8H, s), 6.87 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.55 (2H, d), 7.85 (1H, s), 7.96 (2H, d), 10.45 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 578; HPLC tR = 2.88 min.

4-[4-[1-[(4-Methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline

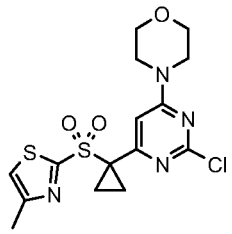


Bis(triphenylphosphine)palladium (II) chloride (0.256 g, 0.37 mmol) was added to 2-chloro-4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidine (2.93 g, 7.31 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.082 g, 9.50 mmol) and 2M aqueous sodium carbonate (13.16 mL, 26.31 mmol) in a solvent mixture of DMF (15 mL), water (37.5 mL), ethanol (15 mL) and DME (15 mL) at RT under an atmosphere of nitrogen. The resulting mixture was stirred at 80°C for 16 hours. The cooled reaction mixture was diluted with ethyl acetate (100 mL) and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in DCM, to give the desired material as a cream solid (2.2 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.72 - 1.75 (2H, m), 1.91 - 1.94 (2H, m), 2.49 (3H, s), 3.62 - 3.71 (8H, m), 5.57 (2H, s), 6.50 (2H, d), 6.71 (1H, s), 7.68 (2H, d), 7.84 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 458; HPLC tR = 2.21min.

2-Chloro-4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidine

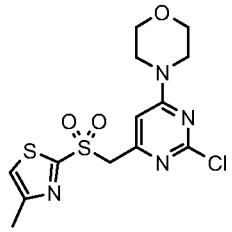


1,2-Dibromoethane (0.230 mL, 2.67 mmol) was added to 2-chloro-4-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]-6-morpholin-4-ylpyrimidine (500 mg, 1.33 mmol), 40% sodium hydroxide solution (1.3 mL,13 mmol) and tetrabutylammonium bromide (86 mg, 0.27 mmol) in toluene (10 mL) at RT. The resulting solution was stirred at 60°C for 3 hours. The cooled reaction mixture was evaporated to dryness and redissolved in ethyl acetate (50 mL), and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as a pale brown gum (528 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.76 - 1.79 (2H, m), 2.09 - 2.12 (2H, m), 2.52 (3H, s), 3.65 - 3.71 (4H, m), 3.77 - 3.79 (4H, m), 7.29 (1H, s), 7.30 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 401; HPLC tR = 2.04 min.

2-Chloro-4-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]-6-morpholin-4-ylpyrimidine



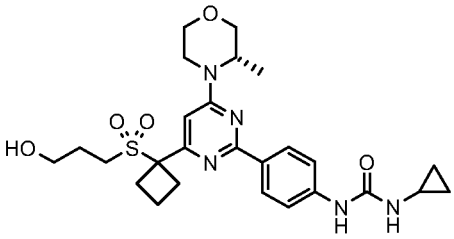
A solution of morpholine (0.994 g, 11.41 mmol) in DCM (25 mL) was added dropwise to a stirred solution of 2,4-dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (3.7 g, 11.41 mmol) and triethylamine (1.155 g, 11.41 mmol) in DCM (50 mL). The resulting solution was stirred at RT for 18 hours. The reaction mixture was washed three times with water and the organic layer dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a yellow solid (2.84 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 2.57 (3H, s), 3.58 - 3.69 (8H, m), 4.56 (2H, s), 6.58 (1H, s), 7.30 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 375; HPLC tR = 2.14 min.

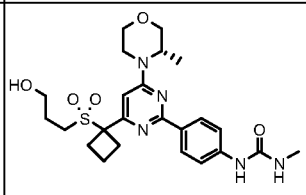
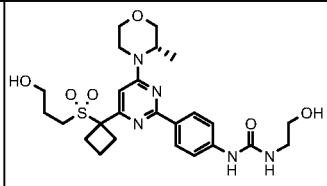
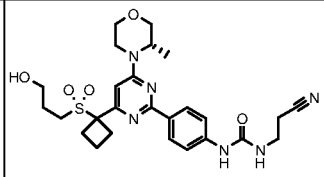
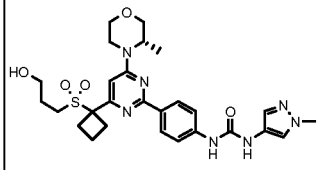
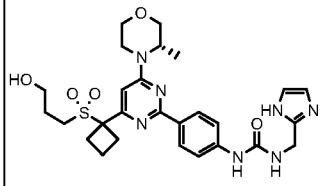
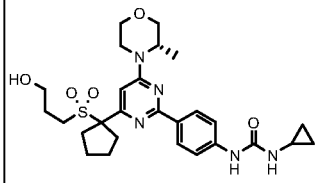
The preparation of 2,4-dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine was described previously.

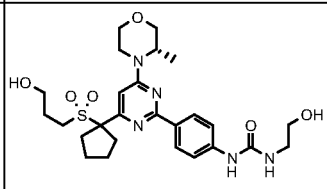
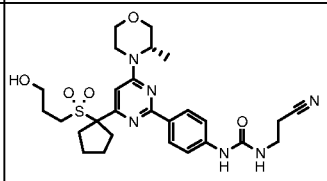
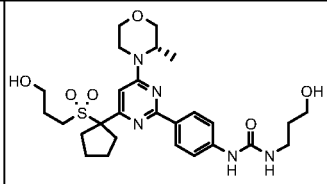
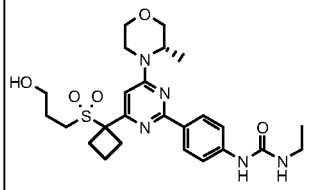
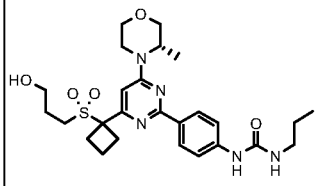
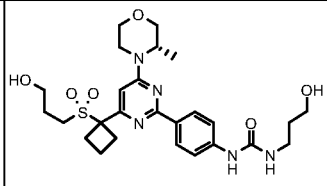
Example 43: 3-Cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

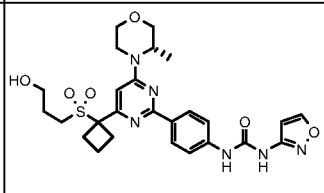
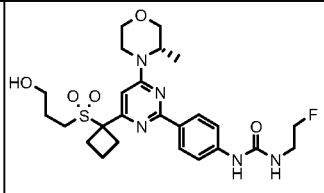
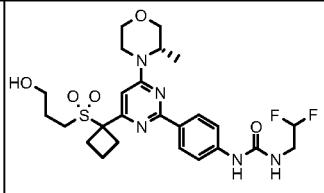
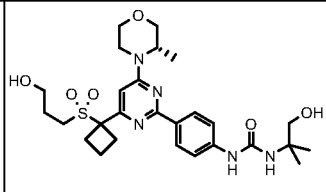
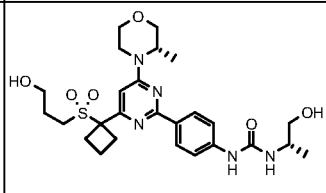
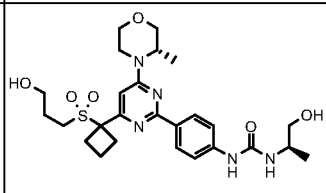


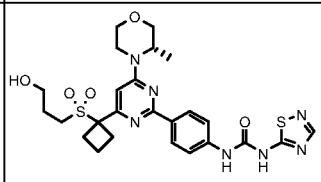
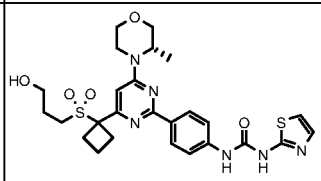
Cyclopropylamine (0.122 mL, 1.76 mmol) was added in one portion to a stirred solution of phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.2 g, 0.35 mmol) and triethylamine (0.148 mL, 1.06 mmol) in DMA (35.3 mL) at RT. The resulting solution was stirred at 50°C for 24 hours. The reaction mixture was then concentrated, and the crude product was purified by flash silica chromatography, elution gradient 0 to 5% methanol in DCM, to give a clear oil which was then triturated with diethyl ether to give the desired material as a white solid (0.126 g).
NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.60 - 0.67 (2H, m), 0.74 - 0.83 (2H, m), 1.33 (3H, d), 1.94 - 2.01 (3H, m), 2.16 - 2.25 (2H, m), 2.57 - 2.63 (1H, m), 2.80 - 2.88 (2H, m), 2.98 - 3.01 (2H, m), 3.09 - 3.16 (2H, m), 3.28 - 3.35 (1H, m), 3.56 - 3.62 (3H, m), 3.71 - 3.75 (1H, m), 3.81 (1H, d), 4.01 - 4.05 (1H, m), 4.16 (1H, d), 4.46 (1H, d), 5.30 (1H, s), 6.55 (1H, s), 7.31 (1H, s), 7.48 (2H, d), 8.32 (2H, d).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 530; HPLC tR = 2.09 min.
mTOR Kinase Assay (Echo): 0.00539μM

The compounds below were prepared in an analogous fashion from either phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
43a		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	504	1.93
43b		3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	534	1.83
43c		3-(2-cyanoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	543	2.00
43d		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	570	1.98
43e		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	570	1.93
43f		3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	544	2.21

Example	Structure	NAME	LCMS MH+	Retention time (min)
43g		3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.91
43h		3-(2-cyanoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	557	2.12
43i		3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	562	1.94
43j*		1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	518	1.89
43k*		3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea	532	2.04
43l*		3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.68

Example	Structure	NAME	LCMS MH+	Retention time (min)
43m*		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	557	2.04
43n*		3-(2-fluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	536	1.88
43o*		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	554	2.00
43p*		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	562	1.88
43q*		3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.72
43r*		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.71

Example	Structure	NAME	LCMS MH+	Retention time (min)
43s*		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	574	1.28
43t*		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea	573	2.05

* The reactions were stirred in NMP at 70°C for 2.5 hours

Example 43a: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.30 (3H, d), 1.94 - 1.99 (3H, m), 2.14 - 2.23 (1H, m), 2.73 (3H, d), 2.79 - 2.90 (3H, m), 2.96 - 3.04 (2H, m), 3.06 - 3.13 (2H, m), 3.24 - 3.32 (1H, m), 3.54 - 3.59 (3H, m), 3.68 - 3.72 (1H, m), 3.78 (1H, d), 3.98 - 4.02 (1H, m), 4.10 - 4.15 (1H, m), 4.43 (1H, s), 5.49 (1H, q), 6.52 (1H, s), 7.41 (2H, d), 7.62 (1H, s), 8.29 (2H, d).

mTOR Kinase Assay (Echo): 0.00479μM

Example 43b: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.28 (3H, d), 1.90 - 2.00 (3H, m), 2.08 - 2.22 (2H, m), 2.79 - 2.88 (2H, m), 2.94 - 3.09 (4H, m), 3.24 - 3.33 (3H, m), 3.45 - 3.56 (6H, m), 3.68 (1H, d), 3.76 (1H, d), 3.98 (1H, d), 4.11 (1H, d), 4.42 (1H, s), 5.84 (1H, t), 6.50 (1H, s), 7.39 (2H, d), 7.89 (1H, s), 8.27 (2H, d).

mTOR Kinase Assay (Echo): 0.00751μM

Example 43c: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.93 - 2.04 (4H, m), 2.16 - 2.25 (1H, m), 2.55 - 2.60 (2H, m), 2.79 - 2.88 (2H, m), 2.97 - 3.06 (2H, m), 3.09 - 3.15 (2H, m), 3.26 - 3.33 (1H, m), 3.43 - 3.49 (2H, m), 3.53 - 3.63 (3H, m), 3.69 - 3.73 (1H, m), 3.79 (1H, d), 3.99 - 4.03 (1H, m), 4.15 (1H, d), 4.44 (1H, s), 5.87 (1H, t), 6.55 (1H, s), 7.42 (2H, d), 7.54 (1H, s), 8.31 (2H, d).

mTOR Kinase Assay (Echo): 0.0288μM

Example 43d: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.30 (3H, d), 1.95 - 2.01 (3H, m), 2.14 - 2.26 (1H, m), 2.78 - 2.91 (2H, m), 3.03 - 3.07 (2H, m), 3.08 - 3.15 (2H, m), 3.25 - 3.32 (1H, m), 3.39 (1H, s), 3.55 - 3.59 (3H, m), 3.67 (3H, s), 3.68 - 3.71 (1H, m), 3.78 (1H, d), 3.98 - 4.02 (1H, m), 4.11 - 4.14 (1H, m), 4.42 (1H, s), 6.53 (1H, s), 7.18 (1H, s), 7.39 (2H, d), 7.44 (1H, s), 7.55 (1H, s), 7.84 (1H, s), 8.29 (2H, d).

mTOR Kinase Assay (Echo): 0.011μM

Example 43e: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.29 (3H, d), 1.92 - 1.99 (3H, m), 2.13 - 2.20 (1H, m), 2.75 - 2.84 (2H, m), 2.96 - 3.01 (2H, m), 3.05 - 3.12 (2H, m), 3.23 - 3.30 (1H, m), 3.48 - 3.55 (4H, m), 3.69 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.11 (1H, d), 4.36 - 4.41 (3H, m), 6.51 (1H, s), 6.91 (2H, s), 7.00 (1H, t), 7.34 (2H, d), 8.23 - 8.25 (2H, m), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.188μM

Example 43f: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.53 - 0.56 (2H, m), 0.73 - 0.76 (2H, m), 1.32 (3H, d), 1.63 - 1.66 (2H, m), 1.91 - 1.97 (4H, m), 2.57 - 2.65 (3H, m), 2.73 - 2.80 (3H, m), 3.05 - 3.11 (2H, m), 3.26 - 3.33 (1H, m), 3.55 - 3.62 (3H, m), 3.71 - 3.75 (1H, m), 3.81 (1H, d), 4.00 - 4.04 (1H, m), 4.17 (1H, d), 4.46 (1H, s), 5.81 (1H, s), 6.66 (1H, s), 7.49 (2H, d), 7.82 (1H, s), 8.31 (2H, d).

mTOR Kinase Assay (Echo): 0.0392μM

Example 43g: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.28 (3H, d), 1.58 - 1.64 (2H, m), 1.85 - 1.95 (4H, m), 2.53 - 2.63 (3H, m), 2.67 - 2.78 (3H, m), 3.12 - 3.16 (2H, m), 3.26 - 3.30 (3H, m), 3.52 - 3.58 (5H, m), 3.36 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.12 (1H, d), 4.41 (1H, s), 5.05 (1H, s), 5.90 (1H, t), 6.61 (1H, s), 7.41 (2H, d), 7.96 (1H, s), 8.29 (2H, d).

mTOR Kinase Assay (Echo): 0.029μM

Example 43h: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.64 - 1.67 (3H, m), 1.92 - 1.99 (5H, m), 2.47 - 2.64 (4H, m), 2.74 - 2.79 (2H, m), 3.13 - 3.17 (2H, m), 3.26 - 3.33 (1H, m), 3.43 - 3.48 (2H, m), 3.53 - 3.63 (3H, m), 3.69 - 3.73 (1H, m), 3.79 (1H, d), 3.99 - 4.03 (1H, m), 4.15 (1H, d), 4.44 (1H, s), 5.89 (1H, t), 6.66 (1H, s), 7.42 (2H, d), 7.58 (1H, s), 8.32 (2H, d).

mTOR Kinase Assay (Echo): 0.133μM

Example 43i: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.29 (3H, d), 1.54 - 1.62 (4H, m), 1.89 - 1.99 (4H, m), 2.55 - 2.64 (2H, m), 2.70 - 2.80 (2H, d), 3.12 - 3.19 (2H, m), 3.24 - 3.29 (4H, m), 3.52 - 3.59 (5H, m), 3.68 - 3.83 (3H, m), 3.98 (1H, d), 4.11 - 4.14 (1H, m), 4.42 (1H, s), 5.75 (1H, t), 6.62 (1H, s), 7.42 (2H, d), 7.79 (1H, s), 8.29 (2H, d).

mTOR Kinase Assay (Echo): 0.102μM

Example 43j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.23 (3H, d), 1.72 - 1.81 (2H, m), 1.88 - 1.96 (1H, m), 1.99 - 2.10 (1H, m), 2.75 - 2.86 (2H, m), 2.90 - 2.96 (2H, m), 2.98 - 3.04 (2H, m), 3.10 - 3.16 (2H, m), 3.19 - 3.25 (1H, m), 3.35 - 3.42 (2H, m), 3.46 - 3.55 (1H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.50 - 4.62 (2H, m), 6.17 (1H, s), 6.72 (1H, s), 7.49 (2H, d), 8.21 (2H, d), 8.66 (1H, s)

Example 43k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.24 (3H, d), 1.39 - 1.50 (2H, m), 1.73 - 1.81 (2H, m), 1.86 - 1.96 (1H, m), 2.00 - 2.09 (1H, m), 2.77 - 2.87 (2H, m), 2.90 - 2.97 (2H, m), 2.97 - 3.08 (4H, m), 3.19 - 3.25 (1H, m), 3.35 - 3.41 (2H, m), 3.46 - 3.55 (1H, m), 3.65 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.24 (1H, d), 4.53 - 4.60 (2H, m), 6.20 (1H, t), 6.71 (1H, s), 7.49 (2H, d), 8.22 (2H, d), 8.65 (1H, s)

Example 43l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.21 (2H, d), 1.23 (3H, d), 1.55 - 1.64 (2H, m), 1.74 - 1.80 (2H, m), 1.88 - 1.98 (1H, m), 2.01 - 2.10 (1H, m), 2.77 - 2.87 (2H, m), 2.90 - 2.97 (2H, m), 2.98 - 3.04 (2H, m), 3.13 - 3.24 (3H, m), 3.34 - 3.42 (2H, m), 3.45 - 3.54 (3H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.47 (1H, t), 4.53 - 4.59 (2H, m), 6.20 (1H, t), 6.71 (1H, s), 7.49 (2H, d), 8.71 (1H, s)

Example 43m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.74 - 1.81 (2H, m), 1.88 - 1.97 (1H, m), 2.01 - 2.11 (1H, m), 2.78 - 2.87 (2H, m), 2.90 - 2.99 (2H, m), 3.00 - 3.06 (2H, m), 3.19 - 3.26 (1H, m), 3.36 - 3.42 (2H, m), 3.47 - 3.56 (1H, m), 3.66 (1H, d), 3.77 (1H, d), 3.99 (1H, d), 4.26 (1H, d), 4.53 - 4.61 (2H, m), 6.75 (1H, s), 6.87 (1H, s), 7.57 (2H, d), 8.30 (2H, d), 8.76 (1H, s), 9.08 (1H, s), 9.62 (1H, s)

Example 43n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.73 - 1.81 (2H, m), 1.86 - 1.96 (1H, m), 2.01 - 2.10 (1H, m), 2.78 - 2.86 (2H, m), 2.90 - 2.98 (2H, m), 2.97 - 3.05 (2H, m), 3.13 - 3.26 (1H, m), 3.34 - 3.41 (2H, m), 3.44 - 3.55 (3H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.42 (1H, t), 4.51 - 4.59 (2H, m), 6.43 (1H, t), 6.72 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.81 (1H, s)

Example 43o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.72 - 1.81 (2H, m), 1.88 - 1.96 (1H, m), 2.02 - 2.10 (1H, m), 2.78 - 2.87 (2H, m), 2.91 - 2.98 (2H, m), 2.98 - 3.05 (2H, m), 3.17 - 3.26 (1H, m), 3.35 - 3.43 (2H, m), 3.47 - 3.60 (3H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.53 - 4.60 (2H, m), 5.91 - 6.27 (1H, m), 6.54 (1H, t), 6.73 (1H, s), 7.51 (2H, d), 8.24 (2H, d), 8.93 (1H, s)

Example 43p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.71 - 1.81 (2H, m), 1.86 - 1.96 (1H, m), 2.02 - 2.11 (1H, m), 2.75 - 2.88 (2H, m), 2.91 - 2.98 (2H, m), 2.99 - 3.05 (2H, m), 3.17 - 3.26 (1H, m), 3.27 - 3.31 (2H, m), 3.35 - 3.42 (2H, m), 3.47 - 3.54 (1H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.51 - 4.60 (2H, m), 4.95 (1H, t), 6.00 (1H, s), 6.71 (1H, s), 7.45 (2H, d), 8.20 (2H, d), 8.73 (1H, s)

Example 43q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.23 (3H, d), 1.72 - 1.82 (2H, m), 1.89 - 1.95 (1H, m), 2.02 - 2.09 (1H, m), 2.75 - 2.85 (2H, m), 2.90 - 2.97 (2H, m), 2.97 - 3.06 (2H, m), 3.17 - 3.25 (1H, m), 3.33 - 3.41 (2H, m), 3.48 - 3.56 (1H, m), 3.63 - 3.79 (4H, m), 3.98 (1H, d), 4.24 (1H, d), 4.51 - 4.59 (2H, m), 4.78 (1H, t), 6.10 (1H, t), 6.72 (1H, s), 7.47 (2H, d), 8.22 (2H, d), 8.71 (1H, s)

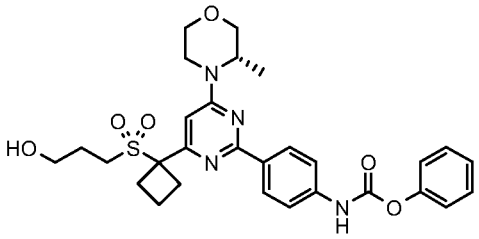
Example 43r: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.29 (3H, d), 1.78 - 1.88 (2H, m), 1.94 - 2.03 (1H, m), 2.07 - 2.16 (1H, m), 2.81 - 2.93 (2H, m), 2.96 - 3.03 (2H, m), 3.03 - 3.10 (2H, m), 3.23 - 3.32 (1H, m), 3.38 - 3.48 (3H, m), 3.53 - 3.61 (1H, m), 3.68 - 3.84 (4H, m), 4.03 (1H, d), 4.30 (1H, d), 4.58 - 4.65 (2H, m), 4.83 (1H, t), 6.15 (1H, t), 6.77 (1H, s), 7.53 (2H, d), 8.27 (2H, d), 8.77 (1H, s)

Example 43s: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.74 - 1.82 (2H, m), 1.89 - 1.98 (1H, m), 2.03 - 2.10 (1H, m), 2.77 - 2.90 (2H, m), 2.92 - 3.00 (2H, m), 3.02 - 3.07 (2H, m), 3.20 - 3.26 (1H, m), 3.36 - 3.44 (2H, m), 3.46 - 3.56 (1H, m), 3.66 (1H, d), 3.78 (1H, d), 3.99 (1H, d), 4.27 (1H, d), 4.51 - 4.63 (2H, m), 6.77 (1H, s), 7.63 (2H, d), 8.28 - 8.39 (3H, m), 9.46 (1H, s)

Example 43t: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.74 - 1.83 (2H, m), 1.88 - 1.96 (1H, m), 2.00 - 2.09 (1H, m), 2.77 - 2.88 (2H, m), 2.91 - 2.98 (2H, m), 3.00 - 3.07 (2H, m), 3.20 - 3.25 (1H, m), 3.37 - 3.43 (2H, m), 3.46 - 3.56 (1H, m), 3.66 (1H, d), 3.78 (1H, d), 3.99 (1H, d), 4.26 (1H, d), 4.53 - 4.62 (2H, m), 6.76 (1H, s), 7.14 (1H, s), 7.40 (1H, s), 7.59 (2H, d), 8.31 (2H, d), 9.20 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

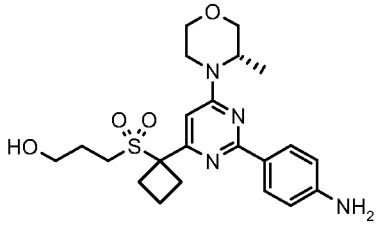
Phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.632 mL, 5.04 mmol) was added dropwise to 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclobutyl]sulfonylpropan-1-ol (1.5 g, 3.36 mmol) and sodium hydrogen carbonate (0.423 g, 5.04 mmol) in dioxane (33.6 mL), cooled to 10ºC under a nitrogen atmosphere. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (300 mL), and washed with water (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product as a yellow gum. This material was used directly in the next step without further purification.

LCMS Spectrum: m/z (ESI+) (M+H)+ = 565; HPLC tR = 2.71 min.

3-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclobutyl]sulfonylpropan-1-ol



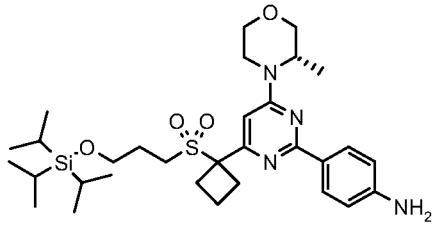
A solution of tetrabutylammonium fluoride (18.25 mL, 18.25 mmol) in THF was added to a stirred solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclobutyl]pyrimidin-2-yl]aniline (2.2 g, 3.65 mmol) in THF (24.33 mL) at RT. The resulting solution was stirred at RT for 2 hours. The reaction mixture was concentrated and diluted with ethyl acetate (150 mL), and washed with water (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% ethyl

acetate in isohexane, to give the desired material as a pale yellow oil which solidified on standing (1.50 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.57 (1H, t), 1.94 - 2.04 (3H, m), 2.18 - 2.25 (1H, m), 2.82 - 2.88 (2H, m), 2.98 (2H, t), 3.09 - 3.16 (2H, m), 3.28 - 3.35 (1H, m), 3.63 (3H, q), 3.73 - 3.76 (1H, m), 3.82 (1H, d), 3.90 (2H, s), 4.01 - 4.05 (1H, m), 4.16 (1H, d), 4.47 (1H, d), 6.51 (1H, s), 6.70 - 6.72 (2H, m), 8.22 - 8.24 (2H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 447; HPLC tR = 2.09 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclobutyl]pyrimidin-2-yl]aniline

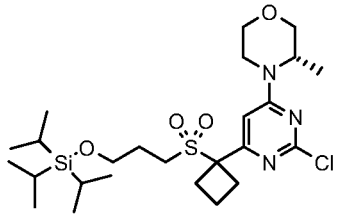


Dichlorobis(triphenylphosphine)palladium(II) (0.132 g, 0.19 mmol) was added in one portion to a carefully degassed solution of 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclobutyl]sulfonylpropoxy-tri(propan-2-yl)silane (2.05 g, 3.75 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.233 g, 5.63 mmol) and 2M aqueous sodium carbonate solution (6.57 mL, 13.14 mmol) in a solvent mixture of DMF (6.82 mL), water (17.06 mL), ethanol (6.82 mL) and DME (6.82 mL). The resulting mixture was stirred at 80°C for 4 hours. The cooled reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in isohexane, to give the desired material as a pale yellow foam which solidified under vacuum (2.2 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.89 - 0.98 (21H, m), 1.32 (3H, s), 1.92 - 1.99 (3H, m), 2.15 - 2.25 (1H, m), 2.84 - 2.87 (2H, m), 2.91 - 2.95 (2H, m), 3.07 - 3.13 (2H, m), 3.26 - 3.34 (1H, m), 3.57 - 3.62 (1H, m), 3.65 (2H, t), 3.74 (1H, dd), 3.81 (1H, d), 3.88 (2H, s), 4.03 (1H, dd), 4.15 (1H, d), 4.47 (1H, s), 6.52 (1H, s), 6.68 - 6.70 (2H, m), 8.21 - 8.23 (2H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 603; HPLC tR = 3.82 min.

3-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclobutyl]sulfonylpropoxy-tri(propan-2-yl)silane



Aqueous sodium hydroxide solution (50% w/w, 48.7 mL) was added to 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane (5.6 g, 11.06 mmol), 1,3-dibromopropane (3.37 mL, 33.19 mmol) and tetrabutylammonium bromide (0.357 g, 1.11 mmol) in toluene (221 mL) at RT. The resulting suspension was stirred at 45°C for 1 hour. Water was added to the solution. The toluene was washed with water twice, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a colourless gum (2.05 g).

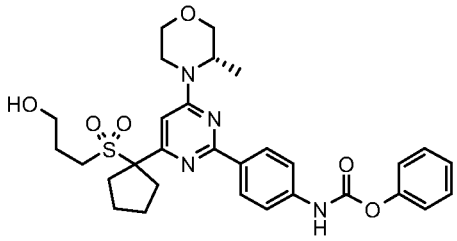
NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.97 - 1.08 (21H, m), 1.32 (3H, d), 1.94 - 2.01 (3H, m), 2.21 - 2.23 (1H, m), 2.70 - 2.76 (2H, m), 2.93 (2H, q), 3.03 - 3.08 (2H, m), 3.28 - 3.32 (1H, m), 3.51 - 3.57 (1H, m), 3.66 - 3.70 (1H, m), 3.76 (3H, t), 3.98 - 4.02 (2H, m), 4.32 (1H, s), 6.55 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 546; HPLC tR = 4.05 min.

The preparation of 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane was described earlier.

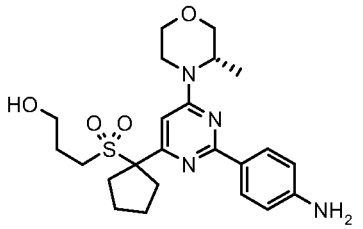
The preparation of phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (1.512 mL, 12.05 mmol) was added dropwise to 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopentyl]sulfonylpropan-1-ol (3.7 g, 8.03 mmol) and sodium hydrogen carbonate (1.012 g, 12.05 mmol) in dioxane (80 mL) cooled to 10°C under a nitrogen atmosphere. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (300 mL), and washed with water (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a yellow solid which was used without further purification (3.60 g). LCMS Spectrum: m/z (ESI+) (M+H)+ = 581; HPLC tR = 2.83 min.

3-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopentyl]sulfonylpropan-1-ol



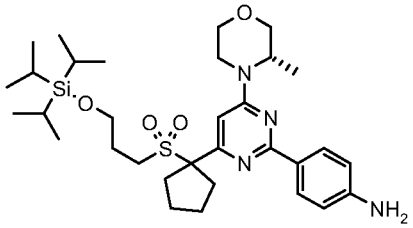
A solution of tetrabutylammonium fluoride (46.2 mL, 46.20 mmol) in THF was added to a stirred solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclopentyl]pyrimidin-2-yl]aniline (5.7 g, 9.24 mmol) in THF (61.6 mL) at RT. The resulting solution was stirred at RT for 2 hours. The reaction mixture was concentrated and diluted with ethyl acetate (250 mL), and washed with water (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% ethyl acetate

in isohexane, to give the desired material as a pale yellow oil which solidified on standing (3.70 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.59 (1H, t), 1.61 - 1.70 (2H, m), 1.92 - 1.98 (4H, m), 2.57 - 2.66 (2H, m), 2.74 - 2.83 (2H, m), 3.07 (2H, t), 3.27 - 3.34 (1H, m), 3.57 - 3.65 (3H, m), 3.73 - 3.77 (1H, m), 3.82 (1H, d), 3.90 (2H, s), 4.01 - 4.05 (1H, m), 4.11 - 4.18 (1H, m), 4.46 (1H, d), 6.63 (1H, s), 6.71 (2H, d), 8.23 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 461; HPLC tR = 2.18 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclopentyl]pyrimidin-2-yl]aniline

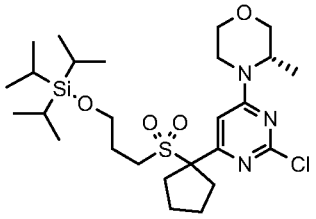


Dichlorobis(triphenylphosphine)palladium(II) (0.345 g, 0.49 mmol) was added in one portion to a carefully degassed solution of 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopentyl]sulfonylpropoxy-tri(propan-2-yl)silane (5.5 g, 9.82 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.23 g, 14.73 mmol) and 2M aqueous sodium carbonate solution (17.18 mL, 34.36 mmol) in a solvent mixture of DMF (17.85 mL), water (44.6 mL), ethanol (17.85 mL) and DME (17.85 mL). The resulting mixture was stirred at 80°C for 4 hours. The cooled reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in DCM, to give the desired material as a pale yellow foam which solidified under vacuum (5.70 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.90 - 0.98 (21H, m), 1.32 (4H, t), 1.63 - 1.66 (2H, m), 1.89 - 1.96 (4H, m), 2.59 - 2.64 (2H, m), 2.77 - 2.81 (2H, m), 2.98 - 3.02 (2H, m), 3.29 - 3.32 (1H, m), 3.57 - 3.63 (1H, m), 3.66 (2H, t), 3.72 - 3.76 (1H, m), 3.81 (1H, d), 3.88 (2H, s), 4.01 - 4.05 (1H, m), 4.15 (1H, d), 4.45 (1H, s), 6.66 (1H, s), 6.69 (2H, d), 8.22 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 617; HPLC tR = 3.91 min.

3-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopentyl]sulfonylpropoxy-tri(propan-2-yl)silane



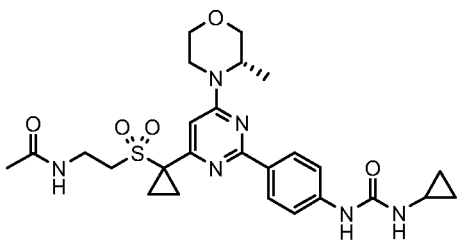
Aqueous sodium hydroxide solution (50% w/w aq, 48.7 mL) was added to 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane (5.6 g, 11.06 mmol), 1,4-dibromobutane (3.93 mL, 33.19 mmol) and tetrabutylammonium bromide (0.357 g, 1.11 mmol) in toluene (221 mL) at RT. The resulting suspension was stirred at 45°C for 1 hour and the toluene washed with water twice, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (5.57 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.98 - 1.08 (21H, m), 1.31 (3H, d), 1.60 - 1.65 (2H, m), 1.88 - 1.99 (4H, m), 2.56 - 2.61 (4H, m), 2.97 - 3.00 (2H, m), 3.28 - 3.32 (1H, m), 3.51 - 3.58 (1H, m), 3.67 - 3.71 (1H, m), 3.76 (3H, t), 3.98 - 4.02 (2H, m), 4.31, (1H, s), 6.71 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 560; HPLC tR = 3.86 min.

The preparation of 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane was described earlier.

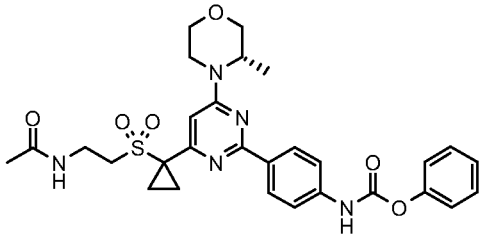
Example 44: *N*-[2-[1-[2-[4-(Cyclopropylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide



Cyclopropylamine (0.120 mL, 1.73 mmol) was added in one portion to a stirred solution of phenyl *N*-[4-[4-[1-(2-acetamidoethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.2 g, 0.35 mmol) in THF (34.5 mL) at RT. The resulting solution was stirred at 40°C for 24 hours. The reaction mixture was then concentrated, and the crude product was purified by flash silica chromatography, elution gradient 0 to 5% methanol in DCM, to give the desired material as a white solid (0.135 g).
NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.66 - 0.70 (2H, m), 0.84 - 0.89 (2H, m), 1.34 (3H, d), 1.49 - 1.58 (2H, m), 1.82 - 1.85 (2H, m), 1.93 (3H, s), 2.61 - 2.66 (1H, m), 3.29 - 3.36 (1H, m), 3.48 - 3.51 (2H, m), 3.56 - 3.63 (1H, m), 3.72 - 3.75 (1H, m), 3.79 - 3.84 (3H, m), 4.03 - 4.06 (1H, m), 4.15 (1H, d), 4.48 (1H, s), 5.05 (1H, s), 6.67 (1H, s), 6.74 (1H, d), 7.13 (1H, s), 7.51 (2H, d), 8.26 (2H, d).
LCMS Spectrum: m/z (ESI+) (M+H)+ = 543; HPLC tR = 1.86 min.
mTOR Kinase Assay (Echo): 0.0234μM

The preparation of phenyl *N*-[4-[4-[1-(2-acetamidoethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(2-acetamidoethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

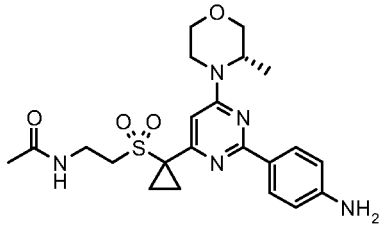


Phenyl chloroformate (0.328 mL, 2.61 mmol) was added dropwise to *N*-[2-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide (800 mg, 1.74 mmol) and sodium hydrogen carbonate (219 mg, 2.61 mmol) in dioxane (174 mL) cooled to 10°C under a nitrogen atmosphere. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (300 mL), and washed with water (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with a mixture

of diethyl ether and isohexane to give the desired material as a yellow solid (741 mg). This material was used directly without further purification.

LCMS Spectrum: m/z (ESI+) (M+H)+ = 580; HPLC tR = 2.44 min.

N-[2-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide

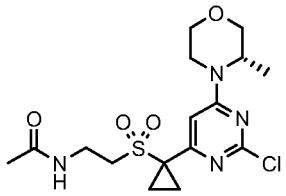


Dichlorobis(triphenylphosphine)palladium(II) (0.174 g, 0.25 mmol) was added in one portion to a carefully degassed solution of *N*-[2-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide (2 g, 4.96 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.414 g, 6.45 mmol) and 2M aqueous sodium carbonate solution (8.69 mL, 17.37 mmol) in a solvent mixture of DMF (9.03 mL), water (22.56 mL), ethanol (9.03 mL) and DME (9.03 mL). The resulting mixture was stirred at 80°C for 4 hours. The cooled reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in DCM, to give the desired material as a pale yellow foam which solidified under vacuum (1.805 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.49 - 1.51 (2H, m), 1.80 - 1.84 (2H, m), 1.93 (3H, s), 3.28 - 3.35 (1H, m), 3.47 - 3.50 (2H, m), 3.55 - 3.62 (1H, m), 3.71 - 3.75 (1H, m), 3.79 - 3.83 (3H, m), 3.92 (2H, s), 4.01 - 4.05 (1H, m), 4.10 - 4.17 (1H, m), 4.47 (1H, s), 6.61 (1H, s), 6.69 - 6.72 (2H, m), 6.81 (1H, s), 8.13 - 8.16 (2H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 460; HPLC tR = 1.79 min.

N-[2-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide

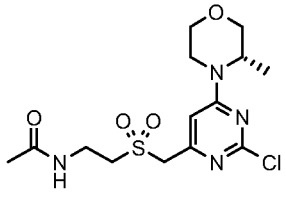


Aqueous sodium hydroxide solution (50% aq, 8.52 mL) was added to *N*-[2-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethyl]acetamide (3.21 g, 8.52 mmol), 1,2-dibromoethane (1.468 mL, 17.03 mmol) and tetrabutylammonium bromide (0.549 g, 1.70 mmol) in toluene (122 mL) at RT. The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was evaporated to dryness and redissolved in ethyl acetate (200 mL), and washed sequentially with water (200 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (2.04 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.44 - 1.47 (2H, m), 1.80 - 1.84 (2H, m), 2.02 (3H, s), 3.27 - 3.34 (1H, m), 3.35 - 3.38 (2H, m), 3.51 - 3.57 (1H, m), 3.66 - 3.70 (1H, m), 3.75 - 3.80 (3H, m), 3.99 - 4.03 (2H, m), 4.34 (1H, s), 6.73 (1H, s), 6.88 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 403; HPLC tR = 1.51 min.

N-[2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethyl]acetamide



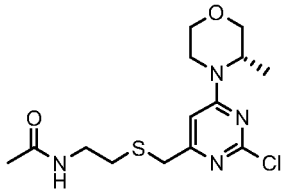
N-[2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide (3.24 g, 9.40 mmol) was dissolved in dioxane (28.2 mL) and 2N sulfuric acid (0.282 mL) was added. The solution was heated to 55°C. Sodium tungstate dihydrate (0.062 g, 0.19 mmol) dissolved in water (2.82 mL) was added to the solution and allowed to stir for 5 minutes. Hydrogen peroxide (5.42 mL, 56.37 mmol) was

then added dropwise over several minutes. The solution was heated at 55°C for 2.5 hours. The heat was removed and water (300 mL) was added. The resulting suspension was stirred for 30 minutes. The solids were filtered, rinsed with water and dried in a vacuum oven at 50°C overnight, to give the desired material as a white solid (3.30 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.82 (3H, s), 3.19 - 3.26 (1H, m), 3.36 - 3.43 (2H, m), 3.45 - 3.51 (3H, m), 3.58 - 3.62 (1H, m), 3.73 (1H, d), 3.92 - 3.96 (2H, m), 4.30 (1H, s), 4.49 (2H, s), 6.92 (1H, s), 8.11 (1H, t).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 377; HPLC tR = 1.37 min.

N-[2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide



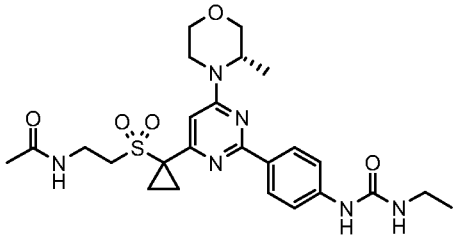
N-Acetylcysteamine (1.804 mL, 16.97 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4 g, 11.31 mmol) and DIPEA (4.93 mL, 28.28 mmol) in acetonitrile (226 mL) at RT. The resulting solution was stirred at RT for 3 hours. The solvent was removed *in vacuo*, and the crude material was then purified by flash silica chromatography, eluting with ethyl acetate, to give the desired material as a white solid (3.24 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.33 (3H, d), 2.01 (3H, s), 2.71 (2H, t), 3.25 - 3.33 (1H, m), 3.48 - 3.58 (3H, m), 3.59 (2H, s), 3.67 - 3.71 (1H, m), 3.79 (1H, d), 3.99 - 4.03 (2H, m), 4.33 (1H, s), 6.40 (1H, s), 6.55 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 345; HPLC tR = 1.54 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 45: *N*-[2-[1-[2-[4-(Ethylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide



A solution of ethylamine (2M in THF, 0.863 mL, 1.73 mmol) was added in one portion to a stirred solution of phenyl *N*-[4-[4-[1-(2-acetamidoethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.2 g, 0.35 mmol) in THF (34.5 mL) at RT. The resulting solution was stirred at 50°C for 2 hours. The product was concentrated *in vacuo*, then purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give a residue that was triturated with acetonitrile to give the desired material as a white solid (0.147 g).

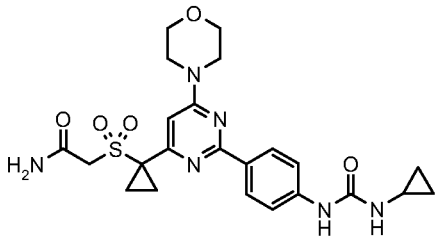
NMR Spectrum: ^{1}H NMR (400.13 MHz, CDCl3) δ 1.16 (3H, t), 1.33 (3H, d), 1.48 - 1.51 (2H, m), 1.81 - 1.84 (2H, m), 1.93 (3H, s), 3.27 - 3.34 (3H, m), 3.49 - 3.52 (2H, m), 3.55 - 3.60 (1H, m), 3.70 - 3.74 (1H, m), 3.78 - 3.83 (3H, m), 4.01 - 4.05 (1H, m), 4.10 - 4.16 (1H, m), 4.46 (1H, s), 5.18 (1H, t), 6.64 (1H, s), 6.89 (1H, t), 7.15 (1H, s), 7.42 (2H, d), 8.23 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 531; HPLC tR = 1.87 min.

mTOR Kinase Assay (Echo): 0.0219μM

The preparation of phenyl *N*-[4-[4-[1-(2-acetamidoethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 46: 2-[1-[2-[4-(Cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropyl]sulfonylacetamide

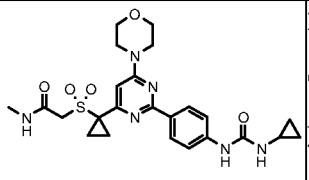


Bis(triphenylphosphine)palladium(II) chloride (19.03 mg, 0.03 mmol) was added to 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetamide (146 mg, 0.40 mmol), 1-cyclopropyl-3-(4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenyl)urea (185 mg, 0.61 mmol) and sodium carbonate (0.809 mL, 1.62 mmol) in a solvent mixture of DMF (3 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT. The resulting mixture was stirred at 90°C for 18 hours under an inert atmosphere.The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (100 mL followed by 75 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of methanol and DCM and the solid removed by filtration. The filtrate was purified by flash silica chromatography, elution gradient 0 to 7% methanol in ethyl acetate, to give a gum which was further purified by ion exchange chromatography on an SCX column, eluting with 7N ammonia in methanol, to give a beige solid which was further purified by prep HPLC to give the desired material (7 mg).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 499; HPLC tR = 1.67 min.

mTOR Kinase Assay (Echo): 0.00456μM

The following compound was prepared in an analogous fashion from 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonyl-*N*-methylacetamide.

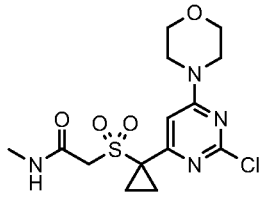
Example	Structure	NAME	LCMS MH+	Retention time (min)
46a		2-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropyl]sulfonyl-N-methylacetamide	515	1.74

Example 46a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.61 - 0.67 (2H, m), 1.57 - 1.61 (2H, m), 1.66 - 1.71 (2H, m), 2.63 (3H, d), 3.72 (8H, s), 4.39 (2H, s), 6.46 (1H, s), 6.87 (1H, s), 7.51 (2H, d), 8.20 (2H, d), 8.29 (1H, d), 8.58 (1H, s).

mTOR Kinase Assay (Echo): 0.0126μM

The preparation of 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonyl-*N*-methylacetamide is described below.

2-[1-(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonyl-*N*-methylacetamide

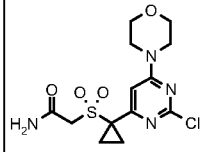


HATU (252 mg, 0.66 mmol) was added to 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetic acid (200 mg, 0.55 mmol) and triethylamine (0.077 mL, 0.55 mmol) in DCM (10 mL) at RT under a nitrogen atmosphere and stirred for 15 minutes. Methylamine (2M in THF, 2 mL) was added and reaction stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with a saturated solution of sodium hydrogen carbonate (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 90% ethyl acetate in isohexane, to give the desired material as a yellow gum (156 mg)

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.51 - 1.54 (2H, m), 1.62 - 1.67 (2H, m), 2.62 (3H, d), 3.66 (8H, m), 4.27 (2H, s), 7.06 (1H, s), 8.22 (1H, s)

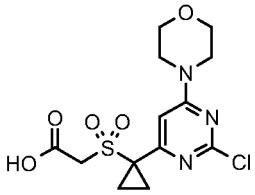
LCMS Spectrum: m/z (ESI+)(M+H)+ = 375; HPLC tR = 1.35 min.

2-[1-(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetamide was made by an analogous procedure to that above (chromatographed using 0 – 4% methanol in ethyl acetate).

Structure	NAME	LCMS MH+	Retention time (min)
	2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetamide	361	1.31

The preparation of 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetic acid is described below.

2-[1-(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetic acid

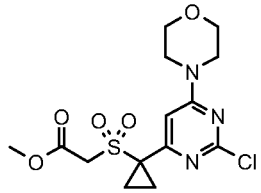


Lithium hydroxide (0.812 g, 33.93 mmol) was added to methyl 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetate (2.55 g, 6.79 mmol), in a mixture of THF (40 mL) and water (8 mL). The resulting mixture was stirred at RT for 2 hours then acidified with 2M hydrochloric acid. The reaction mixture was extracted with ethyl acetate (400 mL) and the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (1.96 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.53 - 1.58 (2H, m), 1.69 - 1.72 (2H, m), 3.66 (8H, s), 4.55 (2H, s), 6.98 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 362; HPLC tR = 0.69 min.

Methyl 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetate



Lithium diisopropylamide (8.92 mL, 16.05 mmol) was added dropwise to 2-chloro-4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidine (4.25 g, 13.37 mmol), in THF (80 mL) at -78ºC under a nitrogen atmosphere. The resulting mixture was stirred at -78°C for 15 minutes. Dimethyl carbonate (5.63 mL, 66.87 mmol) was added and the resulting mixture stirred at -78 °C for 10 minutes, then left to warm to RT. The mixture was cooled back to -78C and additional lithium diisopropylamide (8.92 mL, 16.05 mmol) added. The mixture was stirred at -78°C for 10 minutes, then dimethyl carbonate (5.63 mL, 66.87 mmol) added and the mixture allowed to come to RT and the pH adjusted to 7 with 2M hydrochloric acid. The

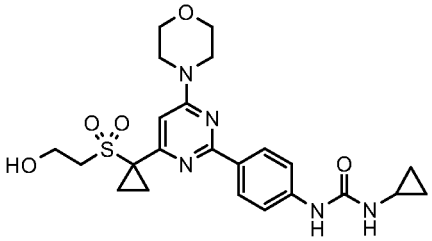
reaction mixture was diluted with ethyl acetate (350 mL), and washed with water (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give a yellow solid which was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (3.10 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.56 - 1.60 (2H, m), 1.68 - 1.72 (2H, m), 3.63 - 3.70 (11H, m), 4.71 (2H, s), 6.97 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 376; HPLC tR = 1.76 min.

The preparation of 2-chloro-4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidine was described earlier.

Example 47: 3-Cyclopropyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea

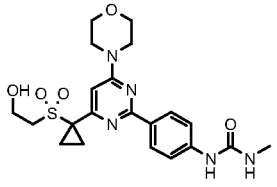
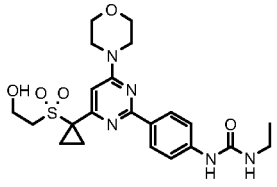


A solution of phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate (50 mg, 0.09 mmol), cyclopropylamine (0.48 mmol) and triethylamine (0.066 mL, 0.048 mmol) in NMP (1 mL) was stirred at RT until the reaction had gone to completion. The crude reaction mixture was purifed by prep HPLC to give the desired material as a solid (31 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.45 (2H, m), 0.61 - 0.67 (2H, m), 1.50 - 1.59 (2H, m), 1.59 - 1.69 (2H, m), 2.54 - 2.61 (1H, m), 3.62 - 3.69 (2H, m), 3.69 - 3.76 (8H, m), 3.86 - 3.92 (2H, m), 5.03 (1H, t), 6.44 (1H, s), 6.81 (1H, s), 7.51 (2H, d), 8.21 (2H, d), 8.54 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 488; HPLC tR = 1.61 min.

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

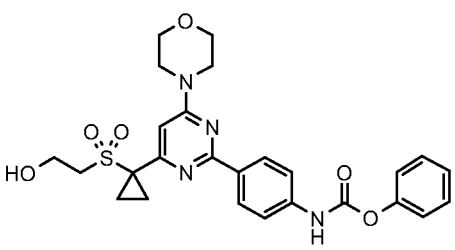
Example	Structure	NAME	LCMS MH+	Retention time (min)
47a		1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea	462	1.45
47b		3-ethyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	476	1.58

Example 47a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.48 - 1.58 (2H, m), 1.62 - 1.69 (2H, m), 2.67 (3H, d), 3.61 - 3.68 (2H, m), 3.69 - 3.76 (8H, m), 3.85 - 3.92 (2H, m), 5.03 (1H, s), 6.09 (1H, t), 6.81 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.76 (1H, s).

Example 47b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.51 - 1.57 (2H, m), 1.62 - 1.68 (2H, m), 3.14 (2H, q), 3.60 - 3.69 (2H, m), 3.69 - 3.77 (8H, m), 3.85 - 3.92 (2H, m), 5.03 (1H, t), 6.16 (1H, t), 6.81 (1H, s), 7.47 (2H, d), 8.20 (2H, d), 8.67 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate

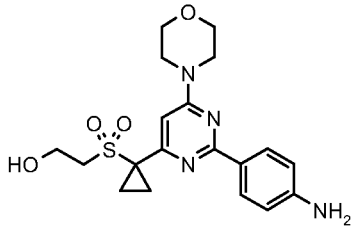


Sodium hydrogen carbonate (65.4 mg, 0.78 mmol) was added to 2-[1-[2-(4-aminophenyl)-6-morpholin-4-ylpyrimidin-4-yl]cyclopropyl]sulfonylethanol (210 mg, 0.52 mmol) in dioxane (8 mL) at 5°C under a nitrogen atmosphere. Phenyl chloroformate (0.072 mL, 0.57 mmol) was added and the mixture stirred at RT for 18 hours. The reaction mixture was diluted with ethyl acetate (50 mL), the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (170 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.52 - 1.60 (2H, m), 1.61 - 1.70 (2H, m), 3.61 - 3.79 (10H, m), 3.82 - 3.96 (2H, m), 6.85 (1H, s), 7.21 - 7.34 (3H, m), 7.45 (2H, d), 7.64 (2H, d), 8.31 (2H, d), 10.45 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 525; HPLC tR = 2.40 min.

2-[1-[2-(4-Aminophenyl)-6-morpholin-4-ylpyrimidin-4-yl]cyclopropyl]sulfonylethanol



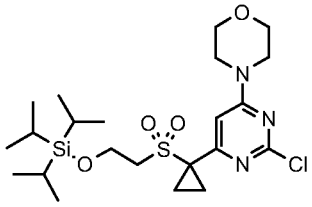
Bis(triphenylphosphine)palladium(II) chloride (48.5 mg, 0.07 mmol) was added to 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane (520 mg, 1.03 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (339 mg, 1.55 mmol) and an aqueous solution of sodium carbonate (1 mL, 2.00 mmol) in a solvent mixture of DMF (5 mL), DME (12 mL), water (1 mL) and ethanol (1 mL) at RT. The atmosphere was replaced with nitrogen and the mixture stirred at 90°C for 18 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2 x 100 mL).The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was dissolved in DCM then tetrabutylammonium fluoride (5.16 mL, 5.16 mmol) added and the mixture left to stir for 1 hour. A saturated solution of ammonium chloride was added, the layers separated and the organics dried (Na_2SO_4), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, and the resultant solid further purified by ion exchange chromatography on an

SCX column, eluting with 7N ammonia in methanol. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (210mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.47 - 1.54 (2H, m), 1.59 - 1.67 (2H, m), 3.59 - 3.77 (10H, m), 3.81 - 3.94 (2H, m), 5.02 (1H, t), 5.57 (2H, s), 6.60 (2H, d), 6.71 (1H, s), 8.04 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 405; HPLC tR = 1.65 min.

2-[1-(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane

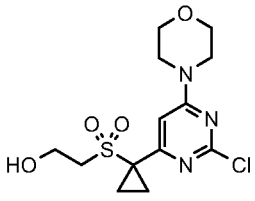


2-[1-(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylethanol (550 mg, 1.58 mmol) was added to triisopropylsilyl chloride (0.406 mL, 1.90 mmol) and imidazole (258 mg, 3.80 mmol) in DMF (10 mL) at RT. The resulting solution was stirred under a nitrogen atmosphere overnight. The DMF was removed *in vacuo* and ethyl acetate added. The solids were removed by filtration and discarded. The filtrate was concentrated *in vacuo* and purified by flash silica chromatography, elution gradient 0 to 4% methanol in DCM, to give material that was further purified by flash silica chromatography, elution gradient 0-10%ethyl acetate in DCM to give the desired material as a clear gum (700 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.02 (18H, d), 1.49 - 1.53 (2H, m), 1.62 - 1.66 (2H, m), 2.00 (2H, s), 3.33 (2H, s), 3.62 - 3.69 (8H, m), 4.03 - 4.09 (3H, m), 6.95 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 504; HPLC tR = 3.63 min.

2-[1-(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylethanol

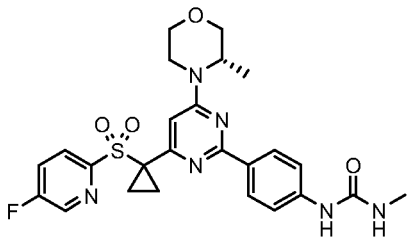


DIPEA (1.052 mL, 6.08 mmol) was added to 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetic acid (1.1 g, 3.04 mmol), in THF (50 mL) at 0°C under a nitrogen atmosphere. The resulting solution was stirred at 0°C for 5 minutes. Ethyl chloroformate (0.349 mL, 3.65 mmol) was added and the reaction stirred at 0°C for 1 hour. The reaction mixture was filtered and filtrate cooled back down to 0°C. Lithium borohydride (13.68 mL, 27.36 mmol) was added and the mixture warmed to allowed to come to RT. The mixture was cooled back to 0°C and additional lithium borohydride (13.68 mL, 27.36 mmol) added and the reaction was allowed to come to RT. The mixture was cooled back to 0°C and additional lithium borohydride (13.68 mL, 27.36 mmol) added and the reaction was allowed to come to RT and stirred for 72 hours. The reaction mixture was adjusted to pH7 with 2M hydrochloric acid and extracted with ethyl acetate (100 mL). The organic layer was washed with water (100 mL), dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 100% ethyl acetate in isohexane, to give the desired material as a white solid (500 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.47 - 1.52 (2H, m), 1.59 - 1.67 (2H, m), 3.49 - 3.57 (2H, m), 3.60 - 3.70 (8H, m), 3.76 - 3.86 (2H, m), 4.99 (1H, t), 6.98 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 348; HPLC tR = 1.38 min.

The preparation of 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetic acid was described earlier.

Example 48: 1-[4-[4-[1-(5-Fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea



Methylamine (0.509 mL, 1.02 mmol) was added to phenyl *N*-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (200 mg, 0.34 mmol) and triethylamine (0.141 mL, 1.02 mmol) in DMF (1.7 mL) and the

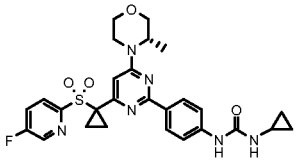
reaction stirred at 50°C for 2 hours. The crude product was purified by prep HPLC to give the desired material as a white solid (70.0 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.69 - 1.72 (2H, m), 1.96 - 1.99 (2H, m), 2.66 (3H, d), 3.12 - 3.18 (1H, m), 3.43 - 3.48 (1H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, d), 4.15 (1H, d), 4.45 (1H, s), 6.02 - 6.04 (1H, m), 6.68 (1H, s), 7.37 (2H, d), 7.68 (2H, d), 7.95 - 8.00 (1H, m), 8.03 - 8.06 (1H, m), 8.72 (1H, s), 8.87 (1H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 527; HPLC tR = 1.61 min.

mTOR Kinase Assay (Echo): 0.00252μM

The following compound was prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

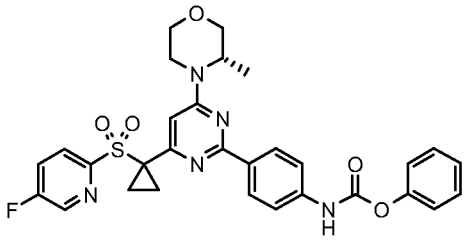
Example	Structure	NAME	LCMS MH+	Retention time (min)
48a		3-cyclopropyl-1-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	553	2.43

Example 48a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.66 - 1.70 (2H, m), 1.96 - 1.99 (2H, m), 3.69 (8H, s), 3.79 (3H, s), 6.74 (1H, s), 7.40 (3H, d), 7.66 (2H, d), 7.77 - 7.78 (3H, m), 8.35 (1H, s), 8.80 (1H, s), 8.87 (2H, d).

mTOR Kinase Assay (Echo): 0.00103μM

The preparation of phenyl *N*-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

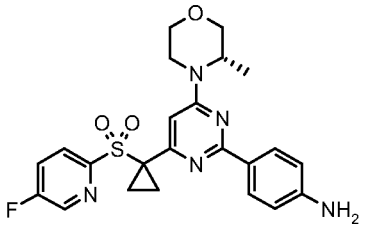


Sodium bicarbonate (0.403 g, 4.79 mmol) was added to 4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.5 g, 3.19 mmol), in 1,4-dioxane (15.97 mL), followed by the dropwise addition of phenyl chloroformate (0.402 mL, 3.19 mmol) over 2 minutes and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM (20 mL), the organics washed with water (20 mL), dried ($MgSO_4$), filtered and evaporated to give the desired material (2.0 g) which was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.71 - 1.76 (2H, m), 1.96 - 1.99 (2H, m), 3.14 - 3.22 (1H, m), 3.42 - 3.49 (1H, m), 3.58 - 3.62 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.19 (1H, s), 4.48 (1H, s), 6.74 (1H, s), 7.24 - 7.26 (2H, m), 7.45 (2H, t), 7.54 (2H, d), 7.80 (2H, d), 7.99 (1H, dt), 8.07 (1H, dd), 8.89 (1H, d), 10.48 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 590; HPLC tR = 2.95 min.

4-[4-[1-(5-Fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



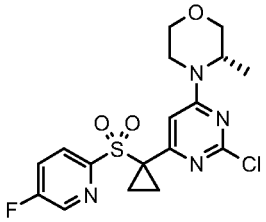
Bis(triphenylphosphine)palladium(II) chloride (0.136 g, 0.19 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.104 g, 5.04 mmol) and 2-chloro-4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.6 g, 3.88 mmol) and an aqueous solution of sodium carbonate (5.81 mL, 11.63 mmol) in a solvent mixture of DMF (0.564 mL), ethanol (4.70 mL) and water (4.70 mL) at RT under an

atmosphere of nitrogen. The resulting mixture was stirred at 85°C for 4 hours. The reaction mixture was diluted with ethyl acetate (20 mL), and the organics washed with water (2 x 20 mL), dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% 3.5N methanolic ammonia in DCM, to give the desired material as a cream solid (1.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.65 - 1.70 (2H, m), 1.94 - 1.97 (2H, m), 3.12 (1H, dt), 3.44 (1H, dt), 3.59 (1H, dd), 3.73 (1H, d), 3.93 (1H, dd), 4.11 - 4.13 (1H, m), 4.41 (1H, s), 6.46 (2H, d), 6.58 (1H, s), 7.49 (2H, d), 7.98 (2H, dt), 8.04 (2H, dd), 8.89 (1H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 470; HPLC tR = 2.30 min.

2-Chloro-4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

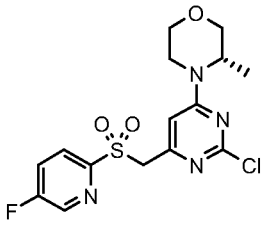


1,2-Dibromoethane (1.025 mL, 11.89 mmol) was added to 2-chloro-4-[(5-fluoropyridin-2-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.3 g, 5.95 mmol), an aqueous solution of sodium hydroxide (2.97 mL, 29.73 mmol) and tetrabutylammonium bromide (0.383 g, 1.19 mmol) in toluene (29.7 mL) and the resulting solution stirred at 60°C for 3 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (50 mL), and the organics washed sequentially with water (50 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 50% ethyl acetate in DCM, to give the desired material as a white solid (1.8 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.63 - 1.66 (2H, m), 1.88 - 1.93 (2H, m), 3.11 - 3.17 (1H, m), 3.39 (1H, dt), 3.54 (1H, dd), 3.69 (1H, d), 3.91 (2H, dd), 4.27 (1H, s), 6.81 (1H, s), 8.02 - 8.11 (2H, m), 8.83 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 413, HPLC tR = 2.10 min

2-Chloro-4-[(5-fluoropyridin-2-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

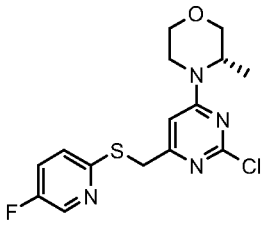


3-Chloroperoxybenzoic acid (5.79 g, 25.15 mmol) was added portionwise to 2-chloro-4-[(5-fluoropyridin-2-yl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.57 g, 10.06 mmol), in DCM (50.3 mL) and the reaction stirred at RT for 2 hours. The reaction mixture was washed with a saturated solution of sodium hydrogen carbonate (50 mL), the organic layer separated, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a white solid (2.3 g).

NMR Spectrum: ^1H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 3.17 (1H, t), 3.42 (1H, dt), 3.57 (1H, dd), 3.71 (1H, d), 3.92 (2H, dd), 4.17 (1H, s), 4.74 (2H, d), 6.82 (1H, s), 8.01 - 8.09 (2H, m), 8.89 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 387, HPLC tR = 1.88 min

2-Chloro-4-[(5-fluoropyridin-2-yl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



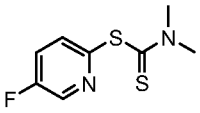
Potassium hydroxide (3.22 g, 57.33 mmol) was added to (5-fluoropyridin-2-yl) dimethylaminomethanedithioate (3.1 g, 14.33 mmol) in ethanol (71.7 mL) and the resulting solution heated at 65°C for 4 hours. The reaction was cooled, 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7.09 g, 20.06 mmol) added and the reaction stirred at RT for 4 hours. Water (50 mL) was added and the reaction extracted with DCM (2 x 100 mL). The organics were dried ($MgSO_4$), filtered and concentrated to give crude product which

was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a beige gum (3.57 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 3.11 - 3.17 (1H, m), 3.41 (1H, dt), 3.54 - 3.57 (1H, m), 3.69 (1H, d), 3.90 (2H, dd), 4.24 - 4.26 (1H, m), 4.29 (2H, d), 6.84 (1H, s), 7.45 (1H, dd), 7.68 (1H, dt), 8.50 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 355, HPLC tR = 2.38 min

(5-Fluoropyridin-2-yl) dimethylaminomethanedithioate



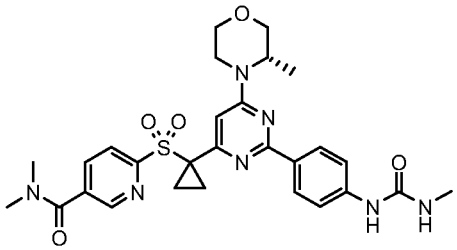
2-Bromo-5-fluoropyridine (4 g, 22.73 mmol) was added portionwise to isopropylmagnesium chloride - lithium chloride complex (14% in THF, 23 mL, 22.73 mmol), at 0ºC, over a period of 2 minutes under a nitrogen atmosphere. The resulting solution was warmed to RT over a period of 2 hours then cooled back to 0°C and tetramethylthiuram disulfide (5.46 g, 22.73 mmol) in DCM (22.73 mL) added. The reaction was warmed to RT and stirred for 6 hours. The reaction was poured into a saturated aqueous solution of ammonium chloride (100 mL) and the aqueous layer extracted with DCM (2 x 100 mL). The organics were dried ($MgSO_4$), concentrated *in vacuo* and the crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a brown oil which solidified on standing (3.10 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.45 (3H, s), 3.46 (3H, s), 7.70 (1H, dd), 7.86 (1H, dt), 8.65 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 217, HPLC tR = 1.70 min

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 49: *N,N*-Dimethyl-6-[1-[2-[4-(methylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpyridine-3-carboxamide



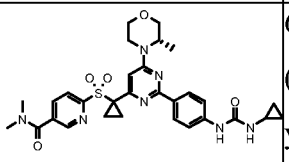
Methylamine (0.250 mL, 0.50 mmol) was added to phenyl *N*-[4-[4-[1-[5-(dimethylcarbamoyl)pyridin-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.064 g, 0.10 mmol) and triethylamine (0.042 mL, 0.30 mmol) in DMF (2 mL) and the resulting solution stirred at 50°C for 18 hours. The reaction was cooled and the mixture purified by preparative HPLC to give the desired material as a white solid (0.03 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ δ 1.16-1.18 (3H, d), 1.73-1.76 (2H, m), 1.99-2.02 (2H, m), 2.65-2.66 (3H, d), 2.88 (3H, s), 3.05 (3H, s), 3.05-3.17 (1H, td), 3.41-3.48 (1H, td), 3.58-3.62 (1H, dd), 3.73-3.76 (1H, d), 3.93-3.97 (1H, dd), 4.15 (1H, bs), 4.44 (1H, bs), 6.07-6.10 (1H, q), 6.65 (1H, s), 7.37-7.39 (2H, d), 7.67-7.69 (2H, d), 8.00-8.01 (1H, d), 8.11-8.13 (1H, dd), 8.72 (1H, s), 8.87-8.88 (1H, dd).

LCMS Spectrum: m/z (ES+) (M+H)+=580; HPLC tR=1.88min.

mTOR Kinase Assay (Echo): 0.00187μM

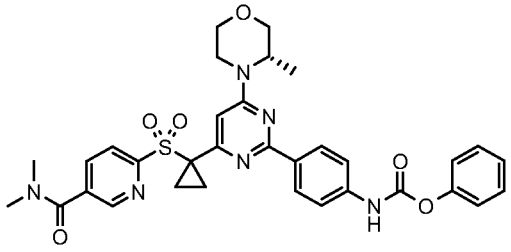
The compound shown in table below was prepared in an analogous manner from phenyl *N*-[4-[4-[1-[5-(dimethylcarbamoyl)pyridin-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
49a		6-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-N,N-dimethylpyridine-3-carboxamide	606	2.00

Example 49a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39-0.43 (2H, m), 0.62-0.67 (2H, m), 1.16-1.18 (3H, d), 1.73-1.76 (2H, m), 2.00-2.02 (2H, m), 2.88 (3H, s), 3.05 (3H, s), 3.11-3.18 (1H, td), 3.42-3.48 (1H, td), 3.58-3.62 (1H, dd), 3.73-3.76 (1H, d), 3.93-3.97 (1H, dd), 4.13 (1H, bs), 4.44 (1H, bs), 6.44-6.45 (1H, d), 6.66 (1H, s), 7.37-7.39 (2H, d), 7.67-7.69 (2H, d), 8.00-8.03 (1H, d), 8.11-8.13 (1H, dd), 8.51 (1H, s), 8.87-8.88 (1H, dd).
mTOR Kinase Assay (Echo): 0.00267μM

The preparation of phenyl *N*-[4-[4-[1-[5-(dimethylcarbamoyl)pyridin-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[5-(dimethylcarbamoyl)pyridin-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



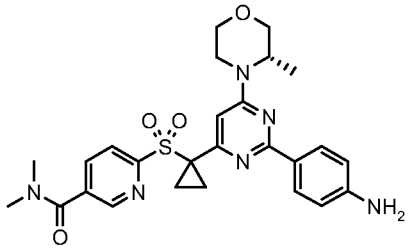
Phenyl chloroformate (0.015 mL, 0.12 mmol) was added dropwise to 6-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-3-carboxamide (0.064 g, 0.12 mmol) and sodium hydrogen carbonate (0.015 g, 0.18 mmol) in dioxane (7.5 mL) and the resulting solution stirred at RT for 1 hour.

The material was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material.

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.29-1.31 (3H, d), 1.66-1.74 (2H, m), 2.17-2.19 (2H, m), 2.88 (3H, s), 3.12 (3H, s), 3.24-3.31 (1H, td), 3.54-3.61 (1H, td), 3.70-3.74 (1H, dd), 3.80-3.83 (1H, d), 4.01-4.05 (1H, dd), 4.16-4.17 (1H, bs), 4.42 (1H, bs), 6.79 (1H, s), .16-7.26 (2H, d), 7.22-7.26 (1H, t), 7.37-7.41 (2H, t), 7.47-7.49 (2H, d), 7.64-7.69 (1H, m), 7.84-7.87 (1H, dd), 7.95-7.97 (3H, m), 8.75-8.76 (1H, d).

LCMS Spectrum: m/z (ES+) (M+H)+=643; HPLC tR=2.62min.

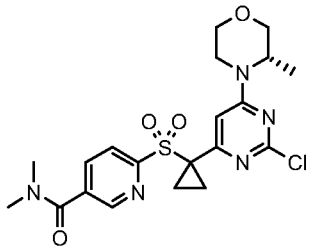
6-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-3-carboxamide



Bis(triphenylphosphine)palladium (II) chloride (0.015 g, 0.02 mmol) was added to 6-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-3-carboxamide (0.203 g, 0.44 mmol), 4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.096 g, 0.44 mmol) and an aqueous solution of sodium carbonate (1.09 mL, 2.18 mmol) in a solvent mixture (2 mL) (the solvent mixture comprised 18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol) at RT under a nitrogen atmosphere. The resulting solution was stirred at 80°C for 3 hours. The reaction was cooled, water added and the solids removed by filtration. The filtrate was extracted twice with ethyl acetate and the combined organics dried ($MgSO_4$), filtered and evaporated. The solids from the filtration were combined with those from the extraction to give the desired material which was used without further purification.

LCMS Spectrum: m/z (ES+) (M+H)+=523; HPLC tR=1.98min.

6-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-3-carboxamide

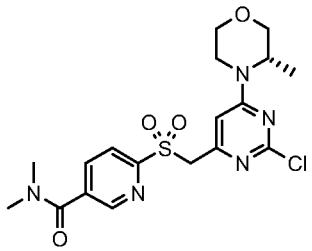


Sodium hydroxide (3.36 g, 83.96 mmol) in water (3.6 mL) was added to 6-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-*N,N*-dimethylpyridine-3-carboxamide (0.666 g, 1.51 mmol), 1,2-dibromoethane (0.652 mL, 7.56 mmol) and tetrabutylammonium bromide (0.049 g, 0.15 mmol) in DCM (20 mL) and the resulting solution stirred at RT for 18 hours. The reaction mixture was diluted with water and extracted with DCM. The organics were washed with saturated brine, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 7% methanol (contaning 0.1% ammonia) in DCM, to give the desired material as a brown gum (0.406 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.27-1.29 (3H, d), 1.61-1.68 (2H, m), 2.07-2.10 (2H, m), 3.00 (3H, s), 3.14 (3H, s), 3.20-3.28 (1H, td), 3.48-3.54 (1H, td), 3.64-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.96-4.02 (2H, m), 4.26 (1H, bs), 6.95 (1H, s), 7.93-7.99 (2H, m), 8.71-8.72 (1H, d).

LCMS Spectrum: m/z (ES+) (M+H)+=466; HPLC tR=1.71min.

6-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-*N,N*-dimethylpyridine-3-carboxamide



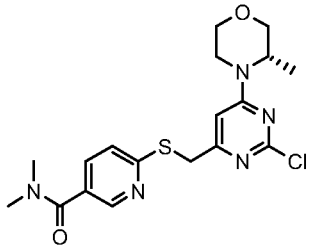
6-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]-*N,N*-dimethylpyridine-3-carboxamide (1.47 g, 3.60 mmol) was dissolved in dioxane (45 mL) and 2N sulfuric acid (0.11 mL) added. The solution was heated to 55°C, a solution of sodium

tungstate dihydrate (0.024 g, 0.07 mmol) in water (1.08 mL) added and the solution allowed to stir for 10 minutes. Hydrogen peroxide (2.229 mL, 72.07 mmol) was then added dropwise over several minutes and the solution heated at 55°C for 3 hours. Water was added and the reaction was allowed to cool. The aqueous solution was extracted with DCM, the organics dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a cream solid (1.45 g).

NMR Spectrum: ^1H NMR (400.132 MHz, $CDCl_3$) δ 1.31-1.33 (3H, d), 3.04 (3H, s), 3.17 (3H, s), 3.24-3.32 (1H, td), 3.50-3.57 (1H, td), 3.66-3.70 (1H, dd), 3.78-3.80 (1H, d), 3.99-4.03 (2H, m), 4.26 (1H, bs), 4.58 (2H, s), 6.52 (1H, s), 7.97-8.03 (2H, m), 8.82-8.83 (1H, m).

LCMS Spectrum: m/z (ES+) (M+H)+=440; HPLC tR=1.59min.

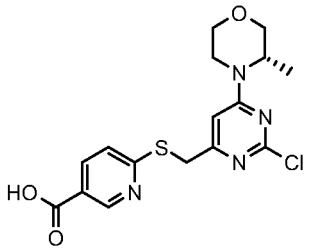
6-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]-*N,N*-dimethylpyridine-3-carboxamide



DIPEA (1.043 mL, 5.99 mmol) was added to 6-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]pyridine-3-carboxylic acid (1.369 g, 3.59 mmol) and HATU (1.366 g, 3.59 mmol) in DMA (10 mL) and the resulting solution stirred at RT for 15 minutes. Dimethylamine (1.497 mL, 2.99 mmol) was added and the reaction allowed to stir for 2.5 hours. Water was added to the solution and the solution extracted with ethyl acetate. The ethyl acetate was washed with a saturated aqueous solution of sodium bicarbonate, dried ($MgSO_4$), filtered and evaporated to give the desired material which was used without further purification.

LCMS Spectrum: m/z (ES+) (M+H)+=408; HPLC tR=1.83min.

6-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]pyridine-3-carboxylic acid



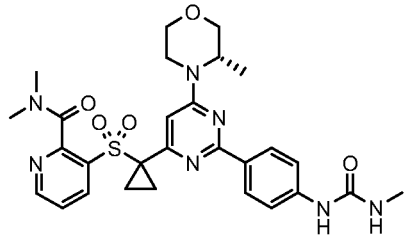
2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.0 g, 5.66 mmol) was added to 6-mercaptonicotinic acid (1.317 g, 8.48 mmol) and DIPEA (2.463 mL, 14.14 mmol) in acetonitrile (100 mL) and the resulting solution stirred at RT for 2 hours. The solvent was removed under vacuum and the residue dissolved in DCM. The organics were washed sequentially with water and saturated brine, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol (containing 0.1% ammonia) in DCM, to give the desired material as a brown solid (1.79 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.19-1.20 (3H, d), 3.16-3.21 (1H, t), 3.40-3.47 (1H, m), 3.58-3.61 (2H, dd), 3.91-3.94 (2H, d), 4.25 (3H, bs), 6.08 (1H, bs), 6.52 (1H, s), 7.01 (1H, bs), 7.89 (1H, bs), 8.89 (1H, bs).

LCMS Spectrum: m/z (ES+) (M+H)+=381; HPLC tR=0.83min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 50: *N,N*-Dimethyl-3-[1-[2-[4-(methylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpyridine-2-carboxamide



Methylamine (0.441 mL, 0.88 mmol) was added to phenyl *N*-[4-[4-[1-[2-(dimethylcarbamoyl)pyridin-3-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-

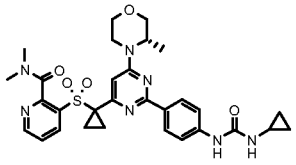
yl]pyrimidin-2-yl]phenyl]carbamate (0.113 g, 0.18 mmol) and triethylamine (0.074 mL, 0.53 mmol) in DMF (2 mL) and the resulting solution stirred at 50°C for 2 hours. The reaction was cooled and purified by preparative HPLC, to give the desired material as a colourless gum (11 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.62 (2H, bs), 1.98 (2H, bs), 2.55 (3H, s), 2.66 (3H, s), 2.96 (3H, s), 3.13-3.19 (1H, td), 3.41-3.47 (1H, td), 3.58-3.61 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.16 (1H, bs), 4.47 (1H, bs), 6.12 (1H, bs), 6.73 (1H, s), 7.43-7.46 (2H, d), 7.59-7.62 (1H, q), 7.85-7.87 (2H, d), 8.16-8.18 (1H, d), 8.82 (1H, bs), 8.85-8.86 (1H, dd).

LCMS Spectrum: m/z (ES+) (M+H)+=580; HPLC tR=1.76min.

mTOR Kinase Assay (Echo): 0.0104μM

The following compound was prepared in an analogous fashion from phenyl *N*-[4-[4-[1-[2-(dimethylcarbamoyl)pyridin-3-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

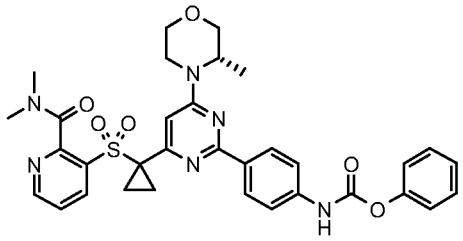
Example	Structure	NAME	LCMS MH+	Retention time (min)
50a		3-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-N,N-dimethylpyridine-2-carboxamide	606	1.92

Example 50a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.67 (2H, m), 1.16-1.17 (3H, d), 1.60 (2H, bs), 1.96 (2H, bs), 2.55 (3H, s), 2.97 (3H, s), 3.10-3.17 (1H, td), 3.42-3.48 (1H, td), 3.58-3.62 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.15 (1H, bs), 4.45 (1H, bs), 6.45-6.46 (1H, d), 6.72 (1H, s), 7.41-7.43 (2H, d), 7.57-7.60 (1H, q), 7.84-7.86 (2H, d), 8.11-8.14 (1H, dd), 8.55 (1H, s), 8.84-8.85 (1H, dd).

mTOR Kinase Assay (Echo): 0.00794μM

The preparation of phenyl *N*-[4-[4-[1-[2-(dimethylcarbamoyl)pyridin-3-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[2-(dimethylcarbamoyl)pyridin-3-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

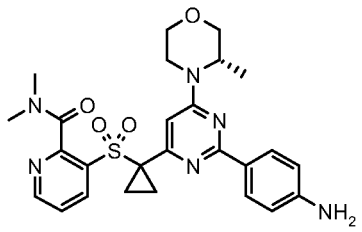


Phenyl chloroformate (0.071 mL, 0.57 mmol) was added dropwise to 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-2-carboxamide (0.296 g, 0.57 mmol) and sodium hydrogen carbonate (0.071 g, 0.85 mmol) in dioxane (18 mL) and the resulting solution stirred at RT for 3 hours. The solids were removed by filtration and the filtrate purified by flash silica chromatography, elution gradient 0 to 100% ethyl acetate in DCM, to give additional desired material as a yellow gum (0.227 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.22-1.24 (3H, d), 1.53-1.60 (2H, m), 2.13-2.17 (2H, m), 2.77 (3H, s), 3.14 (3H, s), 3.18-3.25 (1H, td), 3.50-3.57 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.98-3.99 (1H, dd), 4.08 (1H, bs), 4.38 (1H, bs), 6.69 (1H, s), 7.16-7.18 (2H, d), 7.21-7.25 (2H, m), 7.36-7.40 (2H, t), 7.48-7.50 (2H, d), 7.67 (1H, bs), 7.94-7.96 (1H, dd), 8.15-8.17 (2H, d), 8.70-8.72 (1H, dd).

LCMS Spectrum: m/z (ES+) (M+H)+=643; HPLC tR=3.09min.

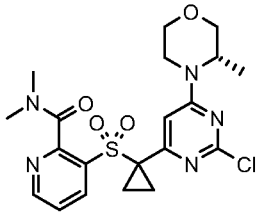
3-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-2-carboxamide



Bis(triphenylphosphine)palladium (II) chloride (0.038 g, 0.05 mmol) was added to 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-2-carboxamide (0.503 g, 1.08 mmol), 4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.237 g, 1.08 mmol) and an aqueous solution of sodium carbonate (2.70 mL, 5.40 mmol) in a solvent mixture (2 mL) (the solvent mixture comprised 18% DMF, 82% of a 7:3:2 mixture of DME:Water:Ethanol) and the resulting solution stirred at 80°C for 15 hours. The reaction was cooled to RT and water was added. The solids were filtered to give the desired material. The filtrate was extracted with ethyl acetate and the organics dried ($MgSO_4$), filtered and evaporated to dryness to yield an additional sample of the desired material. Both crops of the desired material were combined and used without further purification.

LCMS Spectrum: m/z (ES+) (M+H)+=523; HPLC tR=1.85min.

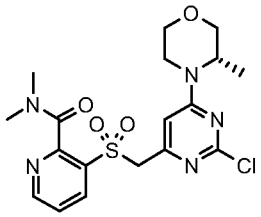
3-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-2-carboxamide



Sodium hydroxide (2.373 g, 59.32 mmol) in water (2.373 mL) was added to 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-*N,N*-dimethylpyridine-2-carboxamide (0.475 g, 1.08 mmol), 1,2-dibromoethane (0.465 mL, 5.39 mmol) and tetrabutylammonium bromide (0.035 g, 0.11 mmol) in DCM and the resulting solution stirred at RT for 18 hours. Water was added and the solution was extracted with DCM. The organic layer was dried ($MgSO_4$) and filtered to give the desired material (0.539 g).

LCMS Spectrum: m/z (ES+) (M+H)+=466; HPLC tR=1.64min.

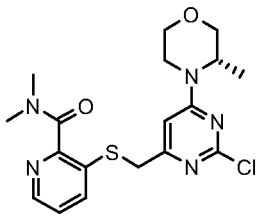
3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-*N,N*-dimethylpyridine-2-carboxamide



3-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]-*N,N*-dimethylpyridine-2-carboxamide (0.533 g, 1.31 mmol) was dissolved in dioxane (15 mL) and 2N sulfuric acid (0.041 mL) was added. The solution was heated to 55°C and a solution of sodium tungstate dihydrate (8.62 mg, 0.03 mmol) in water (0.4 mL) added and the solution allowed to stir for 10 minutes. Hydrogen peroxide (0.808 mL, 26.13 mmol) was then added dropwise over several minutes. The solution was heated at 55°C for 5.5 hours. The heat was removed and the reaction was allowed to stir at RT overnight. Water was added and the reaction was allowed to cool. The aqueous solution was extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 7% methanil (containing 0.1% ammonia) in DCM, to give the desired material as a yellow gum (0.475 g).

LCMS Spectrum: m/z (ES+) (M+H)+=440; HPLC tR=1.62min.

3-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]-*N,N*-dimethylpyridine-2-carboxamide

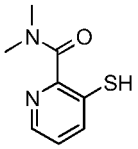


2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.009 g, 2.85 mmol) was added to *N,N*-dimethyl-3-sulfanylpyridine-2-carboxamide (0.520 g, 2.85 mmol) and DIPEA (0.746 mL, 4.28 mmol) in acetonitrile (20 mL) and the resulting solution stirred at RT for 2 hours. Further DIPEA (0.746 mL, 4.28 mmol) was added and the reaction was allowed to stir for several over a weekend. The reaction was heated at 40ºC for 7 days. The solvent was removed and the residue dissolved in DCM and washed with water. The organic layer

was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give material which was further purified by flash silica chromatography, elution gradient 0 to 7% methanol in DCM, to give the desired material as a brown gum (0.533 g).

LCMS Spectrum: m/z (ES+) (M+H)+=408; HPLC tR=1.57min.

N,N-Dimethyl-3-sulfanylpyridine-2-carboxamide

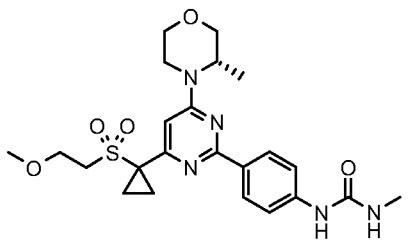


DIPEA (2.164 mL, 12.42 mmol) was added to 3-mercaptopicolinic acid (1.156 g, 7.45 mmol) and HATU (2.83 g, 7.45 mmol) in DMA (30 mL) and the resulting solution stirred at RT for 15 minutes. Dimethylamine (3.11 mL, 6.21 mmol) was added and the reaction was allowed to stir overnight. Water was added to the solution and the solution was extracted with DCM. The organics were washed with a saturated aqueous solution of sodium bicarbonate, dried ($MgSO_4$) and filtered. Most of the solvent was removed and diethyl ether added. The solid was removed by filtration and discarded. Water was added to the filtrate and the product extracted with ethyl acetate. The organics were dried ($MgSO_4$), filtered and evaporated to give the desired material (0.52 g).

LCMS Spectrum: m/z (ES-) (M-H)-=181; HPLC tR=1.17min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 51: 1-[4-[4-[1-(2-Methoxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea



Bis(triphenylphosphine)palladium(II) chloride (5.8 mg, 0.827 mmol) was added to 2-chloro-4-[1-(2-methoxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (0.062 g, 0.17 mmol), 1-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (0.046 g, 0.17 mmol) and an aqueous solution of sodium carbonate (0.414 mL, 0.83 mmol) in a solvent mixture (2 mL) (the solvent mixture comprised 18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol) at RT under an atmosphere of nitrogen. The resulting suspension was stirred at 80°C for 6 hours. The crude reaction mixture was put down an SCX column, eluting with 7M ammonia in methanol, to give a sample that was concentrated *in vacuo* and redissolved in DMF (2 mL). The mixture was purified by preparative HPLC to give the desired material as a white solid (17 mg).

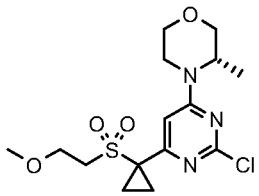
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22-1.23 (3H, d), 1.54-1.57 (2H, m), 1.64-1.66 (2H, m), 2.65-2.66 (3H, d), 3.16-3.23 (1H, td), 3.27 (3H, s), 3.44-3.51 (1H, td), 3.61-3.64 (1H, dd), 3.75-3.78 (1H, d), 3.80-3.81 (4H, t), 3.95-3.99 (1H, dd), 4.21 (1H, bs), 4.57 (1H, bs), 6.07-6.10 (1H, q), 6.76 (1H, s), 7.49-7.51 (2H, d), 8.17-8.19 (2H, d), 8.79 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=490; HPLC tR=1.93min.

mTOR Kinase Assay (Echo): 0.00332μM

The preparation of to 2-chloro-4-[1-(2-methoxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine is described below.

2-Chloro-4-[1-(2-methoxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



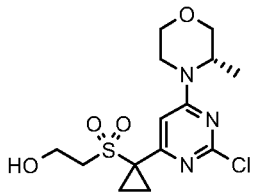
Sodium hydride (0.026 g, 1.07 mmol) was added to (S)-2-(1-(2-chloro-6-(3-methylmorpholino)pyrimidin-4-yl)cyclopropylsulfonyl)ethanol (0.231 g, 0.64 mmol) in THF (20 mL) cooled to 0ºC under a nitrogen atmosphere. The resulting solution was stirred at 0°C for 10 minutes. To this solution, methyl iodide (0.040 mL, 0.64 mmol) was added and the reaction was slowly allowed to warm to RT. Water was carefully added and the reaction was

extracted with DCM. The organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a colourless dry film (0.062 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.31-1.32 (3H, d), 1.47-1.50 (2H, q), 1.79-1.82 (2H, q), 3.25-3.32 (1H, td), 3.35 (3H, s), 3.44-3.47 (2H, t), 3.49-3.56 (1H, td), 3.65-3.69 (1H, dd), 3.76-3.79 (1H, d), 3.79-3.85 (2H, m), 3.98-4.03 (2H, m), 4.33 (1H, bs), 6.84 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=376; HPLC tR=1.87min.

2-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethanol

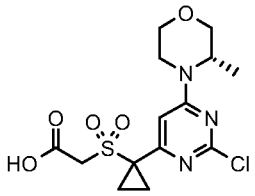


DIPEA (3.70 mL, 21.23 mmol) was added to 2-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylacetic acid (3.99 g, 10.62 mmol) in THF cooled to 0°C under a nitrogen atmosphere. The resulting solution was stirred at 0°C for 5 minutes then ethyl chloroformate (1.117 mL, 11.68 mmol) added dropwise. The solution was allowed to stir for 1 hour, the solids removed by filtration and the filtrate cooled back to 0°C. Lithium borohydride (17.52 mL, 35.03 mmol) was added and the reaction was slowly allowed to warm to RT. Additional lithium borohydride (10.62 mmol) was added and the mixture stirred for several hours. The reaction was quenched with a saturated aqueous solution of ammonium chloride and then extracted with DCM. The organic layer was separated, washed with saturated brine, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a white solid (1.96 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21-1.22(3H, d), 1.49-1.52(2H, m), 1.62-1.65(2H, m), 3.17-3.25(1H, td), 3.40-3.47(1H, td), 3.52-3.55(2H, t), 3.56-3.60(1H, dd), 3.71-3.74(1H, d), 3.79-3.84(2H, q), 3.92-3.95(1H, dd), 4.04(1H, bs), 4.40(1H, bs), 4.98-5.01(1H, t), 6.95(1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=362; HPLC tR=1.67 min.

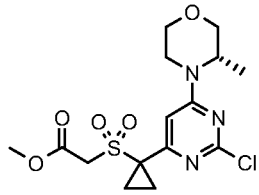
2-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylacetic acid



2 M Sodium hydroxide solution (13.85 mL, 27.70 mmol) was added to methyl 2-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylacetate (3.60 g, 9.23 mmol) in THF (100 mL) and the resulting solution stirred at RT for 6 hours. The solution was adjusted to pH7 with 2M hydrochloric acid and salt was added to concentrate the solution. The aqueous solution was extracted with DCM, the organic layer separated, dried ($MgSO_4$), filtered and evaporated to the desired material as a white solid (3.45 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20-1.22(3H, d), 1.55-1.58(2H, q), 1.69-1.72(2H, q), 3.18-3.24(1H, m), 3.40-3.46(1H, td), 3.56-3.59(1H, dd), 3.71-3.74(1H, d), 3.92-3.95(1H, dd), 4.04(1H, bs), 4.41(1H, bs), 4.55(2H, s), 6.95(1H, s), 13.36(1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=376; HPLC tR=0.71 min.

Methyl 2-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylacetate



A solution of lithium diisopropylamide (2M solution in THF/n-heptane, 5.46 mL, 9.84 mmol) in THF (60 mL) was added to a stirred solution of 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine (2.720 g, 8.20 mmol), and dimethyl carbonate (6.97 mL, 81.97 mmol) in THF (60 mL), cooled to -78°C, over a period of 5 minutes under an atmosphere of nitrogen. The resulting solution was very slowly allowed to come to RT with stirring over 18 hours. The reaction was cooled back to –78°C and further lithium diisopropylamide (2.73 mL , 4.92 mmol), and dimethyl carbonate (6.97 mL, 81.97 mmol) added. Again the mixture was allowed to warm slowly to RT with stirring over 24 hours. The reaction mixture was diluted with ethyl acetate (150 mL), washed with 1M citric acid (150

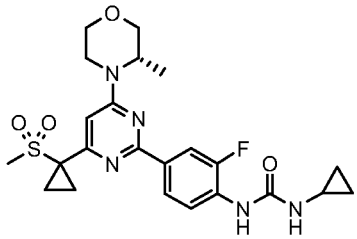
mL) and saturated brine (150 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, to give the desired material as a yellow gum.

NMR Spectrum: ^1H NMR (400.132 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.55 (2H, q), 1.91 (2H, q), 3.30 (1H, m), 3.50 (1H, s), 3.68 (1H, q), 3.79 (4H, t), 4.01 (2H, q), 4.28 (2H, s), 4.41 (1H, s), 6.78 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=390; HPLC tR=2.01 min.

The preparation of 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine was described earlier.

Example 52: 3-Cyclopropyl-1-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



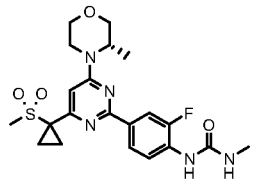
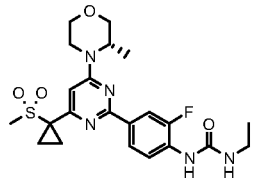
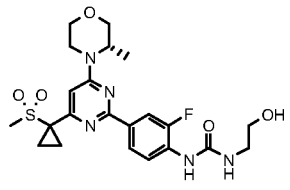
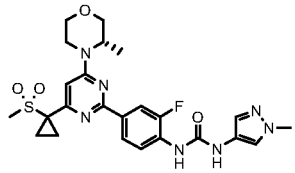
Cyclopropylamine (0.055 mL, 0.80 mmol) followed by triethylamine (0.067 mL, 0.48 mmol) were added to a solution of phenyl *N*-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (85.4mg, 0.16 mmol) in DMF (2 mL) and the reaction heated at 50°C overnight. The crude product was purified by preparative HPLC to give the desired material as a white solid (62 mg).

NMR Spectrum: ^1H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.64-0.69 (2H, m), 1.23-1.25 (3H, d), 1.55-1.58 (2H, q), 1.66-1.69 (2H, q), 2.55-2.61 (1H, m), 3.18-3.25 (1H, td), 3.28 (3H, s), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.81 (1H, s), 6.88-6.89 (1H, d), 8.01-8.04 (1H, dd), 8.06-8.09 (1H, dd), 8.27-8.31 (1H, t), 8.36-8.37 (1H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+490 = HPLC tR =2.28 min.

mTOR Kinase Assay (Echo): 0.0184μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
52a		1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-methylurea	4.64	2.04
52b		3-ethyl-1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	478	2.21
52c		1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	4.94	1.80
52d		1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	530	2.07

Example 52a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.58 (2H, q), 1.66-1.69 (2H, q), 2.68-2.69 (3H, d), 3.18-3.25 (1H, td), 3.28 (3H, s), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.21-4.24 (1H, d), 4.57 (1H, bs), 6.55-6.58 (1H, q), 6.81 (1H, s), 8.00-8.04 (1H, dd), 8.05-8.08 (1H, dd), 8.26-8.31 (1H, t), 8.54-8.55 (1H, d).

mTOR Kinase Assay (Echo): 0.0103μM

Example 52b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06-1.10 (3H, t), 1.23-1.25 (3H, d), 1.55-1.58 (2H, q), 1.66-1.69 (2H, q), 3.11-3.18 (2H, m), 3.18-3.25 (1H, td), 3.28 (3H, s), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.21-4.24 (1H, d), 4.57 (1H, bs), 6.67-6.69 (1H, t), 6.81 (1H, s), 8.01-8.04 (1H, dd), 8.05-8.08 (1H, dd), 8.27-8.31 (1H, t), 8.47-8.48 (1H, d).

mTOR Kinase Assay (Echo): 0.0307μM

Example 52c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.58 (2H, q), 1.66-1.69 (2H, q), 3.17-3.25 (3H, m), 3.28 (3H, s), 3.45-3.65 (3H, m), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, dd), 3.96-3.99 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 4.73-7.76 (1H, t), 6.81 (1H, s), 6.84-6.87 (1H, t), 8.00-8.04 (1H, dd), 8.05-8.08 (1H, dd), 8.27-8.32 (1H, t), 8.63-8.64 (1H, d).

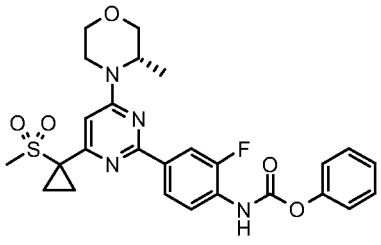
mTOR Kinase Assay (Echo): 0.0296μM

Example 52d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.19-3.26 (1H, td), 3.29 (3H, s), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.80 (3H, s), 3.96-3.99 (1H, dd), 4.22-4.25 (1H, d), 4.58 (1H, bs), 6.83 (1H, s), 7.40 (1H, s), 7.79 (1H, s), 8.04-8.08 (1H, dd), 8.09-8.12 (1H, dd), 8.28-8.33 (1H, t), 8.67-8.68 (1H, d), 8.81 (1H, s).

mTOR Kinase Assay (Echo): 0.0107μM

The preparation of phenyl *N*-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate



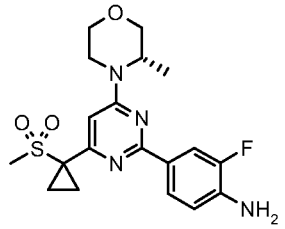
Phenyl chloroformate (0.116 mL, 0.93 mmol) was added to 2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (0.376 g, 0.93 mmol) and sodium hydrogen carbonate (0.117 g, 1.39 mmol) in dioxane (10 mL) and the

resulting solution stirred at RT for 2 hours. Water was added and the solution was extracted with DCM. The organics were dried ($MgSO_4$), filtered and evaporated. The residue was triturated with diethyl ether to give the desired material as a white solid (0.427 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.27-1.60 (2H, q), 1.68-1.70 (2H, q), 3.19-3.27 (1H, td), 3.28 (3H, s), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.23-4.26 (1H, d), 4.59 (1H, bs), 6.87 (1H, s), 7.24-7.30 (3H, m), 7.43-7.47 (2H, t), 7.87-7.91 (1H, t), 8.08-8.18 (2H, dd), 10.15 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=527; HPLC tR=2.93 min.

2-Fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline



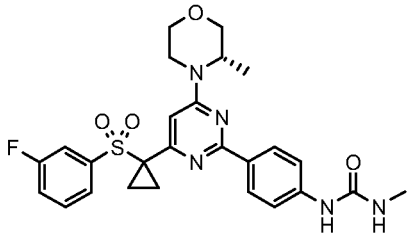
Bis(triphenylphosphine)palladium(II) chloride (0.031 g, 0.04 mmol) was added in one portion to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine (0.297 g, 0.90 mmol), 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.319 g, 1.34 mmol) and an aqueous solution of sodium carbonate (2.24 mL, 4.48 mmol) in a solvent mixture of 18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol. The resulting solution was stirred at 80°C under a nitrogen atmosphere for 30 minutes. The solvent was removed and the residue partitioned between water and ethyl acetate. The organic layer was dried ($MgSO_4$), filtered and purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material as a brown gum (0.376 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.31-1.33 (3H, d), 1.52-1.55 (2H, q), 1.81-1.84 (2H, q), 3.08 (3H, s), 3.26-3.33 (1H, td), 3.54-3.60 (1H, td), 3.70-3.73 (1H, dd), 3.79-3.80 (1H, d), 4.00-4.03 (3H, m), 4.13 (1H, bs), 4.46-4.47 (1H, bs), 6.72 (1H, s), 6.76-6.80 (1H, t), 7.99-8.02 (2H, m).

LCMS Spectrum: m/z (ES+)(M+H)+=407; HPLC tR=2.29 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine was described earlier.

Example 53: 1-[4-[4-[1-(3-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

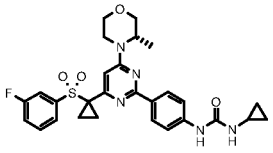
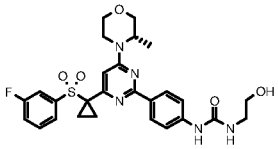
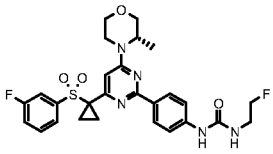
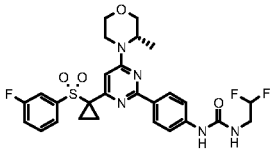


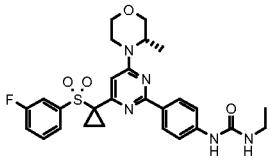
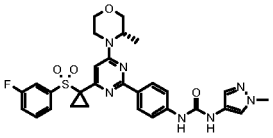
Methylamine (26.4 mg, 0.85 mmol) was added to phenyl *N*-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) in NMP (2 mL). The resulting solution was heated at 50°C for 2 days. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents, to give the desired material as a white solid (41 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.65 (2H, m), 1.94 (2H, m), 2.67 (4H, m), 3.46 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.14 (1H, m), 4.44 (1H, m), 6.05 (1H, m), 6.65 (1H, s), 7.40 (2H, m), 7.63 (4H, m), 7.82 (2H, m), 8.72 (1H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 526; HPLC tR = 2.07 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
53a		3-cyclopropyl-1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	552	2.28
53b		1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	556	1.97
53c		3-(2-fluoroethyl)-1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	558	2.27
53d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	576	2.39

Example	Structure	NAME	LCMS MH+	Retention time (min)
53e		1-ethyl-3-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	540	2.27
53f		1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	592	2.20

Example 53a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.43 (2H, m), 0.66 (2H, m), 1.19 (3H, d), 1.65 (2H, m), 1.94 (2H, m), 2.56 (1H, m), 3.16 (1H, m), 3.46 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.14 (1H, m), 4.44 (1H, m), 6.41 (1H, m), 6.65 (1H, s), 7.40 (2H, m), 7.62 (4H, m), 7.82 (2H, m), 8.52 (1H, s)

Example 53b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.65 (2H, m), 1.93 (2H, m), 3.18 (3H, m), 3.46 (3H, m), 3.62 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.15 (1H, m), 4.43 (1H, m), 4.74 (1H, m), 6.23 (1H, m), 6.65 (1H, s), 7.39 (2H, m), 7.63 (4H, m), 7.83 (2H, m), 8.78 (1H, s)

Example 53c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.65 (2H, m), 1.93 (2H, m), 3.16 (1H, m), 3.43 (3H, m), 3.62 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.43 (2H, m), 4.54 (1H, m), 6.42 (1H, m), 6.66 (1H, s), 7.40 (2H, m), 7.63 (4H, m), 7.83 (2H, m), 8.79 (1H, s)

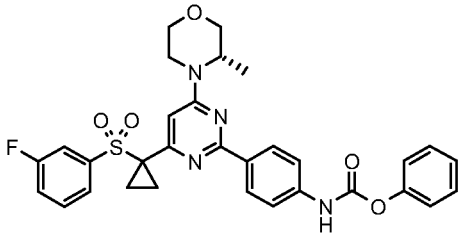
Example 53d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.65 (2H, m), 1.94 (2H, m), 3.16 (1H, m), 3.53 (4H, m), 3.75 (1H, m), 3.96 (1H, m), 4.15 (1H, m), 4.45 (1H, m), 6.07 (1H, m), 6.53 (1H, m), 6.66 (1H, s), 7.41 (2H, m), 7.63 (4H, m), 7.84 (2H, m), 8.91 (1H, s)

Example 53e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.19 (3H, d), 1.65 (2H, m), 1.94 (2H, m), 3.13 (3H, m), 3.47 (1H, m), 3.62 (1H, m), 3.74 (1H, m), 3.96 (1H, m), 4.13 (1H, m), 4.44 (1H, m), 6.14 (1H, m), 6.65 (1H, s), 7.39 (2H, m), 7.63 (4H, m), 7.82 (2H, m), 8.64 (1H, s)

Example 53f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.65 (2H, m), 1.95 (2H, m), 3.17 (1H, m), 3.47 (1H, m), 3.62 (1H, m), 3.78 (4H, m), 3.97 (1H, m), 4.15 (1H, m), 4.45 (1H, m), 6.66 (1H, s), 7.42 (3H, m), 7.65 (4H, m), 7.77 (1H, s), 7.86 (2H, d), 8.38 (1H, s), 8.81 (1H, s)

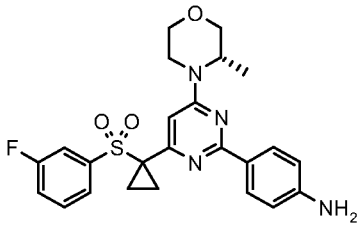
The preparation of phenyl *N*-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamateis described below:

Phenyl *N*-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.206 mL, 1.64 mmol) was added dropwise to 4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (770 mg, 1.64 mmol) and sodium bicarbonate (138 mg, 1.64 mmol) in dioxane (30 mL). The resulting solution was stirred at RT for 3 hours. The reaction mixture was filtered and the precipitate collected and redissolved in DCM (100 mL). This was washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as a yellow gum (722 mg).
NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.65 (2H, m), 1.95 (2H, m), 3.17 (1H, m), 3.46 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.46 (1H, m), 6.70 (1H, s), 7.27 (3H, m), 7.55 (8H, m), 7.92 (2H, m), 10.40 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 589; HPLC tR = 3.02 min.

4-[4-[1-(3-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

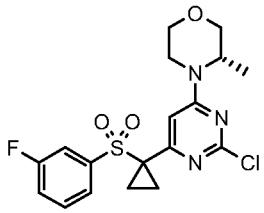


1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.747 g, 1.03 mmol) was added to 2-chloro-4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.25 g, 10.32 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.487 g, 11.35 mmol) in DME (200 mL) and sodium carbonate (5.47 g, 51.59 mmol) in water (25 mL) under nitrogen. The resulting solution was stirred at 80°C for 5 hours. The reaction mixture was diluted with DCM (200 mL), and washed sequentially with water (200 mL) and saturated brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to afford crude product as a yellow gum. The crude product was further purified by flash silica chromatography, elution gradient 0 to 5% ethyl acetate in DCM, to give the desired material as a yellow gum (2.86 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.63 (2H, m), 1.92 (2H, m), 3.12 (1H, m), 3.45 (1H, m), 3.60 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.11 (1H, m), 4.40 (1H, s), 5.52 (2H, s), 6.50 (2H, m), 6.57 (1H, m), 7.63 (6H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 469; HPLC tR = 2.35 min.

2-Chloro-4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



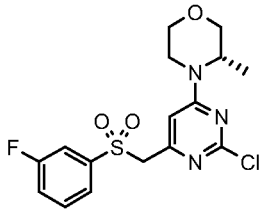
Sodium hydroxide (24.80 g, 620.07 mmol) in water (24.8 mL) was added to 2-chloro-4-[(3-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.35 g, 11.27 mmol), 1,2-dibromoethane (2.91 mL, 33.82 mmol) and tetrabutylammonium bromide (0.363

g, 1.13 mmol) in toluene (200 mL). The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was diluted with DCM (200 mL), and washed twice with water (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a white solid (4.25 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.63 (2H, m), 1.94 (2H, m), 3.18 (1H, m), 3.45 (1H, m), 3.60 (1H, m), 3.74 (1H, m), 3.97 (2H, m), 4.32 (1H, m), 6.76 (1H, s), 7.69 (4H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 412; HPLC tR = 2.27 min.

2-Chloro-4-[(3-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



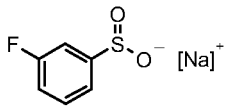
2-Chloro-4-(iodomethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (7 g, 19.80 mmol) was added to sodium 3-fluorobenzenesulfinate (5.41 g, 29.70 mmol) in acetonitrile (100 mL) under nitrogen. The resulting suspension was stirred at 80°C for 3 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (200 mL), and washed sequentially with water (200 mL) and saturated brine (200 mL). The organic layer was dried over MgSO4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% ethyl acetate in DCM, to give the desired material as a white solid (6.38 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 3.16 (1H, m), 3.43 (1H, m), 3.58 (1H, m), 3.73 (1H, m), 3.93 (2H, m), 4.18 (1H, m), 4.71 (2H, s), 6.74 (1H, s), 7.68 (4H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 386; HPLC tR = 2.06 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

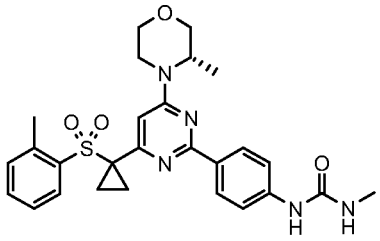
Sodium 3-fluorobenzenesulfinate



A solution of sodium sulphite (7.77 g, 61.66 mmol) in water (60 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (10.36 g, 123.32 mmol) was added and the resulting solution was stirred at 50°C for 1 hour. 3-Fluorobenzene-1-sulfonyl chloride (8.20 mL, 61.66 mmol) was added dropwise and the resulting solution was stirred at 50°C for 20 hours. The reaction mixture was evaporated to dryness and redissolved in MeOH. The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford the desired material (12.60 g) as a white solid, which was air dried overnight under vacuum and used without further purification.

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 7.03 (1H, m), 7.21 (1H, m), 7.29 (1H, m), 7.36 (1H, m)

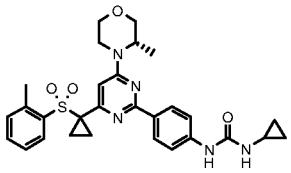
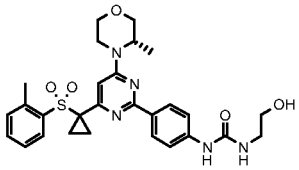
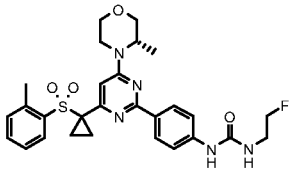
Example 54: 3-Methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea

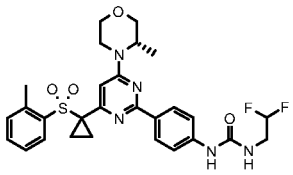
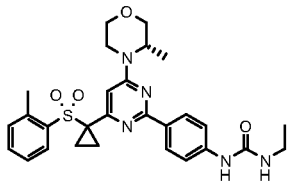
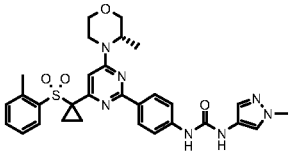


Methylamine (37.27 mg, 1.2 mmol) was added to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate (140 mg, 0.24 mmol) and triethylamine (0.2 mLl, 0.72 mmol) in NMP (2 mL). The resulting solution was heated at 50°C for 2 days. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material (87 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.66 (2H, m), 1.86 (2H, m), 2.45 (3H, s), 2.66 (3H, m), 3.12 (1H, m), 3.45 (1H, m), 3.60 (1H, m), 3.74 (1H, m), 3.94 (1H, m), 4.06 (1H, m), 4.39 (1H, m), 6.05 (1H, m), 6.60 (1H, s), 7.37 (4H, m), 7.51 (1H, m), 7.85 (3H, m), 8.71 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 522; HPLC tR = 2.29 min.The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
54a		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	548	2.47
54b		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	552	2.09
54c		3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	554	2.42

Example	Structure	NAME	LCMS MH+	Retention time (min)
54d		3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	572	2.56
54e		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	536	2.45
54f		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	588	2.31

Example 54a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.42 (2H, m), 0.65 (2H, m), 1.15 (3H, d), 1.66 (2H, m), 1.86 (2H, m), 2.46 (3H, s), 2.56 (1H, m), 3.13 (1H, m), 3.44 (1H, m), 3.59 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.07 (1H, m), 4.39 (1H, m), 6.42 (1H, m), 6.60 (1H, s), 7.37 (4H, m), 7.51 (1H, m), 7.84 (3H, m), 8.51 (1H, s)

Example 54b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.66 (2H, m), 1.86 (2H, m), 2.46 (3H, s), 3.14 (3H, m), 3.45 (3H, m), 3.59 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.07 (1H, m), 4.38 (1H, m), 4.74 (1H, t), 6.24 (1H, m), 6.60 (1H, s), 7.36 (4H, m), 7.51 (1H, m), 7.84 (3H, m), 8.77 (1H, s)

Example 54c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.66 (2H, m), 1.86 (2H, m), 2.45 (3H, s), 3.12 (1H, m), 3.43 (3H, m), 3.60 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.07 (1H, m), 4.40 (2H, m), 4.54 (1H, m), 6.42 (1H, m), 6.61 (1H, s), 7.37 (4H, m), 7.51 (1H, m), 7.85 (3H, m), 8.78 (1H, s)

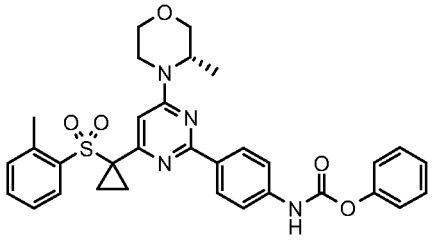
Example 54d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.66 (2H, m), 1.86 (2H, m), 2.46 (3H, s), 3.11 (1H, m), 3.51 (4H, m), 3.75 (1H, m), 3.95 (1H, m), 4.07 (1H, m), 4.39 (1H, m), 6.08 (1H, m), 6.52 (1H, m), 6.61 (1H, s), 7.38 (4H, m), 7.51 (1H, m), 7.85 (3H, m), 8.89 (1H, s)

Example 54e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.15 (3H, d), 1.66 (2H, m), 1.85 (2H, m), 2.45 (3H, s), 3.12 (3H, m), 3.44 (1H, m), 3.60 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.06 (1H, m), 4.39 (1H, m), 6.15 (1H, m), 6.60 (1H, s), 7.37 (4H, m), 7.51 (1H, m), 7.84 (3H, m), 8.63 (1H, s)

Example 54f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.66 (2H, m), 1.86 (2H, m), 2.46 (3H, s), 3.12 (1H, m), 3.45 (1H, m), 3.60 (1H, m), 3.74 (1H, m), 3.80 (3H, s), 3.95 (1H, m), 4.07 (1H, m), 4.39 (1H, m), 6.61 (1H, s), 7.43 (6H, m), 7.80 (2H, m), 7.90 (2H, m), 8.37 (1H, s), 8.80 (1H, s)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl N-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate



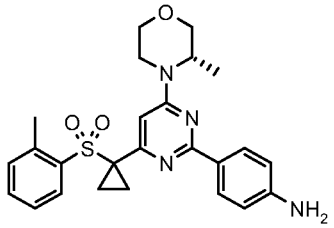
Phenyl chloroformate (0.205 mL, 1.64 mmol) was added dropwise to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]aniline (760 mg, 1.64 mmol) and sodium bicarbonate (151 mg, 1.80 mmol) in dioxane (30 mL). The resulting suspension was stirred at RT for 3 hours. The reaction mixture was filtered and the precipitate was redissolved in DCM (50 mL), and washed sequentially with water (50 mL)

and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as a yellow gum (985 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.67 (2H, m), 1.87 (2H, m), 2.47 (3H, s), 3.12 (1H, m), 3.45 (1H, m), 3.61 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.08 (1H, m), 4.40 (1H, m), 6.64 (1H, s), 7.30 (5H, m), 7.49 (5H, m), 7.81 (1H, m), 7.95 (2H, m), 10.39 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 585; HPLC tR = 3.08 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]aniline

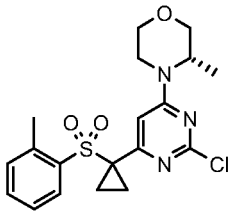


A solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidine (2.04 g, 5.00 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.205 g, 5.50 mmol) and sodium carbonate (2.120 g, 20.00 mmol) in DME (60 mL) and water (15.00 mL) was stirred under nitrogen for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (0.351 g, 0.50 mmol) was added and the resulting solution was stirred at 80°C for 2 hours. The reaction mixture was diluted with DCM (200 mL), and washed with water (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give the desired material as a yellow oil which solidified on standing (2.14 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.69 (2H, m), 1.87 (2H, m), 2.51 (3H, s), 3.12 (1H, m), 3.47 (1H, m), 3.63 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.08 (1H, m), 4.39 (1H, m), 5.56 (2H, s), 6.54 (3H, m), 7.39 (2H, m), 7.56 (1H, m), 7.77 (2H, m), 7.87 (1H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 465; HPLC tR = 2.41 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidine

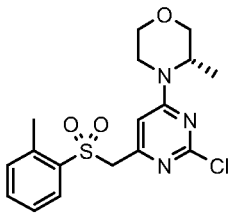


Sodium hydroxide (12.67 g, 317 mmol) in water (12.7 mL) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(2-methylphenyl)sulfonylmethyl]pyrimidine (2.2 g, 5.76 mmol), 1,2-dibromoethane (1.489 mL, 17.28 mmol) and tetrabutylammonium bromide (0.186 g, 0.58 mmol) in toluene (80 mL). The resulting solution was stirred at 60°C for 1 hour. The reaction mixture was diluted with DCM (200 mL), and washed sequentially with water (200 mL) and saturated brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a colourless gum which solidified on standing (2.04 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.63 (2H, m), 1.86 (2H, m), 2.48 (3H, s), 3.14 (1H, m), 3.42 (1H, m), 3.58 (1H, m), 3.74 (1H, m), 3.95 (2H, m), 4.25 (1H, m), 6.70 (1H, s), 7.43 (2H, m), 7.63 (1H, m), 7.79 (1H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 408; HPLC tR = 2.44 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(2-methylphenyl)sulfonylmethyl]pyrimidine



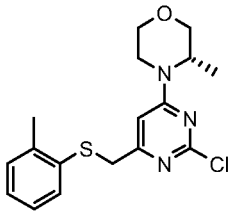
2N sulfuric acid (0.352 mL) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(2-methylphenyl)sulfanylmethyl]pyrimidine (4.37 g, 12.49 mmol) in dioxane (110 mL) and the solution heated to 55°C. Sodium tungstate dihydrate (0.082 g, 0.25 mmol) in water (3.5 mL) was added and the solution was allowed to stir for 5 minutes. Hydrogen peroxide (7.65 mL, 74.94 mmol) was added dropwise to the solution. The resulting solution was stirred at 55°C for 5 hours. The reaction was cooled to RT then water added until precipitation ceased. The

precipitate was collected by filtration, washed with water and dried under vacuum to afford the desired material as a white solid (3.70 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.16 (3H, d), 2.63 (3H, s), 3.14 (1H, m), 3.42 (1H, m), 3.56 (1H, m), 3.72 (1H, m), 3.93 (2H, m), 4.18 (1H, s), 4.59 (2H, s), 6.67 (1H, s), 7.44 (2H, m), 7.65 (2H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 382; HPLC tR = 2.23 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(2-methylphenyl)sulfanylmethyl]pyrimidine



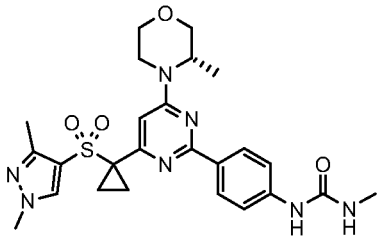
DIPEA (3.70 mL, 21.21 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (5 g, 14.14 mmol) and 2-methylbenzenethiol (2.5 mL, 21.21 mmol) in THF (80 mL). The resulting slurry was stirred at RT for 18 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% ethyl acetate in isohexane, to give the desired material as a yellow gum (4.37 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (3H, d), 2.28 (3H, s), 3.11 (1H, m), 3.40 (1H, m), 3.55 (1H, m), 3.69 (1H, m), 3.90 (2H, m), 4.04 (2H, m), 4.21 (1H, m), 6.65 (1H, s), 7.18 (3H, m), 7.37 (1H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 350; HPLC tR = 2.71 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 55: 1-[4-[4-[1-(1,3-Dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

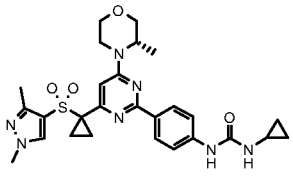


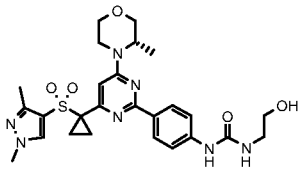
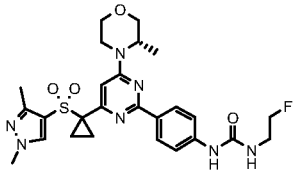
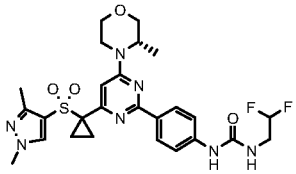
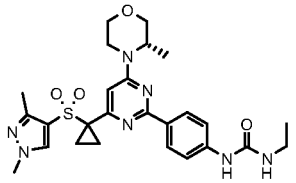
Methylamine (26.4 mg, 0.85 mmol) was added to phenyl *N*-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) and triethylamine (0.2 mL, 0.72 mmol) in NMP (2 mL). The resulting solution was heated at 50°C for 2 days. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material (77 mg).

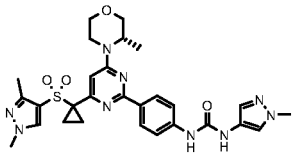
NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.54 (2H, m), 1.74 (2H, m), 2.03 (3H, s), 2.67 (3H, m), 3.20 (1H, m), 3.48 (1H, m), 3.63 (1H, m), 3.77 (4H, m), 3.98 (1H, m), 4.13 (1H, m), 4.46 (1H, m), 6.06 (1H, m), 6.70 (1H, s), 7.45 (2H, d), 7.98 (2H, d), 8.18 (1H, s), 8.72 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 526; HPLC tR = 1.87 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
55a		3-cyclopropyl-1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	552	2.02

Example	Structure	NAME	LCMS MH+	Retention time (min)
55b		1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	556	1.71
55c		1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	558	2.00
55d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	576	2.13
55e		3-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	540	2.00

Example	Structure	NAME	LCMS MH+	Retention time (min)
55f		1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	592	1.92

Example 55a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.42 (2H, m), 0.65 (2H, m), 1.20 (3H, d), 1.54 (2H, m), 1.74 (2H, m), 2.03 (3H, s), 2.56 (1H, m), 3.18 (1H, m), 3.48 (1H, m), 3.63 (1H, m), 3.76 (4H, m), 3.98 (1H, m), 4.14 (1H, m), 4.45 (1H, m), 6.42 (1H, m), 6.70 (1H, s), 7.46 (2H, m), 7.99 (2H, m), 8.19 (1H, s), 8.53 (1H, s)

Example 55b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.54 (2H, m), 1.73 (2H, m), 2.03 (3H, s), 3.18 (3H, m), 3.47 (3H, m), 3.63 (1H, m), 3.76 (4H, m), 3.98 (1H, m), 4.14 (1H, m), 4.46 (1H, m), 4.74 (1H, t), 6.25 (1H, m), 6.70 (1H, s), 7.44 (2H, d), 7.98 (2H, d), 8.19 (1H, s), 8.79 (1H, s)

Example 55c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.54 (2H, m), 1.74 (2H, m), 2.03 (3H, s), 3.18 (2H, m), 3.39 (1H, m), 3.46 (2H, m), 3.63 (1H, m), 3.76 (4H, m), 3.98 (1H, m), 4.14 (1H, m), 4.49 (2H, m), 6.43 (1H, m), 6.70 (1H, s), 7.46 (2H, d), 7.99 (2H, d), 8.18 (1H, s), 8.80 (1H, s)

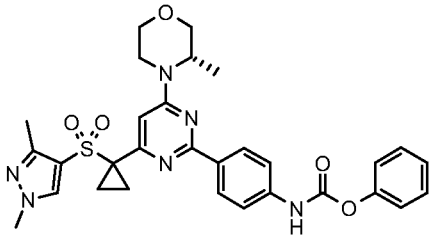
Example 55d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.55 (2H, m), 1.74 (2H, m), 2.02 (3H, s), 3.17 (1H, m), 3.54 (4H, m), 3.76 (4H, m), 3.97 (1H, m), 4.14 (1H, m), 4.47 (1H, m), 6.08 (1H, m), 6.52 (1H, m), 6.71 (1H, s), 7.46 (2H, m), 8.01 (2H, m), 8.19 (1H, s), 8.90 (1H, s)

Example 55e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.20 (3H, d), 1.54 (2H, m), 1.74 (2H, m), 2.03 (3H, s), 3.15 (3H, m), 3.48 (1H, m), 3.63 (1H, m), 3.76 (4H, m), 3.98 (1H, m), 4.13 (1H, m), 4.46 (1H, m), 6.16 (1H, m), 6.70 (1H, s), 7.45 (2H, d), 7.98 (2H, d), 8.19 (1H, s), 8.65 (1H, s)

Example 55f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.54 (2H, m), 1.74 (2H, m), 2.04 (3H, s), 3.18 (1H, m), 3.49 (1H, m), 3.63 (1H, m), 3.77 (7H, m), 3.98 (1H, m), 4.15 (1H, m), 4.47 (1H, m), 6.71 (1H, s), 7.39 (1H, s), 7.50 (2H, d), 7.77 (1H, s), 8.02 (2H, d), 8.19 (1H, s), 8.38 (1H, s), 8.82 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

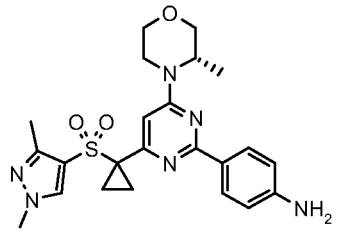


Phenyl chloroformate (0.201 mL, 1.60 mmol) was added dropwise to 4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (750mg, 1.60 mmol) and sodium bicarbonate (148 mg, 1.76 mmol) in dioxane (30 mL). The resulting suspension was stirred at RT for 3 hours. The reaction mixture was filtered and the precipitate was redissolved in DCM (50 mL), and washed sequentially with water (50 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as an orange gum which formed a foam solid when heated in desiccator (1.030 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.55 (2H, m), 1.75 (2H, m), 2.04 (3H, s), 3.20 (1H, m), 3.49 (1H, m), 3.63 (1H, m), 3.76 (4H, m), 3.98 (1H, m), 4.16 (1H, m), 4.48 (1H, m), 6.75 (1H, s), 7.28 (3H, m), 7.45 (2H, m), 7.59 (2H, m), 8.07 (2H, m), 8.20 (1H, s), 10.43 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 589; HPLC tR = 2.63 min.

4-[4-[1-(1,3-Dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

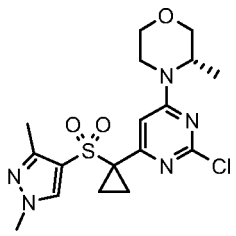


A solution of 2-chloro-4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.44 g, 5.92 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.428 g, 6.52 mmol) and sodium carbonate (2.51 g, 23.69 mmol) in DME (60 mL) and water (15 mL) was stirred under nitrogen for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (0.416 g, 0.59 mmol) was added and the resulting solution was stirred at 80°C for 5 hours. The reaction mixture was diluted with DCM (200 mL), and washed sequentially with water (200 mL) and saturated brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 1% MeOH in DCM, to give crude product. The crude product was further purified by ion exchange chromatography using an SCX column, eluting with 2M ammonia in methanol, to give the desired material as a orange solid (1.25 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.52 (2H, m), 1.72 (2H, m), 2.04 (3H, s), 3.15 (1H, m), 3.47 (1H, m), 3.61 (1H, m), 3.75 (4H, m), 3.97 (1H, m), 4.09 (1H, m), 4.42 (1H, m), 5.52 (2H, s), 6.57 (3H, m), 7.82 (2H, m), 8.17 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 469; HPLC tR = 1.87 min.

2-Chloro-4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

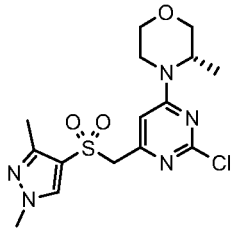


Sodium hydroxide (14.54 g, 363.47 mmol) in water (14.5 mL) was added to a stirred solution of 2-chloro-4-[(1,3-dimethylpyrazol-4-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.55 g, 6.61 mmol), 1,2-dibromoethane (1.708 mL, 19.83 mmol) and tetrabutylammonium bromide (0.213 g, 0.66 mmol) in toluene (100 mL).The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was diluted with DCM (200 mL), and washed sequentially with water (200 mL) and saturated brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material as a white solid (2.44 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.48 (2H, m), 1.70 (2H, m), 2.05 (3H, s), 3.17 (1H, m), 3.42 (1H, m), 3.57 (1H, m), 3.72 (1H, m), 3.80 (3H, s), 3.93 (2H, m), 4.30 (1H, m), 6.77 (1H, s), 8.20 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 412; HPLC tR = 1.69 min.

2-Chloro-4-[(1,3-dimethylpyrazol-4-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



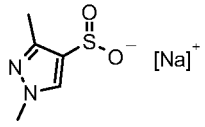
2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (5 g, 14.14 mmol) was added to sodium 1,3-dimethyl-1*H*-pyrazole-4-sulfinate (4.79 g, 26.29 mmol) in DMF (80 mL). The resulting solution was stirred at RT for 18 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a white solid (4.55 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 2.13 (3H, s), 3.18 (1H, m), 3.44 (1H, m), 3.58 (1H, m), 3.73 (1H, m), 3.80 (3H, s), 3.94 (2H, m), 4.22 (1H, s), 4.46 (2H, s), 6.72 (1H, s), 8.14 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 386; HPLC tR = 1.63 min.

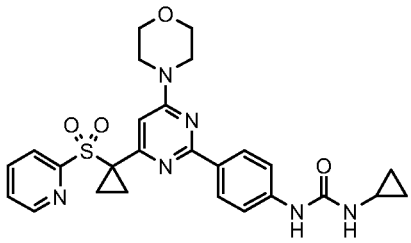
The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Sodium 1,3-dimethyl-1*H*-pyrazole-4-sulfinate



A solution of sodium sulfite (2.82 g, 22.35 mmol) in water (30 mL) was stirred for 10 minutes at RT. Sodium bicarbonate (3.75 g, 44.70 mmol) was added and the solution was stirred for 1 hour at 50°C. 1,3-Dimethyl-1*H*-pyrazole-4-sulfonyl chloride (4.35 g, 22.35 mmol) was added portionwise and the resulting solution was stirred at 50°C for 18 hours. The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford the desired material as a white solid, which was air dried overnight under vacuum and used without further purification (4.79 g).

Example 56: 3-Cyclopropyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



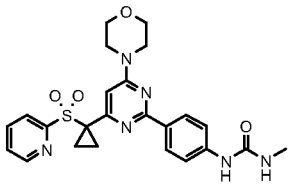
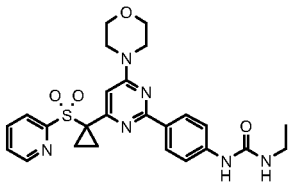
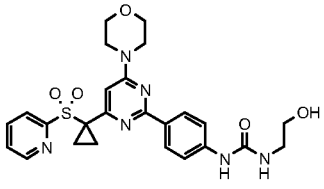
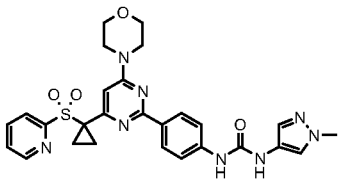
A solution of phenyl *N*-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (0.100g, 0.18mmol), cycloprpylamine (0.90 mmol) and triethylamine (0.076 mL, 0.54 mmol) in NMP (2 mL) was heated at 50°C for 16 hours. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a solid (75 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.67 (2H, m), 1.71-1.74 (2H, q), 1.98-2.01 (2H, q), 2.54-2.58 (1H, m), 3.63-3.65 (4H, m), 3.68-3.70 (4H,

m), 6.40-6.41 (1H, d), 6.71 (1H, s), 7.35-7.37 (2H, d), 7.68-7.70 (2H, d), 7.73-7.76 (1H, m), 7.96-7.99 (1H, dt), 8.06-8.10 (1H, td), 8.49 (1H, s), 8.82-8.83 (1H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 521; HPLC tR = 1.99min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
56a		3-methyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	495	1.82
56b		3-ethyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	509	1.96
56c		3-(2-hydroxyethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	525	1.65
56d		3-(1-methylpyrazol-4-yl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	561	1.88

Example 56a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.70-1.74 (2H, q), 1.98-2.01 (2H, q), 2.65-2.66 (3H, d), 3.63-3.65 (4H, m), 3.68-3.70 (4H, m), 6.02-6.06 (1H, q), 6.71 (1H, s), 7.34-7.37 (2H, d), 7.67-7.70 (2H, d), 7.73-7.76 (1H, m), 7.96-7.98 (1H, dt), 8.06-8.10 (1H, td), 8.69 (1H, s), 8.82-8.84 (1H, m).

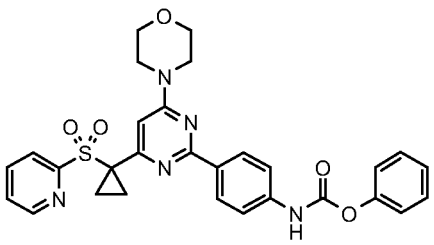
Example 56b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.70-1.73 (2H, q), 1.98-2.01 (2H, q), 3.09-3.16 (2H, m), 3.63-3.64 (4H, m), 3.68-3.69 (4H, m), 6.12-6.15 (1H, t), 6.71 (1H, s), 7.33-7.36 (2H, d), 7.67-7.70 (2H, d), 7.73-7.76 (1H, m), 7.96-7.99 (1H, dt), 8.06-8.10 (1H, td), 8.61 (1H, s), 8.82-8.83 (1H, m).

Example 56c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.70-1.74 (2H, q), 1.98-2.01 (2H, q), 3.15-3.19 (2H, m), 3.44-3.48 (2H, m), 3.63-3.65 (4H, m), 3.68-3.69 (4H, m), 4.71-4.74 (1H, t), 6.23-6.24 (1H, t), 6.71 (1H, s), 7.33-7.35 (2H, d), 7.68-7.70 (2H, d), 7.73-7.76 (1H, m), 7.96-7.99 (1H, dt), 8.06-8.10 (1H, td), 8.76 (1H, s), 8.82-8.84 (1H, m).

Example 56d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.71-1.74 (2H, q), 1.99-2.02 (2H, q), 3.64-3.66 (4H, m), 3.68-3.71 (4H, m), 3.79 (3H, s), 6.73 (1H, s), 7.38-7.41(3H m), 7.71-7.76 (4H, m), 7.97-7.99 (1H, dt), 8.07-8.11 (1H, td), 8.36 (1H, s), 8.79 (1H, s), 8.83-8.84 (1H, m).

The preparation of phenyl *N*-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate

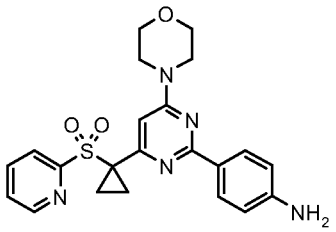


Phenyl chloroformate (0.363 mL, 2.89 mmol) was added to 4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (1.265 g, 2.89 mmol) and sodium hydrogen carbonate (0.364 g, 4.34 mmol) in DCM (50 mL) at RT and the resulting suspension stirred for 2 hours. The mixture was washed with water, dried over $MgSO_4$, filtered and evaporated and the resultant gum dried in the vacuum oven at 50°C overnight to give the desired material as a colorless gum (1.86 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.73-1.77 (2H, q), 1.99-2.03 (2H, q), 3.68-3.69(8H, m), 6.77 (1H, s), 7.24-7.32 (3H, m), 7.44-7.52 (4H, m), 7.74-7.77 (1H, m), 7.80-7.82 (2H, d), 7.98-8.01 (1H, dt), 8.07-8.11 (1H, td), 8.83-8.85 (1H, dq), 10.4 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=558; HPLC tR=2.75 min.

4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline

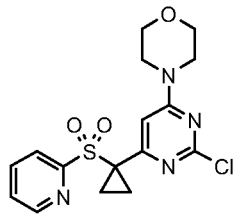


Bis(triphenylphosphine)palladium(II) chloride (0.131 g, 0.19 mmol) was added in one portion to 2-chloro-4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidine (1.42 g, 3.73 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.817 g, 3.73 mmol) and 2M aquoeus sodium carbonate solution (9.32 mL, 18.64 mmol) in a DMF solution (18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol) at 22ºC under nitrogen. The resulting solution was stirred at 80°C for 3 hours. The solvent was removed, ethyl acetate added and the organics washed with water. Precipitate was observed in the aqueous layer and was isolated by filtration to give crude product. This material was dissolved in DCM and insoluble material removed by filtration and discarded. The filtrate was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give material which was further purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a white solid (1.265 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.68-1.71 (2H, q), 1.96-2.00 (2H, q), 3.59-3.61 (4H, m), 3.66-3.69 (4H, m), 5.48-5.50 (1H, d (NH2), 6.45-6.47 (2H, d), 6.61 (1H, s), 7.52-7.54 (2H, d), 7.72-7.75 (1H, m), 7.96-7.98 (1H, dt), 8.05-8.10 (1H, td), 8.81-8.83 (1H, dq).

LCMS Spectrum: m/z (ES+)(M+H)+=438; HPLC tR=1.93 min.

2-Chloro-4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidine

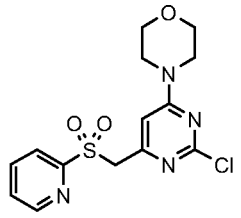


Sodium hydroxide (50%w/w solution) (12.71 g, 317.77 mmol) was added to 2-chloro-4-morpholin-4-yl-6-(pyridin-2-ylsulfonylmethyl)pyrimidine (2.050 g, 5.78 mmol), 1,2-dibromoethane (1.494 mL, 17.33 mmol) and tetrabutylammonium bromide (0.186 g, 0.58 mmol) in toluene (50 mL) at RT. The resulting suspension was stirred at 60°C overnight. Water was added and the layers were separated. The organic layer was washed twice with water, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (1.42 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.63-1.66 (2H, q), 1.91-1.95 (2H, q), 3.55 (4H, bs), 3.63-3.65 (4H, t), 6.84 (1H, s), 7.73-7.76 (1H, m), 7.98-8.00 (1H, dt), 8.10-8.14 (1H, td), 8.77-8.79 (1H, dt).

LCMS Spectrum: m/z (ES+)(M+H)+=381; HPLC tR=1.71 min.

2-Chloro-4-morpholin-4-yl-6-(pyridin-2-ylsulfonylmethyl)pyrimidine

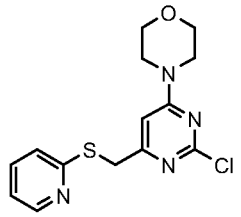


2-Chloro-4-morpholin-4-yl-6-(pyridin-2-ylsulfanylmethyl)pyrimidine (4.96 g, 15.36 mmol) was dissolved in dioxane (70 mL) and 2N sulfuric acid (0.362 mL) was added. The solution was heated to 55°C. Sodium tungstate dihydrate (0.101 g, 0.31 mmol) dissolved in water (3.54 mL) was added to the solution and allowed to stir for 10 minutes. Hydrogen peroxide (9.50 mL, 307.30 mmol) was then added dropwise over several minutes. The solution was heated at 55°C for 4 hours. Water (300mL) was added and the reaction was allowed to cool. The reaction mixture was extracted with DCM, the organic layer dried over $MgSO_4$, filtered and evaporated to afford desired product as a pale yellow solid (5.09g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 3.64 (3H, bs), 3.75-3.77(5H, t), 4.56 (2H, s), 6.60 (1H, s), 7.57-7.61 (1H, m), 7.97-7.97 (2H, m), 8.78-8.80 (1H, dt).

LCMS Spectrum: m/z (ES+)(M+H)+=355; HPLC tR=1.51 min.

2-Chloro-4-morpholin-4-yl-6-(pyridin-2-ylsulfanylmethyl)pyrimidine



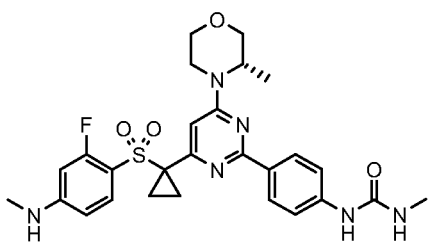
2-Chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine (6.60 g, 19.44 mmol) was added to 2-mercaptopyridine (3.24 g, 29.16 mmol) and DIPEA (5.08 mL, 29.16 mmol) in acetonitrile (140 mL) at RT. The resulting solution was stirred at RT for 2 hours then evaporated to dryness, redissolved in DCM and washed sequentially with water and saturated brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material as a beige oil which solidified on standing (4.96 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 3.52 (4H, bs), 3.64-3.67 (4H, t), 4.27 (2H, s), 6.58 (1H, s), 6.93-6.96 (1H, q), 7.11-7.13 (1H, dd), 7.41-7.45 (1H, td), 8.34-8.36 (1H, dt).

LCMS Spectrum: m/z (ES+)(M+H)+=323; HPLC tR=1.98 min.

The preparation of 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine was described earlier.

Example 57: 1-[4-[4-[1-(2-Fluoro-4-methylaminophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

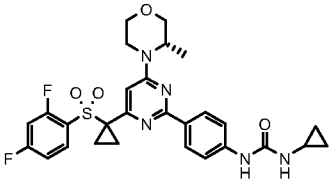
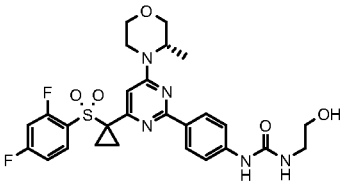


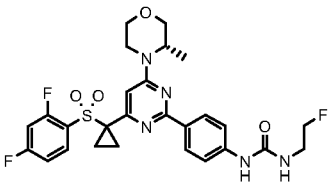
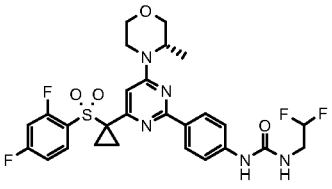
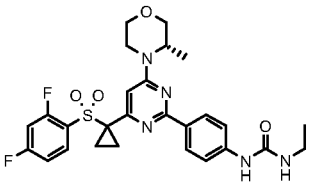
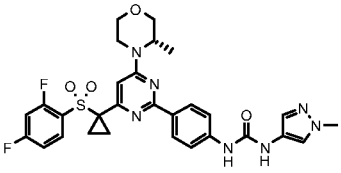
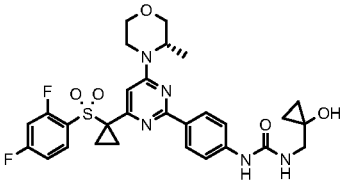
Phenyl *N*-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.15 g, 0.25 mmol), triethylamine (0.103 mL, 0.74 mmol) and methylamine solution (2M in THF, 1.236 mL, 2.47 mmol) were added to dioxane (10 mL) and heated at 50°C over the weekend. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (0.074 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.51 - 1.48 (2H, m), 1.82 - 1.78 (2H, m), 2.66 (3H, d), 3.14 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.06 (1H, d), 4.43 (1H, s), 6.04 (1H, q), 6.33 - 6.32 (1H, m), 6.38 (1H, dd), 6.43 (1H, ddd), 6.54 (1H, s), 7.47 (3H, m), 7.95 (2H, d), 8.72 (1H, s);

LCMS Spectrum: m/z (ES+)(M+H)+=555; HPLC tR=2.40 min.

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
57a		3-cyclopropyl-1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	570	2.51
57b		1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	573	1.96

Example	Structure	NAME	LCMS MH+	Retention time (min)
57c		1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	576	2.47
57d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	595	2.60
57e		3-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	558	2.48
57f		1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	610	2.35
57g		1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea	600	2.31

Example 57a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.43 - 0.40 (2H, m), 0.67 - 0.62 (2H, m), 1.19 (3H, d), 1.67 - 1.64 (2H, m), 1.91 - 1.89 (2H, m), 2.57 - 2.54 (1H, m), 3.16 (1H,

ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.46 (1H, s), 6.39 (1H, s), 6.69 (1H, s), 7.20 (1H, ddd), 7.38 (2H, d), 7.65 - 7.59 (1H, m), 7.77 - 7.72 (3H, m), 8.51 (1H, s).

Example 57b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.67 - 1.63 (2H, m), 1.91 - 1.87 (2H, m), 3.17 (3H, m), 3.48 - 3.42 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, d), 4.15 (1H, d), 4.46 (1H, s), 4.72 (1H, t), 6.22 (1H, t), 6.68 (1H, s), 7.20 (1H, ddd), 7.36 (2H, d), 7.65 - 7.60 (1H, m), 7.77 - 7.72 (3H, m), 8.78 (1H, s).

Example 57c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.67 - 1.64 (2H, m), 1.91 - 1.89 (2H, m), 3.16 (1H, ddd), 3.38 (1H, q), 3.49 - 3.43 (2H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.41 (1H, t), 4.47 (1H, s), 4.53 (1H, t), 6.40 (1H, t), 6.69 (1H, s), 7.20 (1H, ddd), 7.38 (2H, d), 7.65 - 7.60 (1H, m), 7.77 - 7.71 (3H, m), 8.79 (1H, s).

Example 57d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.67 - 1.64 (2H, m), 1.92 - 1.87 (2H, m), 3.16 (1H, ddd), 3.63 - 3.43 (4H, m), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.47 (1H, s), 6.07 (1H, ddt), 6.49 (1H, t), 6.69 (1H, s), 7.20 (1H, t), 7.39 (1H, d), 7.65 - 7.60 (1H, m), 7.76 - 7.71 (4H, m), 8.90 (1H, s).

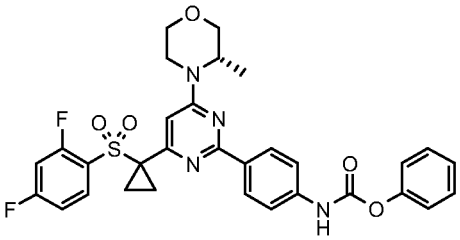
Example 57e: Spectrum not recorded.

Example 57f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.67 - 1.64 (2H, m), 1.92 - 1.90 (2H, m), 3.16 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.75 (1H, d), 3.79 (3H, s), 3.96 (1H, d), 4.16 (1H, d), 4.48 (1H, s), 6.70 (1H, s), 7.20 (1H, ddd), 7.38 (1H, s), 7.42 (2H, d), 7.66 - 7.61 (1H, m), 7.78 - 7.71 (4H, m), 8.34 (1H, s), 8.82 (1H, s).

Example 57g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.51 - 0.48 (2H, m), 0.60 - 0.57 (2H, m), 1.19 (3H, d), 1.67 - 1.62 (2H, m), 1.91 - 1.87 (2H, m), 3.22 (2H, d), 3.29 - 3.27 (1H, m), 3.46 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.17 - 4.14 (1H, m), 4.47 (1H, s), 6.29 (1H, t), 6.68 (1H, s), 7.20 (1H, t), 7.36 (2H, d), 7.63 (1H, t), 7.73 (3H, d), 8.78 (1H, s).

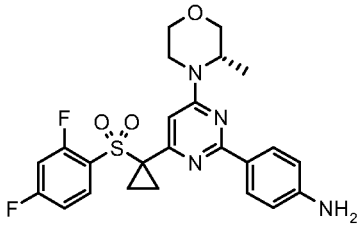
The preparation of phenyl *N*-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



4-[4-[1-(2,4-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (2.1 g, 4.32 mmol) and sodium bicarbonate (0.725 g, 8.63 mmol) were added to dioxane (50 mL) and stirred for 10 minutes. Phenyl chloroformate (0.704 mL, 5.61 mmol) was added slowly and the reaction was stirred for 1 hour. The reaction mixture was quenched with 1.0 N citric acid (50 mL), extracted with ethyl acetate (3 x 75 mL), the organic layer was dried over MgSO4, filtered and evaporated to afford an orange solid. This was dissolved in DCM, the solvent was slowly removed until a solid was observed. Diethyl ether was then added to the solution with rapid stirring to afford the desired material as a white solid (1.65 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.69 - 1.66 (2H, m), 1.92 - 1.89 (2H, m), 3.18 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.36 - 4.10 (1H, m), 4.55 - 4.44 (1H, m), 6.75 (1H, s), 7.30 - 7.18 (4H, m), 7.47 - 7.43 (2H, m), 7.54 (2H, d), 7.64 (1H, t), 7.78 - 7.72 (1H, m), 7.85 (2H, d), 10.43 (1H, s).
LCMS Spectrum: m/z (ESI+) (M+H)+ = 607; HPLC tR = 2.97 min

4-[4-[1-(2,4-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



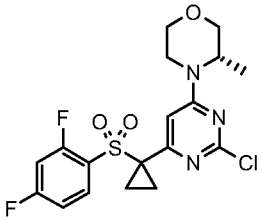
2-Chloro-4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.61 g, 8.40 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.208 g, 10.08 mmol), sodium carbonate (4.45 g, 41.99 mmol) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.608 g, 0.84 mmol) were added to

DME (60.0 mL) and water (15 mL) and heated to 90°C over a period of 2 hours under nitrogen. The solvent was evaporated and the residue was quenched water (100 mL), extracted with ethyl acetate (3 x 75 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford a black gum. The crude product was purified by flash silica chromatography, elution gradient 40 to 100% ethyl acetate in isohexane, to give the desired material as a yellow gum (2.2 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.29 (3H, d), 1.58 - 1.55 (1H, m), 1.66 - 1.62 (1H, m), 2.11 - 2.04 (2H, m), 3.26 (1H, ddd), 3.57 (1H, ddd), 3.72 (1H, dd), 3.80 (1H, d), 3.86 (2H, s), 4.02 (1H, dd), 4.11 (1H, m), 4.43 - 4.36 (1H, m), 6.60 (2H, d), 6.65 (1H, s), 6.86 - 6.82 (1H, m), 6.91 (1H, ddd), 7.75 - 7.69 (1H, m), 7.85 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 487; HPLC tR = 2.56 min.

2-Chloro-4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

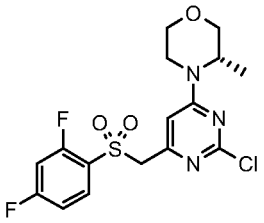


Sodium hydroxide (50%w/w solution) (32.7 g, 817.17 mmol) was added to 2-chloro-4-[(2,4-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (6.0 g, 14.86 mmol), 1,2-dibromoethane (3.84 mL, 44.57 mmol) and tetrabutylammonium bromide (0.479 g, 1.49 mmol) in toluene (75 mL) at RT. The resulting suspension was stirred at 60°C overnight. Water (100 mL) was added and the mixture was extracted with ethyl acetate (3 x 100 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give a crude material which was dissolved in hot diethyl ether and then stirred for 2 hours to afford the desired material as a white solid (3.61 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.30 (3H, d), 1.56 - 1.52 (1H, m), 1.62 - 1.59 (1H, m), 2.10-2.00 (2H, m), 3.26 (1H, ddd), 3.53 (1H, ddd), 3.68 (1H, dd), 3.78 (1H, d), 4.00 (2H, dd), 4.26 (1H, s), 6.81 (1H, s), 6.99 - 6.90 (2H, m), 7.77 - 7.71 (1H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 430; HPLC tR = 2.48 min

2-Chloro-4-[(2,4-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



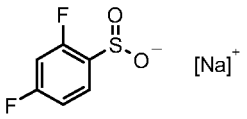
2,4-Difluorobenzenesulfinic acid, sodium salt (3.98 g, 19.80 mmol) and 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7 g, 19.80 mmol) were dissolved in DMF (50 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a brown gun, this was quenched with saturated aqueous ammonium chloride solution (50 mL), extracted with diethyl ether (3 x 75 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford a brown solid. The crude material was passed through a plug of silica, eluting with 80% ethyl acetate in isohexane, to give crude material which was triturated with diethyl ether to give the desired material as a white solid (7.04 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.32 (3H, d), 3.28 (1H, ddd), 3.54 (1H, ddd), 3.69 (1H, dd), 3.79 (1H, d), 4.03 - 3.99 (2H, m), 4.28 (1H, s), 4.43 (2H, s), 6.55 (1H, s), 7.03 - 6.98 (2H, m), 7.78 - 7.72 (1H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 404; HPLC tR = 2.30 min;

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

2,4-Difluorobenzenesulfinic acid, sodium salt

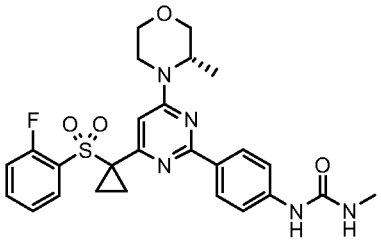


A solution of sodium sulfite (29.6 g, 235.18 mmol) in water (200 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (39.5 g, 470.36 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 10 minutes. 2,4-Difluorobenzene-1-sulfonyl chloride (50 g, 235.18 mmol) was added portion wise to the solution and was stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and re-dissolved in methanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered

and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (41.6 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 7.10 - 7.04 (2H, m), 7.74 - 7.68 (1H, m);

Example 58: 1-[4-[4-[1-(2-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

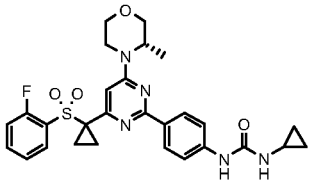
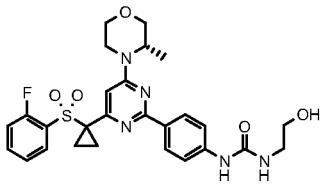
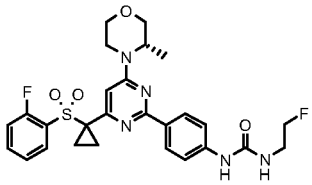
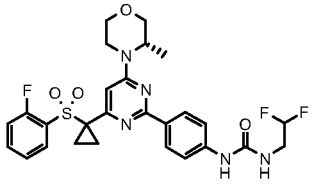
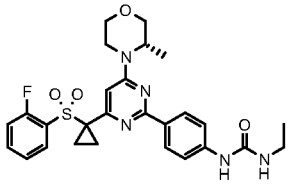
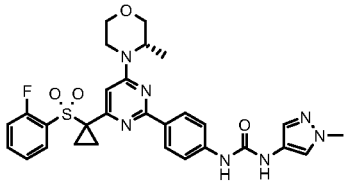


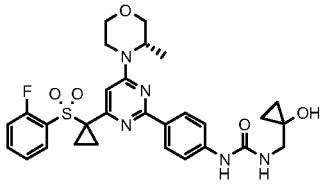
Phenyl *N*-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.2 g, 0.34 mmol) and methylamine solution (2M in THF, 1.699 mL, 3.40 mmol) were added to dioxane (10 mL) and stirred overnight. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (0.119 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.94 - 1.89 (2H, m), 2.66 (3H, d), 3.14 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.42 (1H, s), 6.04 (1H, q), 6.66 (1H, s), 7.37 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.78 - 7.70 (4H, m), 8.69 (1H, s);

m/z (ESI+) (M+H)+ = 526; HPLC tR = 2.34 min;

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
58a		3-cyclopropyl-1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	552	2.45
58b		1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	556	2.09
58c		3-(2-fluoroethyl)-1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	558	2.41
58d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	576	2.53
58e		1-ethyl-3-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	540	2.41
58f		1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	591	2.31

Example	Structure	NAME	LCMS MH+	Retention time (min)
58g		1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea	582	2.26

Example 58a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.43 - 0.40 (2H, m), 0.67 - 0.62 (2H, m), 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.95 - 1.87 (2H, m), 2.58 - 2.51 (1H, m), 3.14 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.43 (1H, s), 6.40 (1H, d), 6.66 (1H, s), 7.37 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.79 - 7.70 (4H, m), 8.48 (1H, s);

Example 58b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.93 - 1.89 (2H, m), 3.19 - 3.10 (3H, m), 3.48 - 3.42 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.43 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.66 (1H, s), 7.35 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.78 - 7.70 (4H, m), 8.75 (1H, s);

Example 58c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.94 - 1.88 (2H, m), 3.14 (1H, ddd), 3.48 - 3.36 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.46 - 4.40 (2H, m), 4.53 (1H, t), 6.41 (1H, t), 6.66 (1H, s), 7.37 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.78 - 7.69 (4H, m), 8.76 (1H, s);

Example 58d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.71 - 1.67 (2H, m), 1.94 - 1.89 (2H, m), 3.14 (1H, ddd), 3.55 - 3.42 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.13 (1H, d), 4.42 (1H, s), 6.07 (1H, ddt), 6.51 (1H, t), 6.67 (1H, s), 7.38 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.78 - 7.70 (4H, m), 8.87 (1H, s);

Example 58e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.94 - 1.88 (2H, m), 3.17 - 3.09 (3H, m), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, ddd), 4.12 (1H, d), 4.42 (1H, s), 6.13 (1H, t), 6.66 (1H, s), 7.36 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.78 - 7.71 (4H, m), 8.60 (1H, s);

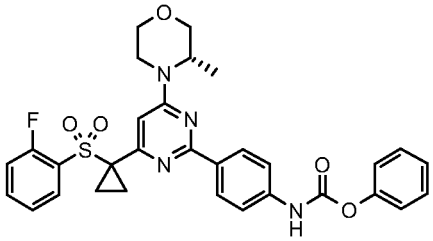
Example 58f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.72 - 1.65 (2H, m), 1.94 - 1.89 (2H, m), 3.15 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.79 (3H, s), 3.95

(1H, dd), 4.13 (1H, d), 4.43 (1H, s), 6.67 (1H, s), 7.34 (1H, t), 7.41 - 7.38 (3H, m), 7.53 - 7.49 (1H, m), 7.79 - 7.70 (5H, m), 8.35 (1H, s), 8.78 (1H, s).

Example 58g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.51 - 0.48 (2H, m), 0.59 - 0.57 (2H, m), 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.94 - 1.90 (2H, m), 3.14 (1H, ddd), 3.22 (2H, d), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.42 (1H, s), 5.36 (1H, s), 6.29 (1H, t), 6.66 (1H, s), 7.35 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.78 - 7.70 (4H, m), 8.76 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



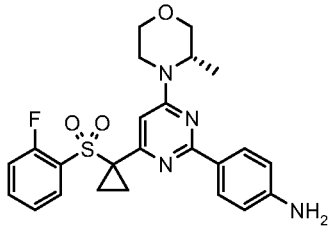
4-[4-[1-(2-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (used as the hydrochloride salt) (3.2 g, 6.83 mmol) and sodium bicarbonate (11.47 g, 136.59 mmol) were added to DCM (75 mL) and stirred for 10 minutes. Phenyl chloroformate (1.114 mL, 8.88 mmol) was added slowly and the reaction was stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to give the desired material as a yellow foam (3.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.72 - 1.66 (2H, m), 1.97 - 1.88 (2H, m), 3.15 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H,

dd), 4.14 (1H, d), 4.44 (1H, s), 6.70 (1H, s), 7.35 - 7.23 (4H, m), 7.53 - 7.42 (5H, m), 7.77 - 7.71 (2H, m), 7.83 (2H, d), 10.37 (1H, s).

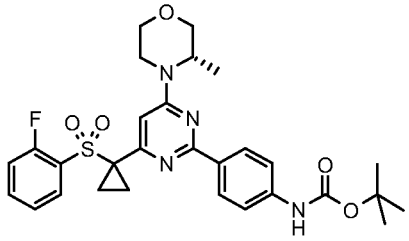
LCMS Spectrum: m/z (ESI+) (M+H)+ = 589; HPLC tR = 3.04 min;

4-[4-[1-(2-Fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



tert-Butyl N-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3.6 g, 6.33 mmol) was added to 6N hydrogen chloride in propan-2-ol (60 mL) and stirred at RT for 5 hours. The solvent was removed to 80% of the initial volume then diethyl ether rapidly added to afford the desired material (as a hydrochloride salt) as a yellow solid (3.20 g). This was used in the next step without any further purification.

tert-Butyl *N*-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



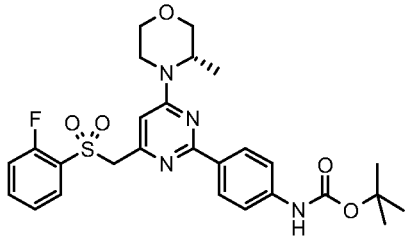
tert-Butyl *N*-[4-[4-[(2-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (5.75 g, 10.60 mmol) was added to sodium hydride (1.526 g, 31.79 mmol) and 1,2-dibromoethane (1.826 mL, 21.19 mmol) in DMF (30 mL) at RT. The resulting suspension was stirred at 45°C for 1 hour. Additional sodium hydride (1.526 g, 31.79 mmol) and 1,2-dibromoethane (1.826 mL, 21.19 mmol) were added and the reaction was stirred at 45°C overnight. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$,

filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give the desired material as a yellow foam (3.60 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.49 (9H, s), 1.71 - 1.65 (2H, m), 1.94 - 1.90 (2H, m), 3.14 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, ddd), 4.13 (1H, d), 4.42 (1H, s), 6.68 (1H, s), 7.33 (1H, t), 7.42 (2H, d), 7.53 - 7.48 (1H, m), 7.78 - 7.70 (4H, m), 9.48 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 569; HPLC tR = 3.13 min;

tert-Butyl *N*-[4-[4-[(2-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

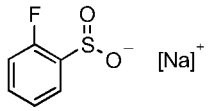


[6-[(3*S*)-3-Methylmorpholin-4-yl]-2-[4-[(2-methylpropan-2-yl)oxycarbonylamino]phenyl]pyrimidin-4-yl]methyl methanesulfonate (4.74 g, 9.90 mmol) and lithium iodide (3.98 g, 29.71 mmol) were added to dioxane (70 mL) and heated at 97°C for 30 minutes. To this was added sodium 2-fluorobenzenesulfinate (2.71 g, 14.86 mmol) and DMF (5 mL), the reaction was stirred at 97°C overnight. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange gum. Diethyl ether (100 mL) was added with vigorous stirring to afford the desired material as a white solid (4.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.49 (9H, s), 3.17 (1H, ddd), 3.48 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 (1H, d), 4.39 (1H, s), 4.76 (2H, s), 6.75 (1H, s), 7.34 (1H, t), 7.41 (2H, d), 7.65 - 7.57 (2H, m), 7.71 (2H, d), 7.83 - 7.77 (1H, m), 9.48 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 543; HPLC tR = 2.92 min;

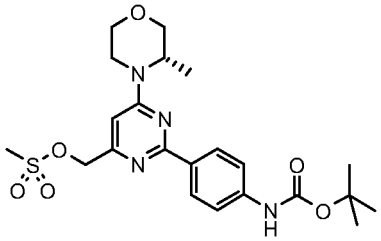
Sodium 2-fluorobenzenesulfinate



A solution of sodium sulfite (32.4 g, 256.92 mmol) in water (200 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (43.2 g, 513.85 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 10 minutes. 2-Fluorobenzene-1-sulfonyl chloride (50 g, 256.92 mmol) was added portionwise to the solution and was stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (41.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 6.99 (1H, t), 7.16 (1H, t), 7.28 - 7.22 (1H, m), 7.61 (1H, t).

[6-[(3*S*)-3-Methylmorpholin-4-yl]-2-[4-[(2-methylpropan-2-yl)oxycarbonylamino]phenyl]pyrimidin-4-yl]methyl methanesulfonate

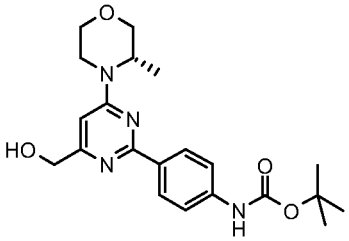


tert-Butyl *N*-[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (23 g, 57.43 mmol) and DIPEA (12.04 mL, 68.92 mmol) were added to DCM (80 mL), to this was slowly added methanesulphonyl chloride (4.48 mL, 57.43 mmol) and the reaction was stirred for 30 minutes. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (100 mL), extracted with DCM (2 x 100 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as a brown gum (27.0 g). This was used without any further purufucation.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.50 (9H, s), 3.22 (1H, ddd), 3.34 (3H, s), 3.50 (1H, ddd), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.53 (1H, s), 5.19 (2H, s), 6.71 (1H, s), 7.56 (2H, d), 8.23 (2H, d), 9.55 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 479; HPLC tR = 2.74 min;

tert-Butyl *N*-[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



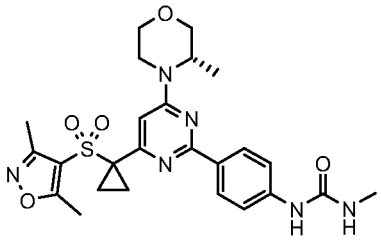
[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (18.00 g, 73.86 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (23.58 g, 73.86 mmol), sodium carbonate (39.1 g, 369.32 mmol) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (5.35 g, 7.39 mmol) were added to DME (300 mL) and water (75 mL) and heated to 90°C overnight under nitrogen. The solvent was evaporated and the residue was quenched with water (100 mL), extracted with ethyl acetate (3 x 100 mL), the aqueous layer was dried over $MgSO_4$, filtered and evaporated to afford black gum. The residue was filtered through a plug of silica eluting with ethyl acetate to give a pale orange gum. This was triturated with diethyl ether to give the desired material as a white solid (24.4 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.49 (9H, s), 3.19 (1H, ddd), 3.49 (1H, ddd), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.50 - 4.46 (3H, m), 5.39 (1H, s), 6.67 (1H, s), 7.54 (2H, d), 8.22 (2H, d), 9.50 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 401; HPLC tR = 2.30 min;

The preparation of [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol was described earlier.

Example 59: 1-[4-[4-[1-[(3,5-Dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

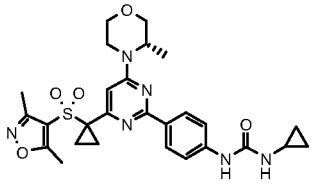


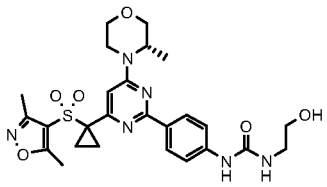
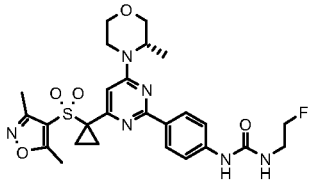
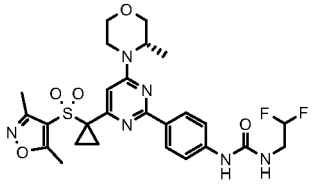
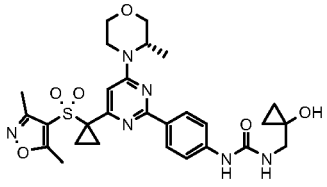
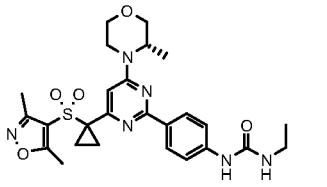
Phenyl *N*-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.15 g, 0.25 mmol) and methylamine (2M in THF, 1.272 mL, 2.54 mmol) were added to dioxane (10 mL) and stirred overnight at 50°C. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (0.098 g).

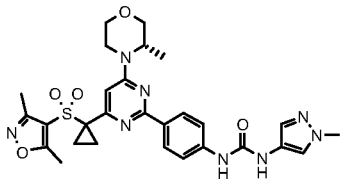
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.59 - 1.52 (2H, m), 1.80 - 1.77 (2H, m), 2.11 (3H, s), 2.33 (3H, s), 2.66 (3H, d), 3.18 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.52 (1H, s), 6.07 (1H, q), 6.75 (1H, s), 7.45 (2H, d), 7.96 (2H, d), 8.72 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 527; HPLC tR = 2.18 min

The following samples were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
59a		3-cyclopropyl-1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	553	2.31

Example	Structure	NAME	LCMS MH+	Retention time (min)
59b		1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	557	2.00
59c		1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	559	2.33
59d		3-(2,2-difluoroethyl)-1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	577	2.44
59e		1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea	583	2.16
59f		3-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	541	2.34

Example	Structure	NAME	LCMS MH+	Retention time (min)
59g		1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	593	2.21

Example 59a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.44 - 0.40 (2H, m), 0.67 - 0.63 (2H, m), 1.21 (3H, d), 1.59 - 1.52 (2H, m), 1.80 - 1.77 (2H, m), 2.11 (3H, s), 2.32 (3H, s), 2.59 - 2.54 (1H, m), 3.18 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.52 (1H, s), 6.44 (1H, d), 6.76 (1H, s), 7.45 (2H, d), 7.96 (2H, d), 8.52 (1H, s).

Example 59b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 - 1.52 (2H, m), 1.80 - 1.75 (2H, m), 2.11 (3H, s), 2.32 (3H, s), 3.22 - 3.14 (3H, m), 3.51 - 3.45 (3H, m), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.52 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.75 (1H, s), 7.43 (2H, d), 7.96 (2H, d), 8.79 (1H, s).

Example 59c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.59 - 1.53 (2H, m), 1.80 - 1.75 (2H, m), 2.11 (3H, s), 2.33 (3H, s), 3.22 - 3.14 (1H, m), 3.39 (1H, q), 3.51 - 3.44 (1H, m), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.42 (1H, t), 4.55 - 4.49 (2H, m), 5.75 (1H, s), 6.44 (1H, t), 6.76 (1H, s), 7.45 (2H, d), 7.97 (2H, d), 8.79 (1H, s);

Example 59d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.60 - 1.52 (2H, m), 1.81 - 1.75 (2H, m), 2.11 (3H, s), 2.33 (3H, s), 3.18 (1H, ddd), 3.64 - 3.44 (4H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.18 (1H, d), 4.52 (1H, s), 6.07 (1H, ddt), 6.54 (1H, t), 6.77 (1H, s), 7.46 (2H, d), 7.98 (2H, d), 8.91 (1H, s).

Example 59e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.53 - 0.49 (2H, m), 0.60 - 0.56 (2H, m), 1.20 (3H, d), 1.59 - 1.52 (2H, m), 1.80 - 1.77 (2H, m), 2.11 (3H, s), 2.32 (3H, s), 3.18 - 3.14 (1H, m), 3.22 (2H, d), 3.47 (1H, ddd), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.52 (1H, s), 5.37 (1H, s), 6.33 (1H, t), 6.76 (1H, s), 7.43 (2H, d), 7.96 (2H, d), 8.80 (1H, s);

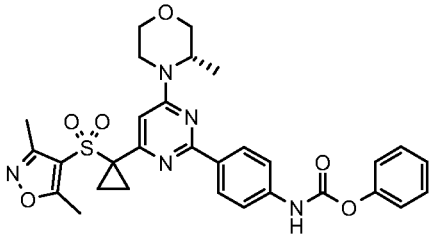
Example 59f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.21 (3H, d), 1.59 - 1.52 (2H, m), 1.80 - 1.77 (2H, m), 2.11 (3H, s), 2.32 (3H, s), 3.22 - 3.09 (3H, m), 3.47 (1H, ddd),

3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.53 (1H, s), 6.17 (1H, t), 6.75 (1H, s), 7.44 (2H, d), 7.95 (2H, d), 8.64 (1H, s);

Example 59g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.59 - 1.53 (2H, m), 1.81 - 1.78 (2H, m), 2.12 (3H, s), 2.33 (3H, s), 3.23 - 3.15 (1H, m), 3.48 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.79 (3H, s), 3.97 (1H, dd), 4.18 (1H, d), 4.53 (1H, s), 6.77 (1H, s), 7.39 (1H, s), 7.49 (2H, d), 7.77 (1H, s), 7.99 (2H, d), 8.40 (1H, s), 8.82 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

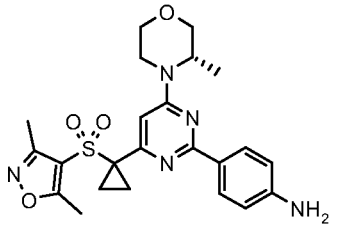


4-[4-[1-[(3,5-Dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (as the hydrochloride salt) (1.94 g, 3.83 mmol) and sodium bicarbonate (1.610 g, 19.17 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.625 mL, 4.98 mmol) was added slowly and the reaction was stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. DCM followed by diethyl ether were added and the solvent was slowly removed until a solid was obtained. The solid was collected by filtration and dried under vacuum to give the desired material as as a white solid (1.89 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.60 - 1.52 (2H, m), 1.81 - 1.78 (2H, m), 2.11 (3H, s), 2.33 (3H, s), 3.19 (1H, ddd), 3.48 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.19 (1H, d), 4.54 (1H, s), 6.80 (1H, s), 7.30 - 7.24 (3H, m), 7.45 (2H, t), 7.57 (2H, d), 8.04 (2H, d), 10.42 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 590; HPLC tR = 2.86 min

4-[4-[1-[(3,5-Dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

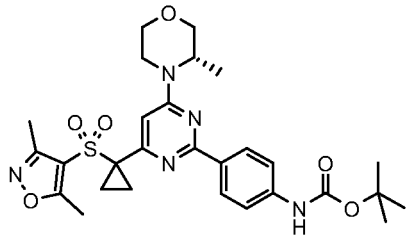


tert-Butyl *N*-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.6 g, 4.56 mmol) was added to 6N hydrogen chloride in propan-2-ol (40 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a yellow solid (1.96 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.69 - 1.58 (2H, m), 1.84 - 1.82 (2H, m), 2.09 (3H, s), 2.38 (3H, s), 3.30 - 3.24 (1H, m), 3.50 - 3.45 (1H, m), 3.62 (1H, dd), 3.81 - 3.75 (1H, m), 3.99 (1H, dd), 4.28 (1H, s), 4.60 (1H, s), 6.93 (1H, s), 7.23 - 7.13 (2H, m), 8.05 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 470; HPLC tR = 1.88 min

tert-Butyl *N*-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



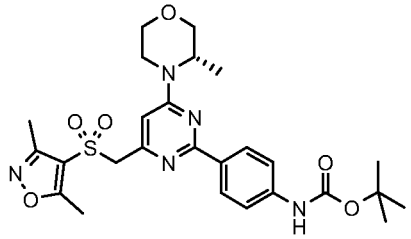
Sodium hydride (2.177 g, 45.36 mmol) and 1,2-dibromoethane (2.61 mL, 30.24 mmol) in DMF (70 mL) were added rapidly to a solution of *tert*-butyl *N*-[4-[4-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (4.11 g, 7.56 mmol) in DMF (70 mL) at RT. The resulting suspension was stirred at RT for 1 hour. Additional sodium hydride (1.1 g, 22.68 mmol) and 1,2-dibromoethane (1.305 mL, 15.12 mmol) were added and the reaction was stirred at RT for 30

minutes. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to afford a yellow foam. This was dissolved in 40% ethyl acetate in isohexane and stirred to give the desired material as a white solid which was collected by filtration (2.60 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.50 (9H, s), 1.59 - 1.53 (2H, m), 1.81 - 1.77 (2H, m), 2.11 (3H, s), 2.32 (3H, s), 3.18 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.18 (1H, d), 4.53 (1H, s), 6.78 (1H, s), 7.51 (2H, d), 7.97 (2H, d), 9.54 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 570; HPLC tR = 2.99 min

tert-Butyl *N*-[4-[4-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

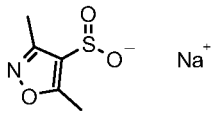


3,5-dimethylisoxazole-4-sulfinic acid, sodium salt (1.443 g, 7.84 mmol) and *tert*-Butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (4 g, 7.84 mmol) were dissolved in DMF (50 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a yellow solid, this was quenched with water (50 mL) and extracted with DCM (2 x 75 mL), dried and solvent evaporated to afford an orange gum, this was rapidly stirred with diethyl ether (100 mL) to afford a solid which was collected by filtration and dried under vacuum to give the desired material as an off white solid (4.11 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.50 (9H, s), 2.19 (3H, s), 2.33 (3H, s), 3.20 (1H, ddd), 3.50 (1H, ddd), 3.65 (1H, dd), 3.78 (1H, d), 3.98 (1H, dd), 4.15 (1H, d), 4.44 (1H, s), 4.69 (2H, s), 6.79 (1H, s), 7.51 (2H, d), 7.97 (2H, d), 9.55 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 544; HPLC tR = 2.76 min

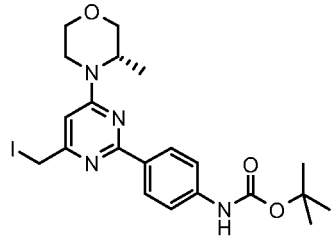
3,5-Dimethylisoxazole-4-sulfinic acid, sodium salt



A solution of sodium sulfite (5.03 g, 39.87 mmol) in water (50 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (6.70 g, 79.74 mmol) was added and the resulting solution was stirred at 50°C for 10 minutes. 3,5-Dimethylisoxazole-4-sulfonyl chloride (7.8 g, 39.87 mmol) was added portion-wise to the solution and was stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and re-dissolved in methanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (7.16 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.24 (3H, s), 2.39 (3H, s).

tert-Butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



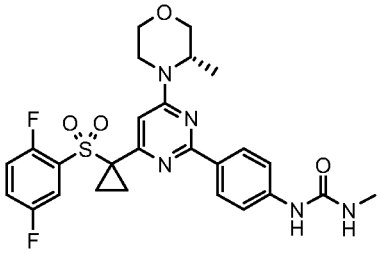
[6-[(3*S*)-3-Methylmorpholin-4-yl]-2-[4-[(2-methylpropan-2-yl)oxycarbonylamino]phenyl]pyrimidin-4-yl]methyl methanesulfonate (27 g, 56.42 mmol) and lithium iodide (4.33 mL, 112.84 mmol) were added to dioxane (250 mL) and heated at 60°C for 1 hour and then at RT overnight. The solvent was evaporated to dryness, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (100 mL) and extracted with DCM (3 x 75 mL). The organic extracts were then flushed through a two inch silica plug, eluting with ethyl acetate, to give a brown foam. This was rapidly dissolved in diethyl ether and stirred to afford the desired material as a white solid (25.2 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.50 (9H, s), 3.19 (1H, ddd), 3.49 (1H, ddd), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.16 (1H, d), 4.39 (2H, s), 4.48 (1H, s), 6.80 (1H, s), 7.55 (2H, d), 8.22 (2H, d), 9.53 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 511; HPLC tR = 2.85 min

The preparation of [6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-[(2-methylpropan-2-yl)oxycarbonylamino]phenyl]pyrimidin-4-yl]methyl methanesulfonate was described earlier.

Example 60: 1-[4-[4-[1-(2,5-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

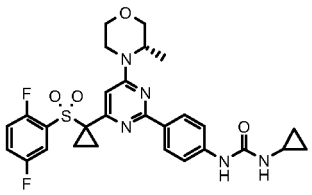
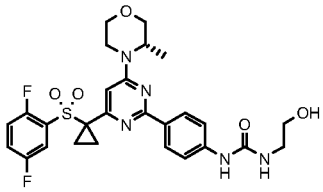
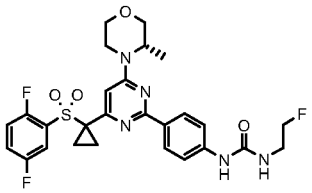
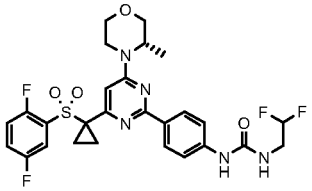
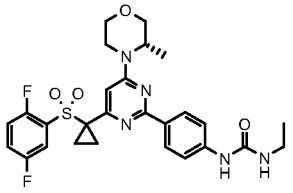


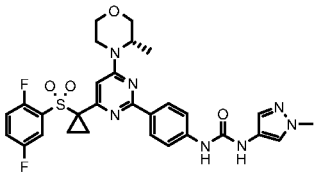
Phenyl *N*-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.15 g, 0.25 mmol) and methylamine (2M in THF, 1.236 mL, 2.47 mmol) were added to dioxane (10 mL) and stirred overnight. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (0.113 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.72 - 1.70 (2H, m), 1.96 - 1.91 (2H, m), 2.66 (3H, d), 3.16 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 6.05 (1H, q), 6.68 (1H, s), 7.37 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.73 (2H, d), 8.70 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 544; HPLC tR= 2.30 min

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
60a		3-cyclopropyl-1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	570	2.51
60b		1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	574	2.11
60c		1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	576	2.48
60d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	594	2.61
60e		3-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	558	2.48

Example	Structure	NAME	LCMS MH+	Retention time (min)
60f		1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	610	2.46

Example 60a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.44 - 0.40 (2H, m), 0.67 - 0.62 (2H, m), 1.19 (3H, d), 1.74 - 1.68 (2H, m), 1.96 - 1.90 (2H, m), 2.58 - 2.53 (1H, m), 3.16 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 6.41 (1H, s), 6.68 (1H, s), 7.38 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.73 (2H, d), 8.50 (1H, s);

Example 60b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.74 - 1.68 (2H, m), 1.98 - 1.89 (2H, m), 2.09 (3H, s), 3.20 - 3.12 (3H, m), 3.49 - 3.42 (3H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 4.73 (1H, t), 6.24 (1H, t), 6.68 (1H, s), 7.36 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.73 (2H, d), 8.77 (1H, s);

Example 60c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.74 - 1.68 (2H, m), 1.96 - 1.90 (2H, m), 3.16 (1H, ddd), 3.48 - 3.36 (3H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.47 (2H, dt), 4.48 (1H, s), 6.41 (1H, t), 6.68 (1H, s), 7.37 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.74 (2H, d), 8.77 (1H, s);

Example 60d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.74 - 1.68 (2H, m), 1.96 - 1.91 (2H, m), 3.16 (1H, ddd), 3.63 - 3.43 (4H, m), 3.74 (1H, d), 3.96 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 6.07 (1H, ddt), 6.51 (1H, t), 6.69 (1H, s), 7.38 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.75 (2H, d), 8.89 (1H, s);

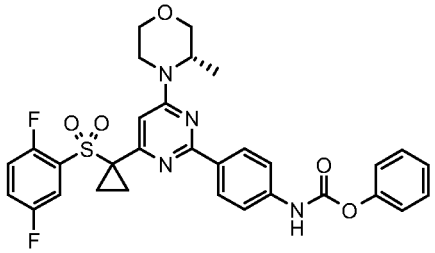
Example 60e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.19 (3H, d), 1.72 - 1.69 (2H, m), 1.95 - 1.91 (2H, m), 3.19 - 3.09 (3H, m), 3.45 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 6.14 (1H, t), 6.68 (1H, s), 7.36 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.72 (2H, d), 8.62 (1H, s);

Example 60f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.74 - 1.68 (2H, m), 1.96 - 1.92 (2H, m), 3.17 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.75 (1H, d), 3.79 (3H, s), 3.96

(1H, dd), 4.17 (1H, d), 4.48 (1H, s), 6.69 (1H, s), 7.38 (1H, s), 7.42 (2H, d), 7.55 - 7.51 (1H, m), 7.70 - 7.58 (2H, m), 7.78 - 7.75 (3H, m), 8.36 (1H, s), 8.80 (1H, s);

The preparation of phenyl *N*-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

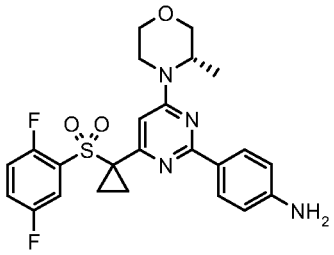


4-[4-[1-(2,5-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (as the hydrochloride salt) (2.54 g, 4.86 mmol) and sodium bicarbonate (2.04 g, 24.28 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.792 mL, 6.31 mmol) was added slowly and the reaction was stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The solid was passed through a plug of silica, eluting with ethyl acetate, to give a solid that was further purified by trituration with diethyl ether to give the desired material as a white solid (2.20 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.73 - 1.69 (2H, m), 1.98 - 1.91 (2H, m), 3.17 (1H, ddd), 3.51 - 3.44 (1H, m), 3.61 (1H, dd), 3.75 (1H, d), 3.95 (1H, d), 4.18 (1H, d), 4.49 (1H, s), 6.72 (1H, s), 7.30 - 7.24 (3H, m), 7.45 (2H, t), 7.55 - 7.50 (3H, m), 7.69 - 7.57 (2H, m), 7.83 (2H, d), 10.39 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 607; HPLC tR = 3.15 min

4-[4-[1-(2,5-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

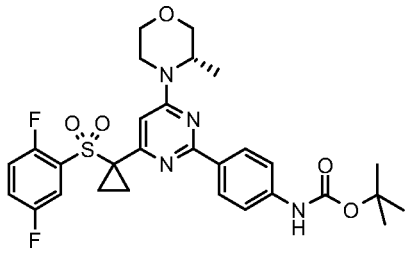


tert-Butyl *N*-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.85 g, 4.86 mmol) was added to 6N hydrogen chloride in propan-2-ol (30 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as a hydrochloride salt) as a yellow solid (2.4 g, 94 %). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.78 - 1.71 (2H, m), 1.97 - 1.93 (2H, m), 3.23 (1H, ddd), 3.45 (1H, ddd), 3.59 (1H, dd), 3.82 - 3.73 (1H, m), 3.96 (1H, dd), 4.29 - 4.18 (1H, m), 4.59 - 4.47 (1H, m), 6.81 (1H, s), 7.25 (2H, d), 7.63 - 7.54 (2H, m), 7.72 - 7.66 (1H, m), 7.95 (2H, d);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 487; HPLC tR = 2.52 min

tert-Butyl *N*-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



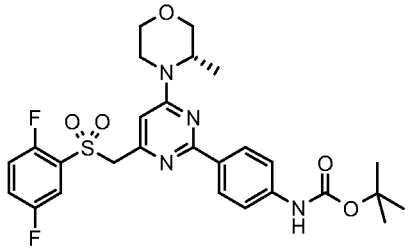
Sodium hydride (1.38 g, 28.56 mmol) was added rapidly to a solution of *tert*-butyl *N*-[4-[4-[(2,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (4.0 g, 7.14 mmol) in DMF (70 mL) and the misture stirred at 40°C for 10 minutes before the slow addition 1,2-dibromoethane (2.459 mL, 28.54 mmol) in DMF (70 mL) at RT. The resulting suspension was stirred at 40°C for 1 hour. Additional sodium hydride (0.69 g, 14.26) and 1,2-dibromoethane (1.23 mL, 14.26 mmol) were added and the reaction was stirred at RT for 30 minutes. The reaction mixture was quenched with water (50

mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give a yellow foam. This was dissolved in 40% ethyl acetate in isohexane and upon stirring the desired material precipitated out as a white solid (2.85 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.49 (9H, s), 1.74 - 1.68 (2H, m), 1.96 - 1.92 (2H, m), 3.16 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.17 (1H, d), 4.48 (1H, s), 6.70 (1H, s), 7.44 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.76 (2H, d), 9.50 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 587; HPLC tR = 2.94 min

tert-Butyl *N*-[4-[4-[(2,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

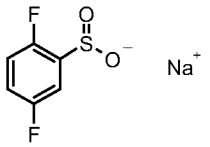


Sodium 2,5-difluorobenzenesulfonate (2.117 g, 9.80 mmol) and *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (5 g, 9.80 mmol) were dissolved in DMF (50 mL) and stirred for 1 hour at RT. The solvent was evaporated and the residue partitioned between water (50 mL) and DCM (75 mL). The layers were separated, the aqueous layer further extracted with DCM (75 mL) and the combined organics passed through a plug of silica, eluting with ethyl acetate, to give a yellow solid. This material was triturated with diethyl ether to give the desired material as a white solid (4.90 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.49 (9H, s), 3.19 (1H, ddd), 3.48 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.13 (1H, d), 4.41 (1H, s), 4.82 (2H, s), 6.78 (1H, s), 7.44 - 7.42 (3H, m), 7.75 - 7.68 (4H, m), 9.50 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 561; HPLC tR = 2.95 min

2,5-Difluorobenzenesulfinic acid, sodium salt

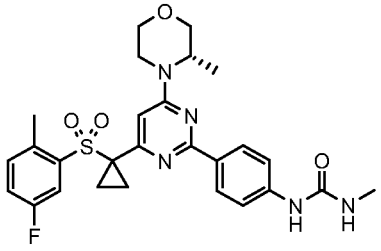


A solution of sodium sulfite (29.6 g, 235.18 mmol) in water (200 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (39.5 g, 470.36 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 10 minutes. 2,5-difluorobenzene-1-sulfonyl chloride (50 g, 235 mmol) was added portionwise and the solution stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in ethanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (43.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.09 - 7.05 (2H, m), 7.36 - 7.32 (1H, m).

The preparation of *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 61: 1-[4-[4-[1-(5-Fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

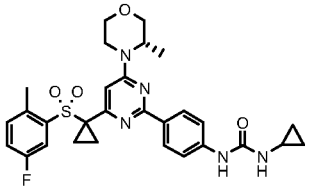
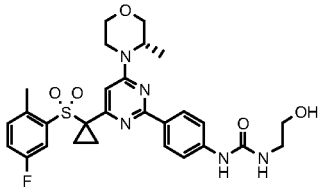
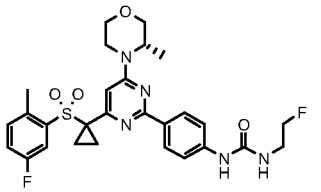


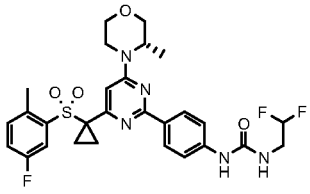
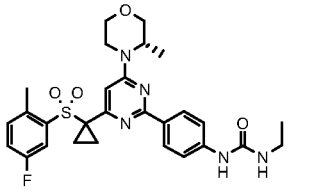
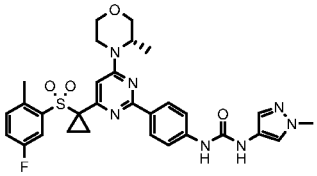
Phenyl *N*-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.15 g, 0.25 mmol) and methylamine (2M in THF, 1.244 mL, 2.49 mmol) were added to dioxane (10 mL) and stirred overnight. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (0.130 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.70 - 1.64 (2H, m), 1.90 - 1.87 (2H, m), 2.41 (3H, s), 2.66 (3H, d), 3.12 (1H, ddd), 3.44 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.43 (1H, s), 6.05 (1H, q), 6.64 (1H, s), 7.42 - 7.38 (4H, m), 7.62 (1H, d), 7.86 (2H, d), 8.71 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 540; HPLC tR = 2.46 min

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
61a		3-cyclopropyl-1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	566	2.65
61b		1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	570	2.28
61c		3-(2-fluoroethyl)-1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	572	2.48

Example	Structure	NAME	LCMS MH+	Retention time (min)
61d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	590	2.74
61e		1-ethyl-3-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	554	2.54
61f		1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	606	2.40

Example 61a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.44 - 0.40 (2H, m), 0.67 - 0.63 (2H, m), 1.16 (3H, d), 1.73 - 1.64 (2H, m), 1.90 - 1.87 (2H, m), 2.41 (3H, s), 2.59 - 2.53 (1H, m), 3.12 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.43 (1H, s), 6.42 (1H, s), 6.64 (1H, s), 7.42 - 7.38 (4H, m), 7.63 - 7.61 (1H, m), 7.86 (2H, d), 8.50 (1H, s).

Example 61b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.70 - 1.64 (2H, m), 1.90 - 1.87 (2H, m), 2.41 (3H, s), 3.20 - 3.09 (3H, m), 3.48 - 3.41 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.43 (1H, s), 4.73 (1H, t), 6.24 (1H, t), 6.64 (1H, s), 7.40 - 7.38 (4H, m), 7.63 - 7.60 (1H, m), 7.86 (2H, d), 8.77 (1H, s);

Example 61c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.70 - 1.64 (2H, m), 1.91 - 1.87 (2H, m), 2.41 (3H, s), 3.13 (1H, ddd), 3.47 - 3.37 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.47 - 4.40 (1H, m), 4.47 (2H, dt), 6.42 (1H, t), 6.64 (1H, s), 7.41 - 7.38 (4H, m), 7.61 (1H, d), 7.87 (2H, d), 8.78 (1H, s).

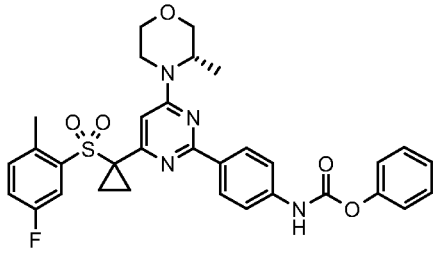
Example 61d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.70 - 1.64 (2H, m), 1.90 - 1.87 (2H, m), 2.41 (3H, s), 3.12 (1H, ddd), 3.62 - 3.41 (4H, m), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.44 (1H, s), 6.08 (1H, ddt), 6.52 (1H, t), 6.65 (1H, s), 7.42 - 7.38 (4H, m), 7.62 - 7.60 (1H, m), 7.88 (2H, d), 8.89 (1H, s).

Example 61e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.16 (3H, d), 1.70 - 1.65 (2H, m), 1.90 - 1.85 (2H, m), 2.4 (S, 3H), 3.15 - 3.09 (3H, m), 3.44 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.43 (1H, s), 6.14 (1H, t), 6.64 (1H, s), 7.39 (4H, d), 7.62 (1H, d), 7.86 (2H, d), 8.63 (1H, s).

Example 61f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.90 - 1.88 (2H, m), 2.41 (3H, s), 3.13 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.77 (3H, s), 3.95 (1H, ddd), 4.43 (1H, s), 6.65 (1H, s), 7.41 - 7.39 (4H, m), 7.45 (2H, d), 7.62 (1H, d), 7.77 (1H, s), 7.89 (2H, d), 8.37 (1H, s), 8.80 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

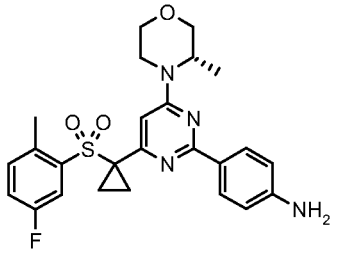


4-[4-[1-(5-Fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (as the hydrochloride salt) (2.4 g, 4.62 mmol) and sodium bicarbonate (1.942 g, 23.12 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.754 mL, 6.01 mmol) was added slowly and the reaction was stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. To this was added DCM and then diethyl ether, the solvent was slowly removed until the desired material precipitated from the mixture as a white solid (2.05 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.72 - 1.66 (2H, m), 1.91 - 1.87 (2H, m), 2.41 (3H, s), 3.14 (1H, ddd), 3.47 - 3.38 (1H, m), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.45 (1H, s), 6.68 (1H, s), 7.30 - 7.24 (3H, m), 7.40 (2H, d), 7.45 (2H, t), 7.54 (2H, d), 7.62 (1H, d), 7.95 (2H, d), 10.39 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 603; HPLC tR = 3.02 min

4-[4-[1-(5-Fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

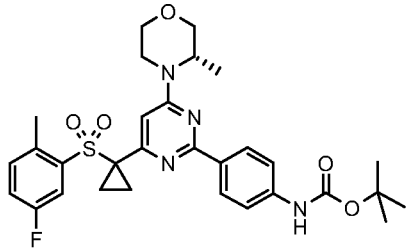


tert-Butyl *N*-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.7 g, 4.63 mmol) was added to 6N hydrogen chloride in propan-2-ol (30 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a yellow solid (2.40 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.73 - 1.69 (2H, m), 1.93 - 1.90 (2H, m), 2.38 (3H, s), 3.20 (1H, ddd), 3.44 (1H, ddd), 3.58 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.26 - 4.12 (1H, m), 4.51 (1H, s), 6.71 (1H, s), 7.17 - 7.13 (2H, m), 7.45 (2H, d), 7.60 (1H, d), 7.97 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 483; HPLC tR = 2.57 min

tert-Butyl *N*-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

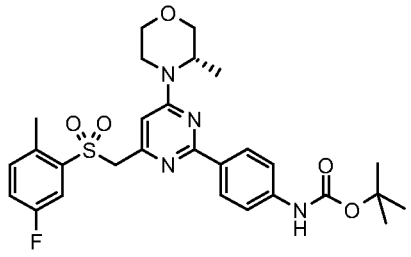


Sodium hydride (1.987 g, 41.39 mmol) was added rapidly to a solution of *tert*-butyl *N*-[4-[4-[(5-fluoro-2-methylphenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3.84 g, 6.90 mmol) in DMF (70 mL) and the mixture stirred at RT for 10 minutes before the slow addition 1,2-dibromoethane (2.38 mL, 27.59 mmol) in DMF (70 mL). The resulting suspension was stirred at RT for 30 minutes. Additional sodium hydride (0.95 g, 20.70 mmol) and 1,2 dibromoethane (1.19 g, 20.70 mmol) were added and the reaction was stirred for a further 30 minutes. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give a material which was further purified by trituration with 40% ethyl acetate in isohexane to give the desired material as a white solid (2.70 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.49 (9H, s), 1.70 - 1.64 (2H, m), 1.90 - 1.87 (2H, m), 2.41 (3H, s), 3.13 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.11 (1H, d), 4.43 (1H, s), 6.66 (1H, s), 7.41 - 7.38 (2H, m), 7.46 (2H, d), 7.62 - 7.60 (1H, m), 7.88 (2H, d), 9.50 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 583; HPLC tR = 3.19 min

tert-Butyl *N*-[4-[4-[(5-fluoro-2-methylphenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

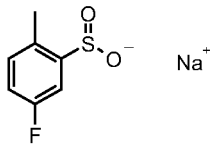


5-Fluoro-2-methylbenzenesulfinic acid, sodium salt (2.079 g, 9.80 mmol) and *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (5 g, 9.80 mmol) were dissolved in DMF (50 mL) and stirred for 1 hour at RT The solvent was evaporated and the residue partitioned between water (50 mL) and DCM (75 mL). The layers were separated, the aqueous layer further extracted with DCM (75 mL) and the combined organics dried and solvent evaporated to afford an orange gum which was further purified by trituration with diethyl ether to give the desired material as an off white solid (4.75 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.50 (9H, s), 2.61 (3H, s), 3.17 (1H, ddd), 3.48 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.40 (1H, s), 4.75 (2H, s), 6.69 (1H, s), 7.50 - 7.41 (4H, m), 7.56 - 7.53 (1H, m), 7.82 (2H, d), 9.50 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 557; HPLC tR = 2.91 min

5-fluoro-2-methylbenzenesulfinic acid, sodium salt

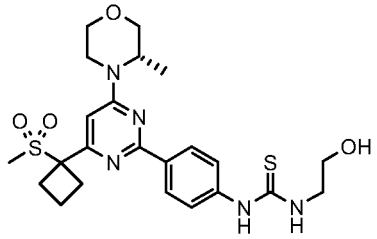


A solution of sodium sulfite (30.2 g, 239.65 mmol) in water (200 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (40.3 g, 479.30 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 10 minutes. 5-Fluoro-2-methyl sulfonyl chloride was added portionwise and the solution stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in ethanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (27.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.41 (3H, s), 6.90 (1H, ddd), 7.05 (1H, dd), 7.36 (1H, dd).

The preparation of *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 62: 3-(2-Hydroxyethyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea



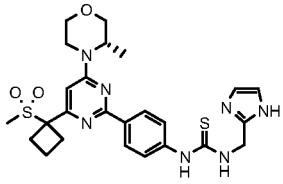
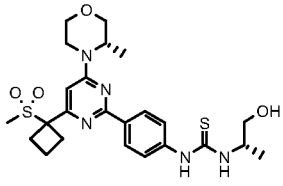
1,1'-Thiocarbonyldiimidazole (57.6 mg, 0.32 mmol) was added to a stirred solution of 4-[4-

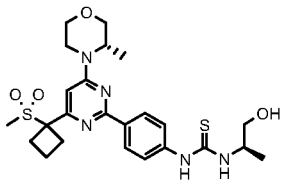
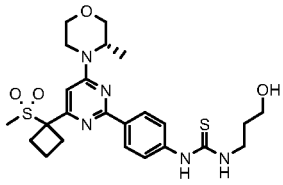
[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]aniline (100 mg, 0.25 mmol) in THF (1.0 mL) and DCM (2.0 mL) at RT. The resulting solution was stirred for 2 hours. Triethylamine (0.035 mL, 0.25 mmol) and ethanolamine (15.18 mg, 0.25 mmol) were added to the reaction mixture and then stirred at RT for a further 1 hour. The reaction mixture was evaporated to dryness and redissolved in acetonitrile (2.0 mL), filtered and purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (73 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.92 (1H, d), 2.07 - 2.09 (1H, m), 2.79 - 2.86 (2H, m), 2.88 (3H, s), 2.87 - 2.95 (2H, m), 3.18 - 3.26 (1H, m), 3.47 - 3.54 (1H, m), 3.57 (3H, s), 3.64 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.30 (1H, d), 4.63 (1H, d), 4.85 (1H, s), 6.75 (1H, s), 7.61 - 7.64 (2H, m), 7.90 (1H, s), 8.27 - 8.30 (2H, m), 9.85 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 506.55; HPLC tR = 2.35 min.

The compounds below were prepared in an analogous fashion from 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]aniline using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
62a		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea	542.6	2.41
62b		3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea	520.6	2.47

Example	Structure	NAME	LCMS MH+	Retention time (min)
62c		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea	520.6	2.47
62d		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea	520.6	2.39

Example 62a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.90 - 1.93 (1H, m), 2.07 - 2.09 (1H, m), 2.79 - 2.86 (2H, m), 2.88 (3H, s), 2.89 - 2.95 (2H, m), 3.20 - 3.26 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.77 (1H, d), 3.97 - 4.00 (1H, m), 4.27 (1H, d), 4.60 (1H, s), 4.71 (2H, s), 6.76 (1H, s), 6.88 (1H, s), 7.09 (1H, s), 7.68 (2H, d), 8.24 (1H, s), 8.28 - 8.32 (2H, m), 10.06 (1H, s).

Example 62b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 - 1.16 (3H, m), 1.24 (3H, s), 1.90 - 1.94 (1H, m), 2.07 - 2.09 (1H, m), 2.79 - 2.84 (2H, m), 2.88 (3H, s), 2.91 - 2.95 (2H, m), 3.20 - 3.26 (1H, m), 3.44 - 3.54 (3H, m), 3.64 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.26 (1H, d), 4.38 (1H, s), 4.60 (1H, s), 4.92 (1H, s), 6.75 (1H, s), 7.63 - 7.66 (2H, m), 7.73 - 7.75 (1H, m), 8.28 (2H, d), 9.75 (1H, s).

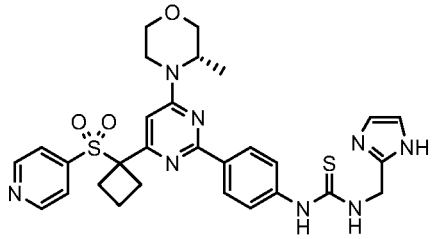
Example 62c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 - 1.16 (3H, m), 1.24 (3H, s), 1.90 - 1.94 (1H, m), 2.07 - 2.09 (1H, m), 2.79 - 2.84 (2H, m), 2.88 (3H, s), 2.91 - 2.95 (2H, m), 3.20 - 3.26 (1H, m), 3.44 - 3.54 (3H, m), 3.64 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.26 (1H, d), 4.38 (1H, s), 4.60 (1H, s), 4.92 (1H, s), 6.75 (1H, s), 7.63 - 7.66 (2H, m), 7.73 - 7.75 (1H, m), 8.28 (2H, d), 9.75 (1H, s).

Example 62d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 - 1.25 (3H, m), 1.68 - 1.75 (2H, m), 1.90 - 1.93 (1H, m), 2.07 - 2.09 (1H, m), 2.79 - 2.86 (2H, m), 2.88 (3H, s), 2.89 - 2.95 (2H, m), 3.18 - 3.25 (1H, m), 3.47 - 3.54 (5H, m), 3.64 - 3.67 (1H, m), 3.77 (1H, d), 3.96 -

4.00 (1H, m), 4.26 (1H, d), 4.58 (2H, s), 6.75 (1H, s), 7.55 - 7.59 (2H, m), 7.93 (1H, s), 8.27 - 8.30 (2H, m), 9.74 (1H, s).

The preparation of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]aniline was described earlier.

Example 63: 3-(1*H*-Imidazol-2-ylmethyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea



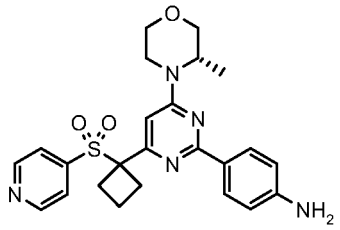
1,1'-Thiocarbonyldiimidazole (49.8 mg, 0.28 mmol) was added to a stirred solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline (100 mg, 0.21 mmol) in THF (1.0 mL) and DCM (2.0 mL) at RT. The resulting solution was stirred for 2 hours. Triethylamine (0.030 mL, 0.21 mmol) and (1H-imidazol-2-yl)methanamine (20.86 mg, 0.21 mmol) were then added to the reaction mixture and stirred at RT for 1 hour. The reaction mixture was evaporated to dryness and redissolved in acetonitrile (2.0 mL), filtered and then purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to afford desired material as a white solid (85mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.21 - 1.23 (3H, d), 1.94 (1H, m), 2.15 (1H, m), 2.82 (2H, m), 3.14 (2H, m), 3.51 (1H, t), 3.63 (1H, d), 3.68 (1H, d), 3.77 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.55 (1H, s), 4.73 (2H, s), 6.57 (1H, s), 6.89 (1H, s), 7.08 (1H, s), 7.48 (2H, d), 7.56 (2H, d), 7.79 (2H, d), 8.20 (1H, s), 8.73 (2H, d), 10.00 (1H, s), 11.94 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 605.51; HPLC tR = 2.03 min.

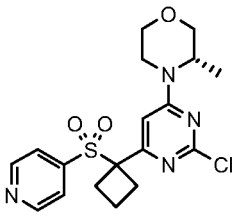
The preparation of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline is described below:

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline



Bis(triphenylphosphine)palladium(II) chloride (79 mg, 0.11 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidine (920 mg, 2.25 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (641 mg, 2.92 mmol) and 2M aqueous sodium carbonate solution (5 mL, 10.0 mmol) in DMF (10 mL), DME (40 mL), ethanol (10 mL) and water (10 mL) at RT under a nitrogen atmosphere. The resulting mixture was stirred at 80°C for 2 hours. The reaction mixture was then diluted with ethyl acetate (400 mL) and washed sequentially with water (200 mL) and then brine (250 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, with an elution gradient of 0% to 50% ethyl acetate in DCM, to afford the desired material as a creamy white solid (1.01 g).
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.19 - 1.21 (3H, m), 1.88 - 1.95 (1H, m), 2.10 - 2.15 (1H, m), 2.76 - 2.83 (2H, m), 3.05 - 3.18 (3H, m), 3.45 - 3.52 (1H, m), 3.62 - 3.65 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.13 (1H, d), 4.47 (1H, d), 5.50 (2H, d), 6.45 - 6.48 (2H, m), 6.52 (1H, s), 7.44 - 7.46 (2H, m), 7.52 - 7.66 (2H, d), 8.70 - 8.72 (2H, m)
LCMS Spectrum: m/z (ESI+) (M+H)+ = 466.20; HPLC tR = 2.06 min

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidine



Sodium hydroxide (50%w/w solution) (24.39 g, 609.89 mmol) was added to a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidine (4.09 g, 11.09 mmol), 1,3-dibromopropane (3.38 mL, 33.27 mmol) and tetrabutylammonium bromide (0.357 g, 1.11 mmol) in toluene (200 mL) at RT under air. The resulting mixture was warmed

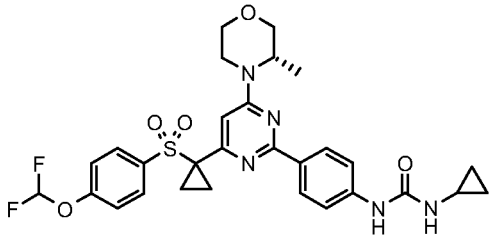
to 45°C for 3 hours. Water (100 mL) was added to the solution and the toluene layer was washed with further water, brine and then dried over $MgSO_4$. The mixture was filtered and the filtrate was evaporated to dryness. The crude product was purified by flash silica chromatography, eluting with a gradient of 30 to 50% ethyl acetate in DCM, to afford desired material as a solid (936 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.17 - 1.19 (3H, m), 1.89 - 1.94 (1H, m), 2.07 - 2.13 (1H, m), 2.68 - 2.75 (2H, m), 2.96 - 3.06 (2H, m), 3.11 - 3.19 (1H, m), 3.39 - 3.46 (1H, m), 3.56 - 3.59 (1H, m), 3.71 (1H, d), 3.91 - 3.94 (2H, m), 4.34 (1H, s), 6.65 (1H, s), 7.47 - 7.49 (2H, m), 8.83 - 8.85 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 409; HPLC tR = 2.04 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidine was described earlier.

Example 64: 3-Cyclopropyl-1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

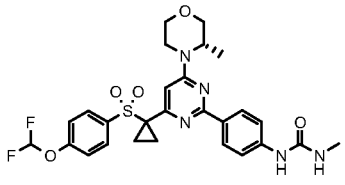
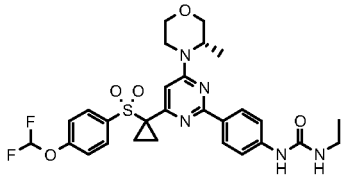
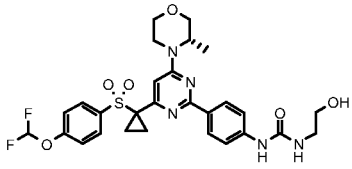
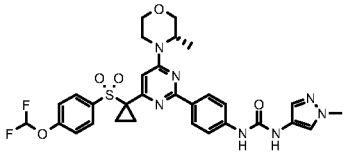


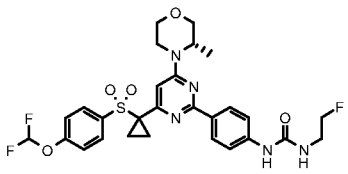
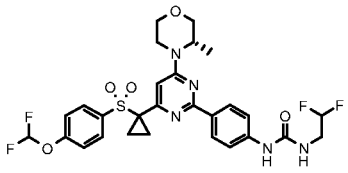
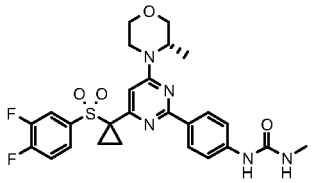
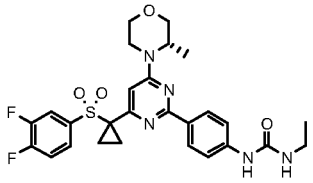
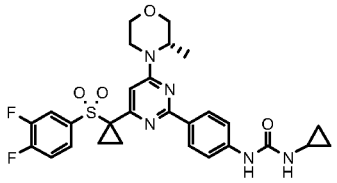
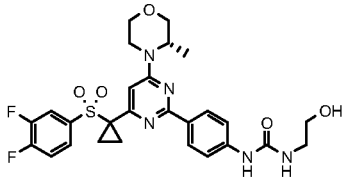
Cyclopropylamine (0.136 mL, 0.80 mmol) was added to a solution of phenyl *N*-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.16 mmol) and triethylamine (0.066 mL, 0.48 mmol) in DMA (1 mL). The reaction was stirred at RT for 18 hours. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile to afford the desired product as a solid (66 mg).

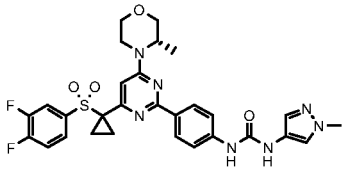
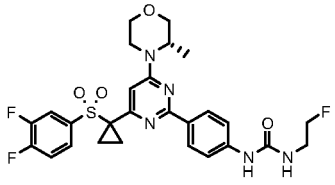
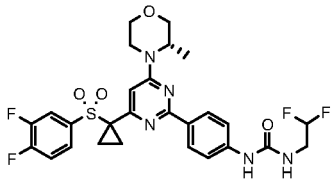
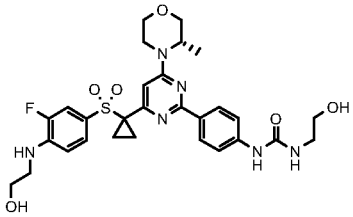
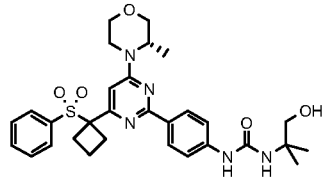
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.41 (2H, m), 0.64 (2H, m), 1.18 (3H, d), 1.61 (2H, m), 1.87 (2H, m), 2.55 (1H, dd), 3.14 (1H, m), 3.46 (1H, td), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.14 (1H, s), 4.40 (1H, s), 6.40 (1H, d), 6.63 (1H, s), 7.37 – 7.58 (5H, m), 7.84 (4H, m), 8.50 (1H, s)

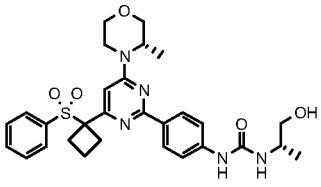
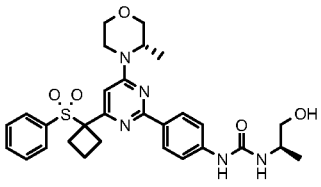
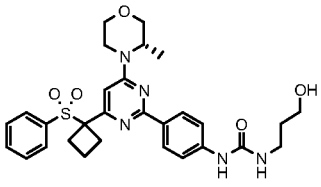
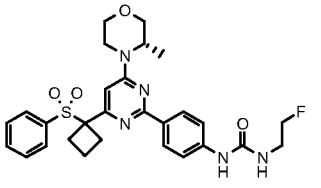
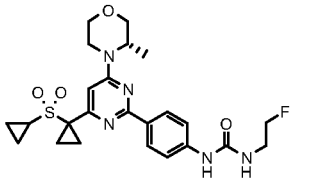
LCMS Spectrum: m/z (ESI+)(M+H)+ = 600; HPLC tR = 2.36 min.

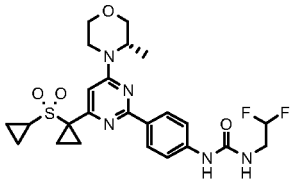
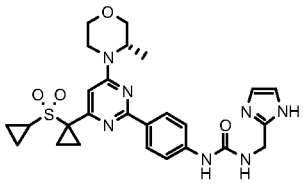
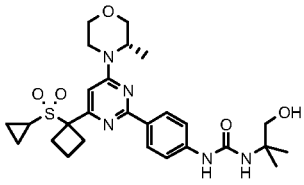
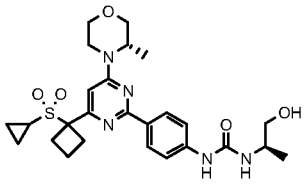
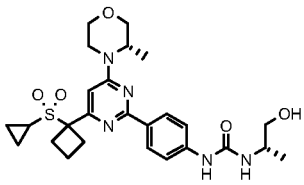
The compounds below were prepared in an analogous fashion using the appropriate carbamate and the appropriate amine.

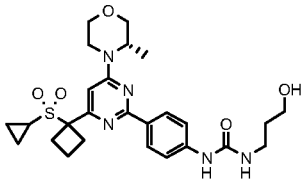
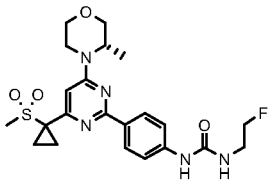
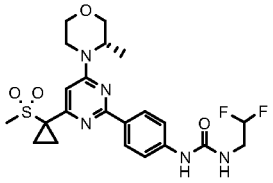
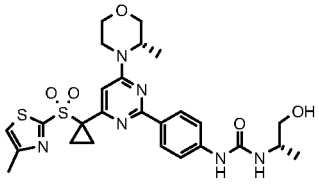
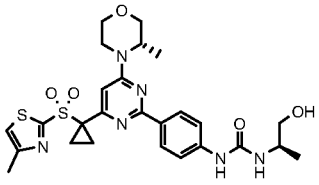
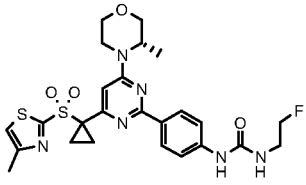
Example	Structure	NAME	LCMS MH+	Retention time (min)
64a*		1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	574	2.21
64b*		3-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	588	2.35
64c*		1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	604	2.05
64d**		1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	640	2.22

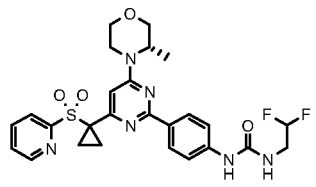
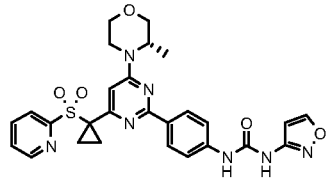
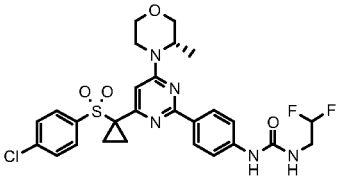
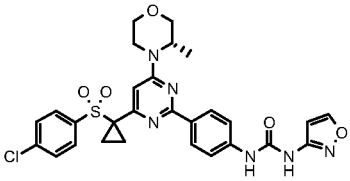
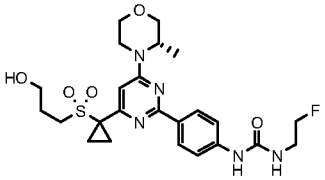
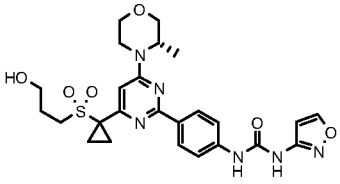
Example	Structure	NAME	LCMS MH+	Retention time (min)
64e**		1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	606	2.33
64f**		3-(2,2-difluoroethyl)-1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	624	2.45
64g*		1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	544	2.21
64h*		3-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	558	2.40
64i		3-cyclopropyl-1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	570	2.47
64j		1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	574	2.06

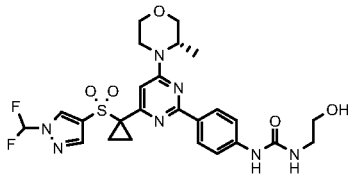
Example	Structure	NAME	LCMS MH+	Retention time (min)
64k**		1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	610	2.22
64l**		1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	576	2.34
64m**		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	594	2.45
64n***		1-[4-[4-[1-[3-fluoro-4-(2-hydroxyethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	615	1.72
64o		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	580	2.30

Example	Structure	NAME	LCMS MH+	Retention time (min)
64p		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea	566	2.11
64q		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea	566	2.11
64r		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	566	2.05
64s**		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	554	2.32
64t**		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	504	1.95

Example	Structure	NAME	LCMS MH+	Retention time (min)
64u**		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	522	2.10
64v		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	538	1.77
64w		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	544	2.11
64x		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea	530	1.91
64y		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea	530	1.91

Example	Structure	NAME	LCMS MH+	Retention time (min)
64z		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	530	1.86
64aa**		3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	478	1.84
64ab**		3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	496	2.03
64ac		3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	573	1.92
64ad		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	573	1.92
64ae**		3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	561	2.14

Example	Structure	NAME	LCMS MH+	Retention time (min)
64af**		3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	559	2.07
64ag		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	562	2.12
64ah**		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	592	2.48
64ai		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	595	2.51
64aj**		3-(2-fluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	522	1.72
64ak		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	543	1.77

Example	Structure	NAME	LCMS MH+	Retention time (min)
64al*		1-[4-[4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	578	2.00

* 1.2 Equivalents of amine used

** Reaction heated at 50°C for 3 hours

*** By product formed and isolated when preparing **Example 64j**

Example 64a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.60 (2H, m), 1.89 (2H, m), 2.66 (3H, d), 3.14 (1H, td), 3.46 (1H, td), 3.62 (1H, dd), 3.74 (1H, d), 3.94 (1H, dd), 4.15 (1H, d), 4.40 (1H, s), 6.04 (1H, q), 6.63 (1H, s), 7.36 – 7.61 (5H, m), 7.84 (4H, m), 8.70 (1H, s)

Example 64b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.18 (3H, d), 1.61 (2H, m), 1.88 (2H, m), 3.13 (3H, m), 3.46 (1H, td), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.40 (1H, s), 6.13 (1H, t), 6.63 (1H, s), 7.37 – 7.59 (5H, m), 7.84 (4H, m), 8.62 (1H, s)

Example 64c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.60 (2H, m), 1.87 (2H, m), 3.16 - 3.18 (3H, m), 3.46 (3H, m), 3.61 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.40 (1H, s), 4.72 (1H, t), 6.24 (1H, t), 6.63 (1H, s), 7.37 – 7.60 (5H, m), 7.84 (4H, m), 8.76 (1H, s)

Example 64d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.61 (2H, m), 1.89 (2H, m), 3.17 (1H, td), 3.46 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.79 (3H, s), 3.96 (1H, dd), 4.15 (1H, d), 4.40 (1H, s), 6.65 (1H, s), 7.36 – 7.60 (6H, m), 7.76 (1H, s), 7.84 - 7.86 (4H, dd), 8.35 (1H, s), 8.80 (1H, s)

Example 64e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.61 (2H, m), 1.89 (2H, m), 3.16 (1H, td), 3.38 (1H, m), 3.45 (2H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.15

(1H, d), 4.41 (2H, t), 4.53 (1H, t), 6.41 (1H, t), 6.64 (1H, s), 7.37-7.60 (5H, m), 7.84 (4H, m), 8.77 (1H, s)

Example 64f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.60 (2H, m), 1.89 (2H, m), 3.16 (1H, td), 3.48 -3.54 (3H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.40 (1H, s), 5.90 - 6.40 (1H, m), 6.50 (1H, t), 6.64 (1H, s), 7.38 - 7.60 (5H, m), 7.85 (4H, m), 8.88 (1H, s)

Example 64g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, m), 1.61 (2H, dd), 1.93 (2H, dd), 2.67 (3H, t), 3.17 (1H, m), 3.46 (1H, td), 3.62 (1H, dd), 3.75 (1H, m), 3.92 (1H, dd), 4.20 (1H, d), 4.45 (1H br s), 6.04 (1H, q), 6.67 (1H, s), 7.40 (2H, m), 7.67 (2H, m), 7.79 (2H, m), 7.91 (1H, m), 8.73 (1H, s)

Example 64h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.19 (3H, d), 1.61 (2H, dd), 1.93 (2H, dd), 3.12 (2H, m), 3.16 (1H, m), 3.45 (1H, td), 3.62 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.45 (1H, br s), 6.13 (1H, t), 6.67 (1H, s), 7.39 (2H, m), 7.65 (1H, d), 7.67 (1H, t), 7.79 (2H, m), 7.91 (1H, m), 8.65 (1H, s)

Example 64i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.42 (2H, dt), 0.65 (2H, td), 1.19 (3H, d), 1.61 (2H, dd), 1.93 (2H, dd), 2.56 (1H, m), 3.18 (1H, td), 3.46 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.47 (1H, br s), 6.30 (1H, s), 6.67 (1H, s), 7.40 (2H, m), 7.66 (2H, m), 7.80 (2H, m), 7.90 (1H, td), 8.53 (1H, s)

Example 64j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.61 (2H, dd), 1.93 (2H, m), 3.17 (3H, q), 3.45 (3H, m), 3.61 (1H, dd), 3.73 (1H, d), 3.91 (1H, dd), 4.15 (1H, d), 4.50 (1H, br s), 4.72 (1H, t), 6.22 (1H, s), 6.67 (1H, s), 7.38 (2H, m), 7.66 (1H, t), 7.67 (1H, s), 7.79 (2H, m), 7.90 (1H, m), 8.79 (1H, s)

Example 64k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.62 (2H, dd), 1.94 (2H, dd), 3.17 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.74 (1H, d), 3.79 (3H, s), 3.96 (1H, dd), 4.17 (1H, d), 4.47 (1H, br s), 6.68 (1H, s), 7.38 (1H, d), 7.45 (2H, m), 7.67 (2H, m), 7.77 (1H, d), 7.83 (2H, d), 7.91 (1H, t), 8.35 (1H, s), 8.84 (1H, s)

Example 64l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, m), 1.61 (2H, dd), 1.93 (2H, dd), 3.17 (1H, td), 3.39 (1H, t), 3.45 (2H, q), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.42 (1H, t), 4.50 (1H, br s), 4.53 (1H, t), 6.40 (1H, t), 6.67 (1H, s), 7.40 (2H, m), 7.66 (1H, d), 7.67 (1H, t), 7.80 (2H, d), 7.90 (1H, m), 8.80 (1H, s)

Example 64m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.61 (2H, dd), 1.94 (2H, dd), 3.17 (1H, td), 3.45 (1H, td), 3.54 (2H, m), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.17

(1H, d), 4.47 (1H, br s), 5.90-6.20 (1H, tt), 6.50 (1H, t), 6.68 (1H, s), 7.41 (2H, m), 7.67 (2H, m), 7.82 (2H, m), 7.90 (1H, m), 8.92 (1H, s)

Example 64n: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.56 (2H, m), 1.81 (2H, m), 3.15 (1H, m), 3.17 (2H, m), 3.46 (3H, q), 3.57 (2H, q), 3.62 (1H, m), 3.75 (1H, d), 3.96 (1H, dd), 4.06 (1H, m), 4.37 (1H, br s), 4.73 (2H, q), 6.25 (1H, t), 6.36 (1H, m), 6.58 (1H, s), 6.82 (1H, t), 7.33 (1H, m), 7.41 (3H, m), 7.96 (2H, m), 8.76 (1H, s)

Example 64o: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.22 (6H, s), 1.87 (1H, m), 2.08 (1H, m), 2.78 (2H, m), 3.04-3.20 (3H, m), 3.38 (2H, d), 3.48 (1H, td), 3.63 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.08 (1H, d), 4.44 (1H, br s), 4.95 (1H, t), 5.97 (1H, s), 6.46 (1H, s), 7.32 (2H, m), 7.47 (4H, m), 7.60 (1H, m), 7.78 (2H, d), 8.67 (1H, s)

Example 64p: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.20 (3H, d), 1.87 (1H, m), 2.08 (1H, m), 2.79 (2H, m), 3.04-3.20 (3H, m), 3.36 (2H, m), 3.48 (1H, td), 3.63 (1H, dd), 3.71 (2H, m), 3.96 (1H, dd), 4.07 (1H, d), 4.45 (1H, br s), 4.78 (1H, t), 6.07 (1H, m), 6.46 (1H, s), 7.35 (2H, m), 7.47 (4H, m), 7.60 (1H, m), 7.79 (2H, d), 8.65 (1H, s)

Example 64q: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.20 (3H, d), 1.87 (1H, m), 2.08 (1H, m), 2.79 (2H, m), 3.04 -3.20 (3H, m), 3.36 (2H, m), 3.48 (1H, td), 3.63 (1H, dd), 3.71 (1H, m), 3.73 (1H, m), 3.96 (1H, dd), 4.07 (1H, d), 4.45 (1H, br s), 4.78 (1H, t), 6.07 (1H, d), 6.46 (1H, s), 7.35 (2H, d), 7.47 (4H, m), 7.59 (1H, td), 7.79 (2H, m), 8.65 (1H, s)

Example 64r: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 (2H, m), 1.87 (1H, m), 2.08 (1H, m), 2.79 (2H, m), 3.04 (2H, m), 3.12 (1H, m), 3.25 (2H, d), 3.46 (3H, m), 3.63 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.07 (1H, m), 4.47 (2H, m), 6.18 (1H, t), 6.46 (1H, s), 7.36 (2H, m), 7.48 (4H, m), 7.59 (1H, m), 7.79 (2H, d), 8.65 (1H, s)

Example 64s: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.87 (1H, m), 2.12 (1H, m), 2.75 (2H, m), 3.00-3.20 (3H, m), 3.40 (1H, t), 3.45 (2H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.92 (1H, dd), 4.15 (1H, d), 4.41 (2H, m), 4.53 (1H, t), 6.41 (1H, t), 6.47 (1H, s), 7.37 (2H, m), 7.48 (4H, m), 7.60 (1H, t), 7.80 (2H, m), 8.75 (1H, s)

Example 64t: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.94 (2H, m), 1.03 (2H, m), 1.24 (3H, d), 1.58 (2H, m), 1.65 (2H, m), 3.00 (1H, m), 3.15 (1H, td), 3.36 (1H, m), 3.46 (2H, m), 3.61 (1H, dd), 3.77 (1H, d), 3.94 (1H, dd), 4.20 (1H, d), 4.42 (1H, t), 4.53 (2H, t), 6.43 (1H, t), 6.85 (1H, s), 7.50 (2H, m), 8.22 (2H, m), 8.80 (1H, s)

Example 64u: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.94 (2H, m), 1.03 (2H, m), 1.24 (3H, d), 1.59 (2H, m), 1.65 (2H, m), 3.00 (1H, m), 3.21 (1H, td), 3.54 (3H, m), 3.64 (1H, dd), 3.77

(1H, d), 3.98 (1H, dd), 4.20 (1H, d), 4.54 (1H, br s), 5.90-6.20 (1H, tt), 6.53 (1H, t), 6.85 (1H, s), 7.51 (2H, m), 8.23 (2H, m), 8.91 (1H, s)

Example 64v: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.94 (2H, m), 1.03 (2H, m), 1.24 (3H, d), 1.59 (2H, m), 1.65 (2H, m), 3.00 (1H, m), 3.19 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.96 (1H, dd), 4.20 (1H, d), 4.32 (2H, d), 4.54 (1H, br s), 6.62 (1H, t), 6.85 (1H, s), 6.95 (1H, br s), 7.51 (2H, m), 8.22 (2H, m), 8.92 (1H, s)

Example 64w: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.76 (2H, m), 0.85 (2H, m), 1.24 (9H, m), 1.90 (1H, m), 2.10 (1H, m), 2.45 (1H, m), 2.80 – 3.30 (4H, m), 3.20 (1H, td), 3.39 (2H, d), 3.50 (1H, td), 3.65 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.20 (1H, d), 4.50 (1H, br s), 4.95 (1H, t), 6.00 (1H, s), 6.70 (1H, s), 7.45 (2H, m), 8.22 (2H, m), 8.72 (1H, s)

Example 64x: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70 (2H, m), 0.85 (2H, m), 1.10 (3H, d), 1.25 (3H, d), 1.90 (1H, m), 2.10 (1H, m), 2.45 (1H, m), 2.80 -3.00 (4H, m), 3.15 (1H, td), 3.35 (2H, m), 3.50 (1H, td), 3.60-3.80 (3H, m), 3.95 (1H, dd), 4.20 (1H, d), 4.55 (1H, br s), 4.75 (1H, t), 6.10 (1H, d), 6.70 (1H, s), 7.45 (2H, m), 8.20 (2H, m), 8.70 (1H, s)

Example 64y: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70 (2H, m), 0.84 (2H, m), 1.08 (3H, d), 1.23 (3H, d), 1.89 (1H, m), 2.10 (1H, m), 2.46 (1H, m), 2.84-3.00 (4H, m), 3.15 (1H, td), 3.36 (2H, m), 3.51 (1H, td), 3.67 (1H, td), 3.77 (2H, m), 3.95 (1H, dd), 4.20 (1H, d), 4.55 (1H, br s), 4.78 (1H, t), 6.09 (1H, d), 6.70 (1H, s), 7.47 (2H, m), 8.23 (2H, m), 8.70 (1H, s)

Example 64z: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70 (2H, m), 0.84 (2H, m), 1.20 (3H, d), 1.57 (2H, m), 1.89 (1H, m), 2.10 (1H, m), 2.46 (1H, m), 2.80-3.00 (4H, m), 3.15 (4H, m), 3.45 (2H, m), 3.55 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.95 (1H, dd), 4.20 (1H, d), 4.45 (1H, t), 4.55 (1H, br s), 6.20 (1H, t), 6.70 (1H, s), 7.47 (2H, m), 8.25 (2H, m), 8.70 (1H, s)

Example 64aa: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, m), 1.58 (2H, m), 1.67 (2H, m), 2.47 (3H, s), 3.20 (1H, td), 3.39 (1H, q), 3.46 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.21 (1H, d), 4.42 (1H, t), 4.54 (1H, br s), 4.55 (1H, t), 6.43 (1H, t), 6.77 (1H, s), 7.51 (2H, m), 8.21 (2H, m), 8.82 (1H, s)

Example 64ab: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.56 (2H, m), 1.67 (2H, m), 2.46 (3H, s), 3.15 (1H, td), 3.47 -3.63 (4H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.21 (1H, d), 4.57 (1H, br s), 5.90 – 6.20 (1H, m), 6.53 (1H, t), 6.78 (1H, s), 7.52 (2H, m), 8.22 (2H, m), 8.93 (1H, s

Example 64ac: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.21 (3H, d), 1.77 (2H, m), 1.94 (2H, m), 2.48 (3H, d), 3.18 (1H, td), 3.36 (2H, m), 3.40 (1H, td), 3.63 (1H, dd), 3.71

(1H, m), 3.76 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.45 (1H, br s), 4.78 (1H, t), 6.07 (1H, m), 6.77 (1H, s), 7.39 (2H, m), 7.84-7.90 (3H, m), 8.69 (1H, s)

Example 64ad: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.21 (3H, d), 1.77 (2H, m), 1.94 (2H, m), 2.48 (3H, d), 3.18 (1H, td), 3.36 (2H, m), 3.40 (1H, td), 3.63 (1H, dd), 3.71 (1H, m), 3.76 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.45 (1H, br s), 4.78 (1H, t), 6.07 (1H, m), 6.77 (1H, s), 7.39 (2H, m), 7.84-7.90 (3H, m), 8.70 (1H, s)

Example 64ae: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.77 (2H, m), 1.96 (2H, m), 2.48 (3H, d), 3.18 (1H, td), 3.38 (1H, m), 3.45 (2H, m), 3.62 (1H, dd), 3.76 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.41 (1H, t), 4.45 (1H, br s), 4.53 (1H, t), 6.41 (1H, t), 6.78 (1H, s), 7.42 (2H, m), 7.84 (1H, s), 7.90 (2H, m), 8.79 (1H, s)

Example 64af: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.74 (2H, m), 1.97 (2H, m), 3.15 (1H, td), 3.40(1H, td), 3.50 -3.60 (3H, m), 3.74 (1H, d), 3.95 (1H, dd), 4.13 (1H, d), 4.40 (1H, br s), 5.90-6.20 (1H, m), 6.50 (1H, t), 6.70 (1H, s), 7.35 (2H, m), 7.76 (3H, m), 7.95 (1H, m), 8.09 (1H, td), 8.75 (1H, d), 8.83 (1H, s)

Example 64ag: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.74 (2H, m), 2.00 (2H, m), 3.15 (1H, td), 3.52 (1H, td), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.13 (1H, d), 4.40 (1H, br s), 6.70 (1H, s), 6.87 (1H, s), 7.43 (2H, m), 7.76-7.81 (3H, m), 7.99 (1H, m), 8.09 (1H, td), 8.75 (1H, s), 8.83 (1H, m), 9.02 (1H, s), 9.60 (1H, s)

Example 64ah: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.61 (2H, dd), 1.90 (2H, dd), 3.17 (1H, m), 3.40 - 3.64 (4H, m), 3.75 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.45 (1H, br s), 5.90 - 6.20(1H, t), 6.49 (1H, t), 6.64 (1H, s), 7.41 (2H, d), 7.66 (2H, m), 7.78 (4H, m), 8.90 (1H, s)

Example 64ai: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, m), 1.62 (2H, m), 1.91 (2H, m), 3.15 (1H, td), 3,45 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.45 (1H, br s), 6.66 (1H, s), 6.87 (1H, s), 7.47 (2H, d), 7.67 (2H, d), 7.79 (2H, d), 7.84 (2H, m), 8.75 (1H, s), 9.10 (1H, s), 9.60 (1H, s)

Example 64aj: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.56 (2H, m), 1.64 (2H, m), 1.94 (2H, m), 3.15-3.25 (2H, m), 3.39 (1H, m), 3.40 - 3.52 (5H, m), 3.65 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.20 (1H, br s, 4.42 (1H, t), 4.54 (2H, m), 4.69 (1H, t), 6.43 (1H, t), 6.77 (1H, s), 7.50 (2H, m), 8.22 (2H, m), 8.81 (1H, s)

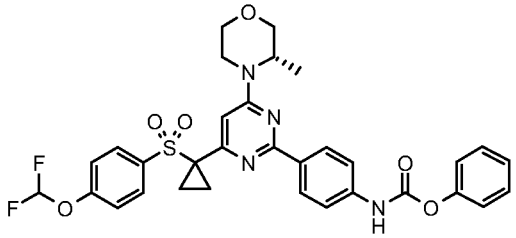
Example 64ak: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.57 (2H, m), 1.64 (2H, m), 1.94 (2H, m), 3.25 (1H, m), 3.51 (1H, m), 3.53 (4H, m), 3.76 (1H, dd), 3.86 (1H, d), 4.10

(1H, dd), 4.30 (1H, d), 4.65 (1H, br s), 4.70 (1H, t), 6.80 (1H, s), 6.87 (1H, s), 7.57 (2H, m), 8.29 (2H, m), 8.76 (1H, s), 9.07 (1H, s), 9.62 (1H, s)

Example 64al: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.60 (2H, m), 1.85 (2H, m), 2.78 (1H, s), 2.95 (1H, s), 3.15 (2H, m), 3.42 (2H, m), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.45 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.70 (1H, s), 7.40 (2H, m), 7.70 -8.00 (3H, m), 8.20 (1H, s), 8.80 (1H, s), 8.91 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

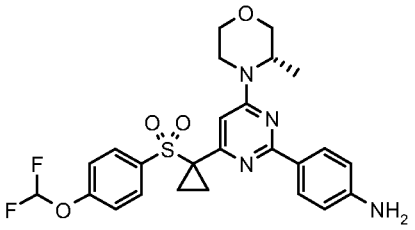


Phenyl chloroformate (0.170 mL, 1.36 mmol) was added dropwise to 4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.700 g, 1.36 mmol) and sodium hydrogen carbonate (0.114 g, 1.36 mmol) in dioxane and the resulting suspension stirred at RT for 6 hours. The reaction mixture was concentrated and diluted with DCM (50 mL), and washed sequentially with water (10 mL), water (10 mL), and saturated brine(10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether:isohexane (20:80) to give the desired material as a white solid (0.710 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, m), 1.62 (2H, dd), 1.90 (2H, dd), 3.16 (1H, td), 3.46 (1H, td), 3.60 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.42 (1H, s), 6.67 (1H, s), 7.24 -7.27 (3H, m), 7.37 (3H, m), 7.45 (2H, m), 7.53 (2H, m), 7.84 (2H, m), 7.93 (2H, m), 10.40 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=637; HPLC tR=3.04 min.

4-[4-[1-[4-(Difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

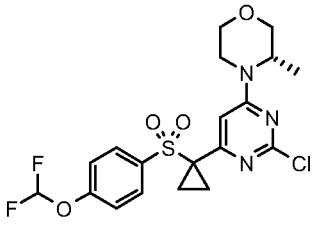


Trans-Dichlorobis(triphenylphosphine)palladium (II) (0.225 g, 0.32 mmol) was added to 2-chloro-4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.95 g, 6.41 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.476 g, 6.74 mmol) and 2M aqueous solution of sodium carbonate (16.04 mL, 32.07 mmol) in the DMF solution (150mL) (DMF solution was 18% DMF, 82% of a 7:3:2 mixture of DME:H_2O:Ethanol) at RT under nitrogen. The resulting solution was stirred at 80°C for 5 hours. The reaction was cooled and the reaction mixture diluted with ethyl acetate and water. The reaction mixture was extracted with ethyl acetate and the combined organics dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% ethyl acetate in DCM, to give the desired material as a beige solid (1.35 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 (2H, dd), 1.87 (2H, dd), 3.26 (1H, td), 3.50 (1H, td), 3.61 (1H, dd), 3.73 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.40 (1H, br s), 5.51 (2H, br s), 6.50 (2H, m), 6.53 (1H, s), 7.21 - 7.60 (1H, m), 7.35 (2H, m), 7.68 (2H, m), 7.83 (2H, m).

LCMS Spectrum: m/z (ES+)(M+H)+=517; HPLC tR=2.53 min.

2-Chloro-4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



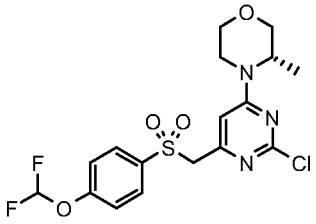
A solution of 50% w/v sodium hydroxide (14.2 mL, 354.96 mmol) was added portionwise to a stirred solution of 2-chloro-4-[[4-(difluoromethoxy)phenyl]sulfonylmethyl]-6-[(3*S*)-3-

methylmorpholin-4-yl]pyrimidine (2.8 g, 6.45 mmol), tetrabutylammonium bromide (0.208 g, 0.65 mmol) and 1,2-dibromoethane (1.668 mL, 19.36 mmol) in toluene (150 mL) and the resulting suspension stirred at 60°C for 6 hours. The reaction mixture was diluted with water (50 mL), and the washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% ethyl acetate in DCM, to give the desired material as a colourless oil which solidified on standing (2.95 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, dd), 1.55 (2H, dd), 1.83 (2H, dd), 3.13 (1H, td), 3.40 (1H, td), 3.54 (1H, dd), 3.69 (1H, d), 3.90 (2H, dd), 4.23 (1H, br s), 6.68 (1H, s), 7.23-7.60 (1H, t), 7.37 (2H, d), 7.82 (2H, d).

LCMS Spectrum: m/z (ES+)(M+H)+=459; HPLC tR=2.49 min.

2-Chloro-4-[[4-(difluoromethoxy)phenyl]sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

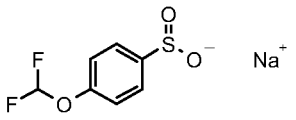


Sodium 4-(difluoromethoxy)benzenesulfinate (2.54 g, 11.03 mmol) was added portionwise to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.25 g, 9.19 mmol) in acetonitrile (125 mL) and the resulting suspension stirred at 80°C for 6 hours. Additional sodium 4-(difluoromethoxy)benzenesulfinate (680mg, 3.39 mmol) was added in one portion and the suspension was stirred at 80°C for a further 2 hours. The reaction mixture was concentrated and diluted with DCM (200 mL) and washed sequentially with 10% aqueous sodium thiosulfate solution (50 mL), water (50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude gum was triturated with diethyl ether to give the desired material as a beige solid (2.94 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 3.15 (1H, td), 3.42 (1H, m), 3.57 (1H, dd), 3.71 (1H, d), 3.91 (1H, br s), 3.92 (1H, dd), 4.17 (1H, br s), 4.64 (2H, s), 6.68 (1H, s), 7.25-7.60 (1H, t), 7.41 (2H, m), 7.84 (2H, m).

LCMS Spectrum: m/z (ES+)(M+H)+=434; HPLC tR=2.29 min.

Sodium 4-(difluoromethoxy)benzenesulfinate

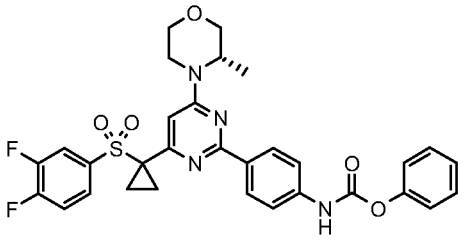


A solution of sodium sulfite (1.470 g, 11.66 mmol) in water (15 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (1.960 g, 23.33 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 1 hour. 4-(Difluoromethoxy)benzene-1-sulfonyl chloride (2.83 g, 11.66 mmol) was added dropwise with caution to the solution and was stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (15 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate was evaporated to give a crude product that was triturated with isohexane to give the desired material as a cream solid (2.85 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.10 (2H, dd), 7.50 (2H, dd).

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl N-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



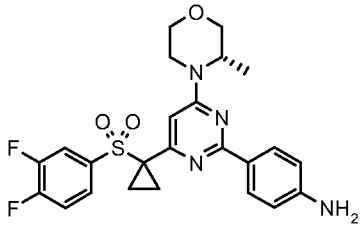
Phenyl chloroformate (0.206 mL, 1.64 mmol) was added dropwise to 4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (800 mg, 1.64 mmol) and sodium hydrogen carbonate (138 mg, 1.64 mmol) in dioxane and

the resulting suspension was stirred at RT for 6 hours. The reaction mixture was concentrated and diluted with DCM (50 mL), and washed sequentially with water (2 x 10 mL), and saturated brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude solid was triturated with acetonitrile to give the desired material as a white solid (1.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.63 (2H, dd), 1.94 (2H, dd), 3.17 (1H, td), 3.47 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.18 (1H, d), 4.50 (1H, br s), 6.71 (1H, s), 7.25 (2H, dt), 7.29 (1H, m), 7.45 (2H, dd), 7.54 (2H, d), 7.67 (2H, m), 7.91 (3H, dd), 10.40 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=607; HPLC tR=3.05 min.

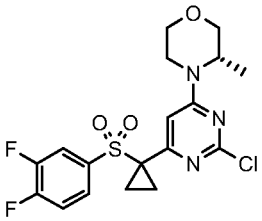
4-[4-[1-(3,4-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Trans-Dichlorobis(triphenylphosphine)palladium (II) (0.252 g, 0.36 mmol) was added to 2-chloro-4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.09 g, 7.19 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.575 g, 7.19 mmol)and a 2M aqueous solution of sodium carbonate (17.97 mL, 35.94 mmol) in the DMF solution (DMF solution was 18% DMF, 82% of a 7:3:2 mixture of DME:H_2O:Ethanol) (150mL) at RT under nitrogen. The resulting solution was stirred at 80°C for 5 hours. The reaction was cooled and the mixture diluted with ethyl acetate and water. The reaction mixture was extracted with ethyl acetate and the combined organics dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0to 5% ethyl acetate in DCM, to give a material which was further purified by ion exchange chromatography using an SCXcolumn, eluting with 7M ammonia in methanol, to give the desired material as a tan solid (1.94 g).

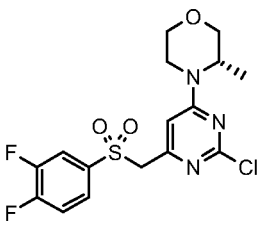
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 (2H, dd), 1.91 (2H, dd), 3.10 (1H, td), 3.45 (1H, td), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.13 (1H, m), 4.43 (1H, br s), 5.53 (2H, d), 6.50 (2H, m), 6.57 (1H, s), 7.64 (1H, m), 7.65 (3H, m), 7.89 (1H, m).
LCMS Spectrum: m/z (ES+)(M+H)+=487; HPLC tR=2.55 min.

2-Chloro-4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



A solution of 50% w/v sodium hydroxide (17.32 mL, 433.10 mmol) was added portionwise to a stirred solution of 2-chloro-4-[(3,4-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.18 g, 7.87 mmol), tetrabutylammonium bromide (0.254 g, 0.79 mmol) and 1,2-dibromoethane (2.036 mL, 23.62 mmol) in toluene (200 mL) and the resulting suspension stirred at 60°C for 6 hours. The reaction mixture was diluted with water (50 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a white solid (3.09 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.56 (2H, dd), 1.88 (2H, dd), 3.15 (1H, td), 3.40 (1H, td), 3.54 (1H, dd), 3.69 (1H, d), 3.91 (1H, dd), 3.97 (1H, d), 4.29 (1H, br s), 6.73 (1H, s), 7.65 (1H, m), 7.66 (1H, m), 7.92 (1H, ddd).
LCMS Spectrum: m/z (ES+)(M+H)+=430; HPLC tR=2.41 min.

2-Chloro-4-[(3,4-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

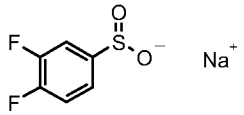


Sodium 3,4-difluorobenzenesulfinate (3.40 g, 16.97 mmol) was added portionwise to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (6 g, 16.97 mmol) in acetonitrile (200 mL) and the resulting suspension stirred at 80°C for 6 hours. Additional sodium 3,4-difluorobenzenesulfinate (680mg, 3.39mmol) was added in one portion and the suspension was stirred at 80°C for a further 2 hours. The reaction mixture was concentrated and diluted with DCM (200 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% ethyl acetate in DCM, to give the desired material as a yellow solid (4.58 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, m), 3.10-3.20 (1H, td), 3.40-3.45 (1H, td), 3.55-3.60 (1H, dd), 3.70 (1H, d), 3.90-4.00 (2H, dd), 4.20 (1H, br s), 4.70 (2H, s), 6.77 (1H, s), 7.66 (1H, m), 7.74 (1H, dt), 7.95 (1H, ddd).

LCMS Spectrum: m/z (ES+)(M+H)+=404; HPLC tR=2.24 min.

Sodium 3,4-difluorobenzenesulfinate



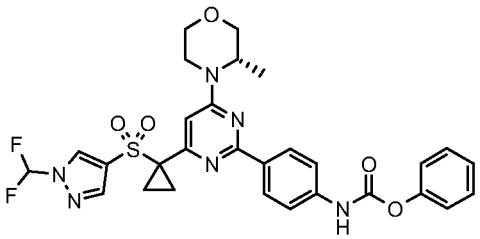
A solution of sodium sulfite (2.96 g, 23.52 mmol) in water (25 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (3.95 g, 47.04 mmol) was added to the stirred solution. The resulting solutionwas stirred at 50°C for 1 hour. 3,4-Difluorobenzene-1-sulfonyl chloride (5 g, 23.52 mmol) was added portionwise to the solution and was stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (15 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate was evaporated to afford the desired material as a white solid (5.30 g), which was dried overnight under vacuum and used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.28 (1H, ddd), 7.37 (2H, m).

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier

The preparation of phenyl *N*-[4-[4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

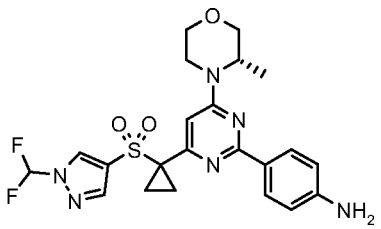


Phenyl chloroformate (0.018 mL, 0.14 mmol) was added dropwise to 4-[4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (70 mg, 0.14 mmol) and sodium hydrogen carbonate (11.99 mg, 0.14 mmol) in dioxane and the resulting suspension stirred at RT for 6 hours. The reaction mixture was concentrated and diluted with DCM (50 mL), and washed sequentially with water (2 x 10 mL), and saturated brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude solid was triturated with diethyl ether:isohexane (20:80) to give the desired material as a white solid (80 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 (2H, m), 1.89 (2H, m), 3.15 (1H, td), 3.45 (1H, td), 3.63 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.50 (1H, br s), 6.75 (1H, m), 7.26 (3H, m), 7.45 (2H, m), 7.56 (2H, m), 7.70-8.00 (1H, t),8.00 (2H, m), 8.17 (1H, s), 8.93 (1H, s), 10.40 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=611; HPLC tR=2.83 min.

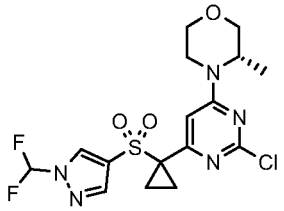
4-[4-[1-[1-(Difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Trans-Dichlorobis(triphenylphosphine)palladium (II) (0.197 g, 0.28 mmol) was added to 2-chloro-4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.44 g, 5.62 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.232 g, 5.62 mmol) and a 2M aqueous solution of sodium carbonate (14.06 mL, 28.12 mmol) in the DMF solution (DMF solution was 18% DMF, 82% of a 7:3:2 mixture of DME:H_2O:Ethanol) (150mL) and the resulting solution stirred at 80°C for 5 hours. The reaction mixture was partitioned between ethyl acetate and water, the layers separated and the aqueous layer extracted with ethyl acetate. The combined organics were dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% ethyl acetate in DCM, to give the desired material as a tan solid (0.070 g).

LCMS Spectrum: m/z (ES+)(M+H)+=491; HPLC tR=2.23 min.

2-Chloro-4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



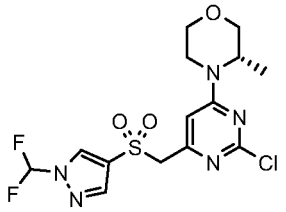
A solution of 50% w/v sodium hydroxide (16.18 mL, 404.59 mmol) was added portionwise to a stirred solution of 2-chloro-4-[[1-(difluoromethyl)pyrazol-4-yl]sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3 g, 7.36 mmol), tetrabutylammonium bromide (0.237 g, 0.74 mmol) and 1,2-dibromoethane (1.902 mL, 22.07 mmol) in toluene (200 mL) and the resulting suspension stirred at RT for 6 hours. The reaction mixture was diluted with water (50 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% ethyl acetate in DCM, to give the desired material as a yellow oil (2.44 g) which solidified on standing.

NMR Spectrum: ^1H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.57 (2H, dd), 1.82 (2H, dd), 3.16 (1H, td), 3.40 (1H, td), 3.56 (1H, dd), 3.70 (1H, d), 3.92 (1H, dd), 4.04 (1H, d), 4.30

(1H, br s), 6.78 (1H, s), 7.70-8.00 (1H, t), 8.19 (1H, s), 8.93 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=434; HPLC tR=2.15 min.

2-Chloro-4-[[1-(difluoromethyl)pyrazol-4-yl]sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

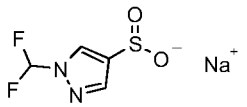


Sodium 1-(difluoromethyl)-1H-pyrazole-4-sulfinate (3.28 g, 16.09 mmol) was added portionwise to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.74 g, 13.41 mmol) in acetonitrile (150 mL) and the resulting suspension stirred at 80°C for 6 hours. Additional sodium 1-(difluoromethyl)-1H-pyrazole-4-sulfinate (680 mg, 3.39mmol) was added in one portion and the suspension was stirred at 80°C for a further 2 hours. The reaction mixture was concentrated and diluted with DCM (200 mL), and washed sequentially with 10% aqueous sodium thiosulfate solution (50 mL), water (50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude residue was triturated with diethyl ether to give the desired material as a beige solid (4.50 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 3.18 (1H, td), 3.43 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (2H, dd), 4.21 (1H, br s), 4.67 (2H, s), 6.77 (1H, s), 7.70-8.05 (1H, t), 8.13 (1H, s), 8.87 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=408; HPLC tR=1.91 min.

Sodium 1-(difluoromethyl)-1H-pyrazole-4-sulfinate



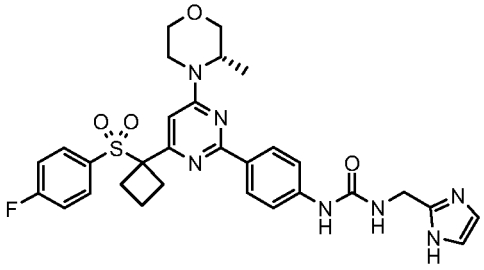
A solution of sodium sulfite (2.87 g, 22.81 mmol) in water (25 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (3.83 g, 45.62 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 1hour. 1-(Difluoromethyl)-1H-pyrazole-4-sulfonyl chloride (4.94 g, 22.81 mmol) was added dropwise with caution to the solution and was

stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (15 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to give a solid which was triturated with isohexane to give the desired material as a white solid (5.85 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.60 (1H, m), 7.74 (1H, s), 7.90 (1H, m).

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier

Example 65: 1-[4-[4-[1-(4-Fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea

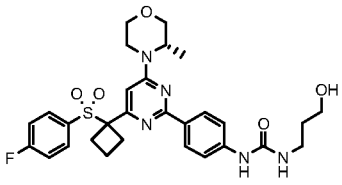
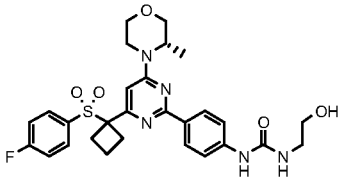
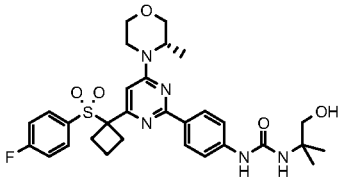
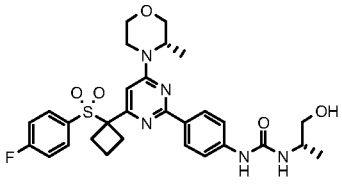


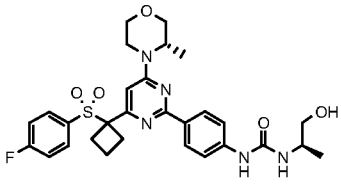
C-(1*H*-Imidazol-2-yl)-methylamine (17.73 mg, 0.18 mmol) was added in one portion to phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) and triethylamine (0.069 mL, 0.50 mmol) in NMP (2 mL) at RT and stirred for a period of 16 hours under air. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a cream solid (42 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (d, 3H), 1.83 - 1.93 (m, 1H), 2.04 - 2.15 (m, 1H), 2.75 - 2.82 (m, 2H), 3.02 - 3.11 (m, 2H), 3.16 (td, 1H), 3.49 (td, 1H), 3.64 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.15 (d, 1H), 4.32 (d, 2H), 4.44 - 4.54 (m, 1H), 6.55 (s, 1H), 6.60 (t, 1H), 6.80 - 6.90 (m, 1H), 7.00 - 7.08 (m, 1H), 7.29 (dd, 2H), 7.40 (dt, 2H), 7.55 (ddd, 2H), 7.80 (d, 2H), 8.90 (s, 1H), 11.85 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 606.55; HPLC tR = 2.09 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
65a		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	584.5	2.15
65b		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	570.5	2.05
65c		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	598.6	2.33
65d		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea	584.5	2.15

Example	Structure	NAME	LCMS MH+	Retention time (min)
65e		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea	584.5	2.13

Example 65a : ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (d, 3H), 1.57 - 1.63 (m, 2H), 1.83 - 1.94 (m, 1H), 2.05 - 2.15 (m, 1H), 2.75 - 2.82 (m, 2H), 3.01 - 3.09 (m, 2H), 3.17 (dd, 3H), 3.48 (dd, 3H), 3.64 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.10 - 4.19 (m, 1H), 4.48 (t, 2H), 6.18 (t, 1H), 6.54 (s, 1H), 7.29 (t, 2H), 7.38 (d, 2H), 7.55 (ddd, 2H), 7.78 (d, 2H), 8.68 (s, 1H)

Example 65b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (d, 3H), 1.83 - 1.94 (m, 1H), 2.04 - 2.15 (m, 1H), 2.75 - 2.82 (m, 2H), 3.01 - 3.09 (m, 2H), 3.16 - 3.20 (m, 3H), 3.44 - 3.50 (m, 3H), 3.64 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.09 - 4.19 (m, 1H), 4.43 - 4.53 (m, 1H), 4.73 (t, 1H), 6.23 (t, 1H), 6.54 (s, 1H), 7.29 (t, 2H), 7.37 (d, 2H), 7.55 (ddd, 2H), 7.78 (d, 2H), 8.77 (s, 1H)

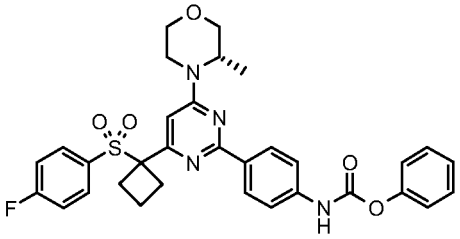
Example 65c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (d, 3H), 1.25 (s, 6H), 1.83 - 1.94 (m, 1H), 2.05 - 2.15 (m, 1H), 2.73 - 2.83 (m, 2H), 3.01 - 3.09 (m, 2H), 3.12 - 3.20 (m, 1H), 3.39 (d, 2H), 3.49 (td, 1H), 3.64 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.10 - 4.18 (m, 1H), 4.43 - 4.53 (m, 1H), 4.96 (t, 1H), 5.98 (s, 1H), 6.54 (s, 1H), 7.27 - 7.35 (m, 4H), 7.53 - 7.57 (m, 2H), 7.77 (d, 2H), 8.70 (s, 1H)

Example 65d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.09 (d, 3H), 1.21 (d, 3H), 1.82 - 1.93 (m, 1H), 2.02 - 2.15 (m, 1H), 2.75 - 2.82 (m, 2H), 3.01 - 3.11 (m, 2H), 3.16 (td, 1H), 3.33 - 3.43 (m, 2H), 3.49 (td, 1H), 3.64 (dd, 1H), 3.69 - 3.73 (m, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.11 - 4.19 (m, 1H), 4.44 - 4.53 (m, 1H), 4.79 (t, 1H), 6.08 (d, 1H), 6.54 (s, 1H), 7.29 (ddd, 2H), 7.36 (d, 2H), 7.55 (ddd, 2H), 7.78 (d, 2H), 8.68 (s, 1H)

Example 65e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.09 (d, 3H), 1.21 (d, 3H), 1.83 - 1.94 (m, 1H), 2.05 - 2.15 (m, 1H), 2.75 - 2.82 (m, 2H), 3.01 - 3.09 (m, 2H), 3.16 (td, 1H), 3.33 - 3.43 (m, 2H), 3.49 (td, 1H), 3.64 (dd, 1H), 3.69 - 3.73 (m, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.10 - 4.18 (m, 1H), 4.44 - 4.53 (m, 1H), 4.79 (t, 1H), 6.08 (d, 1H), 6.54 (s, 1H), 7.29 (ddd, 2H), 7.36 (d, 2H), 7.55 (ddd, 2H), 7.78 (d, 2H), 8.68 (s, 1H)

The preparation of phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

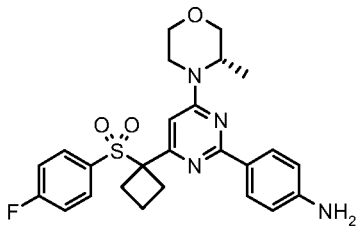


Phenyl chloroformate (0.285 mL, 2.27 mmol) was added dropwise to 4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.095 g, 2.27 mmol) and sodium hydrogencarbonate (0.191 g, 2.27 mmol) in dioxane (20 mL) and the resulting suspension was stirred at RT for 3 hours. The reaction mixture was evaporated and DCM (50 mL) added and washed sequentially with water (2 x 20 mL), and saturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford desired material as a dry film (1.4 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.22 (d, 3H), 1.84 - 1.95 (m, 1H), 2.05 - 2.16 (m, 1H), 2.74 - 2.86 (m, 2H), 3.02 - 3.12 (m, 2H), 3.17 (td, 1H), 3.45 - 3.55 (m, 1H), 3.61 - 3.69 (m, 1H), 3.71 - 3.85 (m, 1H), 3.93 - 4.03 (m, 1H), 4.11 - 4.24 (m, 1H), 4.45 - 4.58 (m, 1H), 7.22 - 7.35 (m, 5H), 7.42 - 7.49 (m, 2H), 7.50 - 7.60 (m, 4H), 7.88 (d, 2H), 10.40 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 603.17; HPLC tR = 3.15 min.

4-[4-[1-(4-Fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

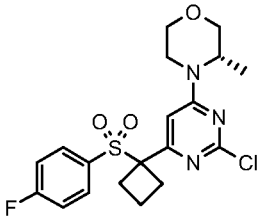


Bis(triphenylphosphine)palladium(II) chloride (0.086 g, 0.12 mmol) was added in one portion to 2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.046 g, 2.46 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.538 g, 2.46 mmol) and sodium carbonate (6.14 mL, 12.28 mmol) in a DMF:DME :water:ethanol solution and the reaction mixture thoroughly degassed and stirred at 80°C for 3 hours under a nitrogen atmosphere. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL), and washed sequentially with water (50 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 100% ethyl acetate in isohexane, to afford desired material as a colourless dry film (1.1 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (d, 3H), 1.82 - 1.95 (m, 1H), 2.03 - 2.14 (m, 1H), 2.71 - 2.82 (m, 2H), 2.98 - 3.08 (m, 2H), 3.13 (td, 1H), 3.48 (td, 1H), 3.63 (dd, 1H), 3.75 (d, 1H), 3.93 - 3.99 (m, 1H), 4.07 - 4.15 (m, 1H), 4.41 - 4.49 (m, 1H), 5.49 (d, 1H), 6.44 (s, 1H), 6.49 (d, 2H), 7.28 (ddd, 2H), 7.54 (ddd, 2H), 7.62 (d, 2H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 483.27; HPLC tR = 2.39 min.

2-Chloro-4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



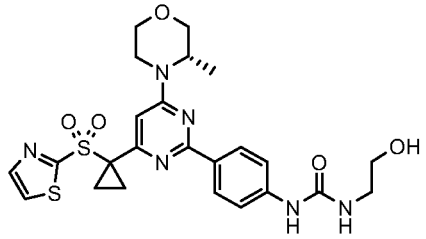
Sodium hydroxide (50%w/w solution) (16.91 g, 422.79 mmol) was added to 2-chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.966 g, 7.69 mmol), 1,3-dibromopropane (2.341 mL, 23.06 mmol) and tetrabutylammonium bromide (0.248 g, 0.77 mmol) in toluene (150 mL) and the resulting suspension stirred at 45°C for 1 hour. The organics were washed with water twice, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 10 to 30% ethyl acetate in DCM, to afford desired material as a colourless dry film (1.055 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (d, 3H), 1.81 - 1.92 (m, 1H), 2.01 - 2.12 (m, 1H), 2.65 - 2.72 (m, 2H), 2.91 - 3.01 (m, 2H), 3.14 (td, 1H), 3.42 (td, 1H), 3.57 (dd, 1H), 3.71 (d, 1H), 3.88 - 4.00 (m, 2H), 4.23 - 4.40 (m, 1H), 6.56 (s, 1H), 7.38 - 7.44 (m, 2H), 7.54 - 7.60 (m, 2H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 426.06; HPLC tR = 2.52 min.

The preparation of 2-chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 66: 3-(2-Hydroxyethyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

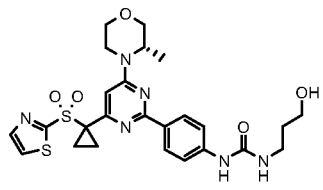
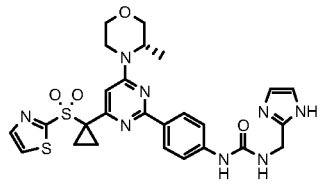


Ethanolamine (0.052 mL, 0.87 mmol) was added in one portion to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) and triethylamine (0.072 mL, 0.52 mmol) in NMP (2 mL) and warmed to 55ºC over a period of 16 hours under air. The crude reaction mixture was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to afford the desired material as a colourless dry film. (84 mg)

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (d, 3H), 1.77 - 1.82 (m, 2H), 1.98 - 2.02 (m, 2H), 3.14 - 3.21 (m, 3H), 3.44 - 3.50 (m, 3H), 3.62 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.10 - 4.21 (m, 1H), 4.40 - 4.51 (m, 1H), 4.74 (t, 1H), 6.25 (t, 1H), 6.74 (s, 1H), 7.40 (d, 2H), 7.85 (d, 2H), 8.24 (d, 1H), 8.29 (d, 1H), 8.78 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 545.75; HPLC tR = 1.79 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

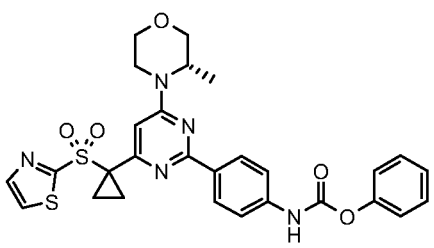
Example	Structure	NAME	LCMS MH+	Retention time (min)
66a		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	559.8	1.84
66b		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	581.8	1.30

Example 66a : ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21, 1.60, 1.77 - 1.82, 1.97 - 2.03, 3.14 - 3.21, 3.44 - 3.50, 3.62, 3.76, 3.97, 4.12 - 4.20, 4.40 - 4.52, 4.49, 6.19, 6.74, 7.40, 7.85, 8.23, 8.28, 8.68

Example 66b : ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (d, 3H), 1.77 - 1.82 (m, 2H), 1.97 - 2.03 (m, 2H), 3.14 - 3.21 (m, 1H), 3.47 (td, 1H), 3.62 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.11 - 4.21 (m, 1H), 4.32 (d, 2H), 4.39 - 4.54 (m, 1H), 6.62 (t, 1H), 6.74 (s, 1H), 6.88 - 7.01 (m, 2H), 7.43 (d, 2H), 7.87 (d, 2H), 8.23 (d, 1H), 8.28 (d, 1H), 8.90 (s, 1H), 11.85 (s, 1H)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate

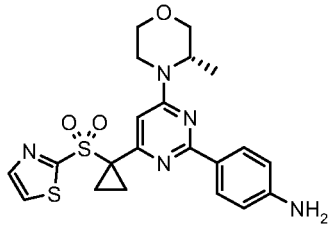


Phenyl chloroformate (0.123 mL, 0.98 mmol) was added dropwise to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline (450 mg, 0.98 mmol) and sodium hydrogencarbonate (83 mg, 0.98 mmol) in dioxane and the resulting suspension stirred at RT for 3 hours. The reaction mixture was evaporated and DCM (50 mL) added and washed sequentially with water (2 x 20 mL), and saturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford desired product as a dry film (522 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.22 (d, 3H), 1.78 - 1.84 (m, 2H), 1.98 - 2.04 (m, 2H), 3.19 (td, 1H), 3.48 (td, 1H), 3.63 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.12 - 4.24 (m, 1H), 4.40 - 4.52 (m, 1H), 6.79 (s, 1H), 7.23 - 7.32 (m, 3H), 7.46 (t, 2H), 7.55 (d, 2H), 7.95 (d, 2H), 8.24 (d, 1H), 8.29 (d, 1H), 10.41 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 578.04; HPLC tR = 2.83 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline



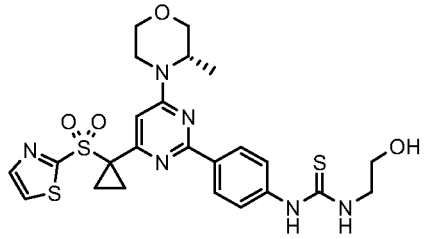
Bis(triphenylphosphine)palladium(II) chloride (0.139 g, 0.20 mmol) was added in one portion to 2-chloro-4-[(*3S)*-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidine (1.59 g, 3.97 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.869 g, 3.97 mmol) and sodium carbonate (9.92 mL, 19.83 mmol) in a DMF, DME, water and ethanol solution at RT under nitrogen. The reaction mixture was thoroughly degassed and was stirred at 80°C for 3 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL), and washed sequentially with water (50 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 100 % ethyl acetate in isohexane, to afford desired material as a beige dry film (1.430 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.16 - 1.21 (m, 3H), 1.75 - 1.79 (m, 2H), 1.96 - 2.01 (m, 2H), 3.14 (td, 1H), 3.46 (td, 1H), 3.61 (dd, 1H), 3.75 (d, 1H), 3.96 (dd, 1H), 4.07 - 4.17 (m, 1H), 4.35 - 4.48 (m, 1H), 5.50 - 5.55 (m, 1H), 6.52 (d, 2H), 6.63 (s, 1H), 7.69 (d, 2H), 8.22 (d, 1H), 8.27 (d, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 458.16; HPLC tR = 1.68 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidine was described earlier.

Example 67: 3-(2-Hydroxyethyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]thiourea



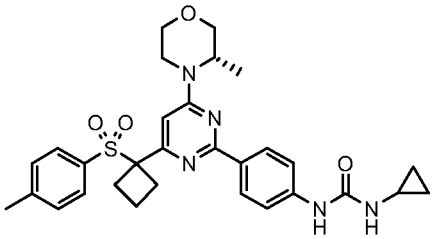
A solution of 1,1'-thiocarbonyldiimidazole (50.6 mg, 0.28 mmol) in DCM (2 mL) was added to a stirred solution 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline (100 mg, 0.22 mmol) in THF (1 mL) and DCM (2 mL) at RT, over a period of 2 minutes under nitrogen. The resulting solution was stirred at RT for 2 hours. Triethylamine (0.030 mL, 0.22 mmol) and ethanolamine (0.066 mL, 1.09 mmol) were added to the reaction mixture. The resulting solution was stirred at RT for 60 hours. The reaction mixture was evaporated to dryness and redissolved in acetonitrile (2 mL), filtered and purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to afford desired material as a beige solid (88 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.22 (d, 3H), 1.78 - 1.84 (m, 2H), 1.98 - 2.03 (m, 2H), 3.19 (td, 1H), 3.48 (td, 1H), 3.54 - 3.60 (m, 3H), 3.63 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.16 (d, 1H), 4.41 - 4.53 (m, 1H), 4.78 - 4.88 (m, 1H), 6.79 (s, 1H), 7.54 (d, 2H), 7.82 - 7.89 (m, 1H), 7.92 (dt, 2H), 8.24 (d, 1H), 8.28 (d, 1H), 9.78 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 561.82; HPLC tR = 2.12 min.

The preparation of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline was described earlier.

Example 68: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]phenyl]urea

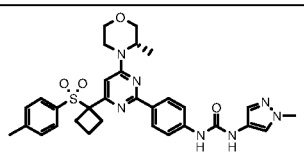


Triethylamine (0.057 mL, 0.41 mmol) was added to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]phenyl]carbamate (82 mg, 0.14 mmol) and cyclopropylamine (0.047 mL, 0.68 mmol) in NMP (2 mL) and the resulting solution stirred at 50°C overnight. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (43 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44(2H, m), 0.63-0.67(2H, m), 1.19-1.20(3H, d), 1.81-1.92(1H, m), 2.02-2.13(1H, m), 2.27(3H, s), 2.54-2.59(1H, m), 2.73-2.79(2H, m), 2.99-3.07(2H, m), 3.09-3.17(1H, td), 3.45-3.51(1H, td), 3.62-3.65(1H, dd), 3.74-3.77(1H, d), 3.95-3.98(1H, dd), 4.07-4.10(1H, d), 4.44(1H, bs), 6.40-6.41(1H, d), 6.45(1H, s), 7.24-7.26(2H, d), 7.35-7.40(4H, m), 7.76-7.78(2H, d), 8.49(1H, s).

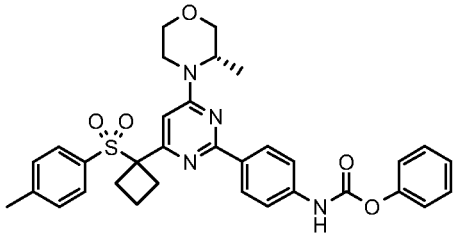
LCMS Spectrum: m/z (ESI+)(M+H)+562 = HPLC tR =2.60 min.

The following compound was made in an analogous fashion using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
68a		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	601	2.44

Example 68a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21(3H, d), 1.83-1.90(1H, m), 2.04-2.12(1H, m), 2.28(3H, s), 2.73-2.80(2H, m), 3.00-3.07(2H, m), 3.10-3.15(1H, td), 3.45-3.52(1H, td), 3.62-3.66(1H, dd), 3.75-3.78(1H, d), 3.79(3H, s), 3.95-3.99(1H, dd), 4.08-4.11(1H, d), 4.45(1H, bs), 6.46(1H, s), 7.24-7.26(2H, d), 7.35-7.38(3H, m), 7.42-7.44(2H, d), 7.77(1H, s), 7.79-7.81(2H, d), 8.35(1H, s), 8.79(1H, s).

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]phenyl]carbamate

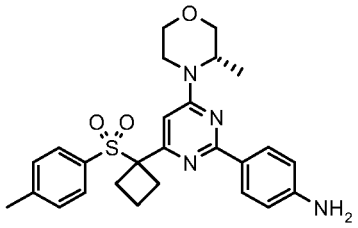


Phenyl chloroformate (0.034 mL, 0.27 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]aniline (129 mg, 0.27 mmol)and sodium hydrogen carbonate (34.0 mg, 0.40 mmol) in dioxane (10 mL). The resulting suspension was stirred at RT for 5 hours. The reaction mixture was evaporated to dryness and redissolved in ethyl acetate(125 mL), and washed sequentially with water (125 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material (182 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, CDCl3) δ 1.34 (3H, d), 1.87 - 1.98 (1H, m), 2.19 - 2.30 (4H, m), 2.72 - 2.81 (2H, m), 3.15 - 3.25 (2H, m), 3.30 (1H, td), 3.63 (1H, td), 3.70 (1H, s), 3.72 - 3.82 (3H, m), 4.03 - 4.16 (3H, m), 4.46 (1H, q), 6.56 (1H, s), 7.01 (21H, s), 7.07 (2H, d), 7.19 - 7.27 (3H, m, obscured by CDCL3 peak), 7.35 - 7.42 (6H, m), 7.91 (2H, d).

LCMS Spectrum: m/z (ES+)(M+H)+=599; HPLC tR=3.25 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]aniline

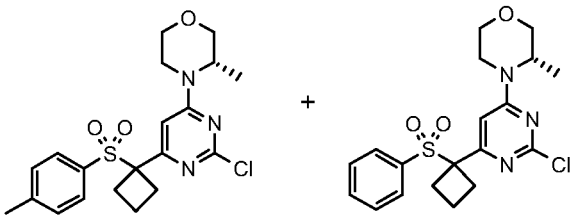


Bis(triphenylphosphine)palladium(II) chloride (0.131 g, 0.19 mmol) was added in one portion to a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidine and 4-[1-(benzenesulfonyl)cyclobutyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.522 g), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.817 g, 3.73 mmol) and a solution of sodium carbonate (9.33 mL, 18.66 mmol) in DMF (18 mL), DME (47.8 mL), water (20.5 mL)and ethanol (13.5 mL) and the resulting solution stirred at 80°C for 2 hours. The reaction mixture was concentrated *in vacuo* to remove the ethanol then the reaction mixture was acidified with 2M hydrochloric acid. The resulting suspension was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, followed by preparative HPLC, to give the desired material as an off white solid (0.136 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.85 - 1.97 (1H, m), 2.17 - 2.29 (4H, m), 2.71 - 2.81 (2H, m), 3.11 - 3.33 (3H, m), 3.61 (1H, t), 3.74 - 3.90 (4H, m), 4.03 (1H, d), 4.09 - 4.15 (1H, m), 4.44 (1H, q), 6.48 (1H, s), 6.57 (2H, d), 7.07 (2H, d), 7.36 (2H, d), 7.75 (2H, d).

LCMS Spectrum: m/z (ES+)(M+H)+=479; HPLC tR=2.23 min.

Mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidine and 4-[1-(benzenesulfonyl)cyclobutyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

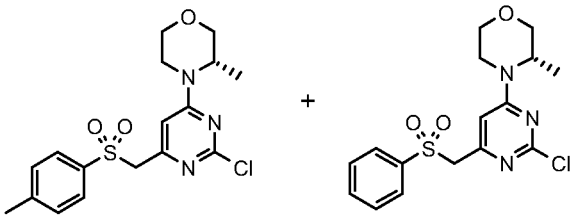


Sodium hydroxide (50%w/w solution) (52.4 g, 654.89 mmol) was added to a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine and 4-(benzenesulfonylmethyl)-2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (4.38 g), 1,3-dibromopropane (3.63 mL, 35.72 mmol) and tetrabutylammonium bromide (0.384 g, 1.19 mmol) in toluene (270 mL). The resulting suspension was stirred at 45°C for 1 hour. The reaction mixture was diluted with water (300 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give a white solid (1.522 g) which appeared to be a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidine (12%) and 4-[1-(benzenesulfonyl)cyclobutyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (83%). The mixture was taken through into the next step with no further purification.

LCMS Spectrum: m/z (ES+)(M+H)+=422; HPLC tR=2.59 min.

LCMS Spectrum: m/z (ES+)(M+H)+=408; HPLC tR=2.45 min.

Mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine and 4-(benzenesulfonylmethyl)-2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine



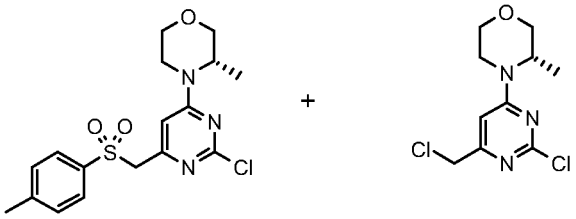
Benzenesulfinic acid, sodium salt (3.66 g, 22.32 mmol) was added to a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine and 2-chloro-4-(chloromethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (5.85 g) in acetonitrile (200 mL) under argon. The resulting suspension was stirred at reflux for 18 hours. Additional benzenesulfinic acid, sodium salt (1.2 g, 7.31 mmol) and sodium iodide (0.335 g, 2.23 mmol) were added and the suspension was stirred at reflux for a further 24 hours. The reaction mixture was evaporated to dryness, redissolved in DCM (500 mL) and washed with water (250 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude material was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate

in DCM, to give a white solid (4.38 g) which appeared to be a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine (7%) and 4-(benzenesulfonylmethyl)-2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (93%). The mixture was taken through into the next step with no further purification.

LCMS Spectrum: m/z (ES+)(M+H)+=382; HPLC tR=2.23 min.

LCMS Spectrum: m/z (ES+)(M+H)+=368; HPLC tR=2.06 min.

Mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine and 2-chloro-4-(chloromethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine



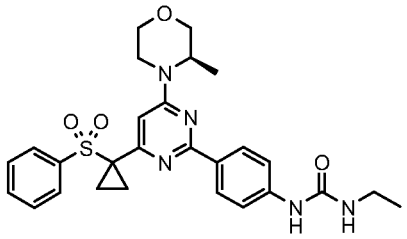
A solution of p-toluenesulfonyl chloride (23.47 g, 123.11 mmol) in DCM (50 mL) was added dropwise to a stirred solution of [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (20 g, 82.07 mmol) and DIPEA (21.44 mL, 123.11 mmol) in DCM (200 mL) cooled to 5ºC, over a period of 1 hour under nitrogen. The resulting solution was stirred at 5°C for 72 hours and then at reflux for 24 hours. The reaction mixture was washed with water and the organic layer was dried over $MgSO_4$, filtered and evaporated to afford a brown gum which appeared to be a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine (11%) and 2-chloro-4-(chloromethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (87%). The mixture was taken through into the next step with no further purification.

LCMS Spectrum: m/z (ES+)(M+H)+=398; HPLC tR=2.52 min.

LCMS Spectrum: m/z (ES+)(M+H)+=262; HPLC tR=1.97 min.

The preparation of [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol was described earlier.

Example 69: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*R*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea

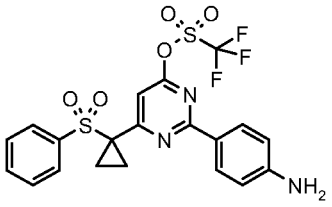


Triethylamine (0.064 mL, 0.46 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.104 g, 0.21 mmol), (*R*)-3-methylmorpholine (0.042 g, 0.42 mmol) in dioxane (5 mL) and the resulting solution stirred at RT overnight. Ethyl isocyanate (0.494 mL, 6.25 mmol) was added and the solution was allowed to stir at RT overnight. Methanol was added carefully and then all of the solvent was removed. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a tan solid (0.052 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) 1.05-1.08 (3H, t), 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.88-1.92 (2H, m), 3.09-3.19 (3H, m), 3.42-3.49 (1H, td), 3.59-3.62 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.08-4.12 (1H, d), 4.37(1H, bs), 6.13-6.16 (1H, t), 6.62 (1H, s), 7.37-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.85 (4H, m), 8.63 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=522; HPLC tR=2.32min.

[2-(4-Aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate



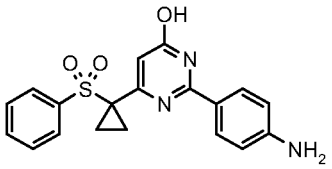
2-(4-Aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-ol (4.0 g, 10.89 mmol), 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methanesulfonamide (4.28 g, 11.98 mmol)were dissolved in DCM (75 mL), to this was added DBU (1.791 mL, 11.98 mmol) and the reaction was stirred at RT overnight. The solvent was evaporated to dryness and the gum

was quenched with 1.0N citric acid (100 mL) and extracted with diethyl ether (3 x 100 mL). The combined organics were dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The solid was passed through a silica plug, eluting with diethyl ether, to give a yellow solid. This solid was dissolved in a minimum amount hot diethyl ether, to which iso-hexane was added and the system was stirred to afford the desired material as a yellow solid (1.5 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) 1.79 (2H, q), 2.02 (2H, q), 5.43 (2H, s), 6.62 (2H, d), 7.43 (1H, s), 7.59 (2H, t), 7.68 (2H, d), 7.72 (1H, t), 7.80 (2H, d).

LCMS Spectrum: m/z (ES+)(M+H)+=500; HPLC tR=2.96min

2-(4-Aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-ol

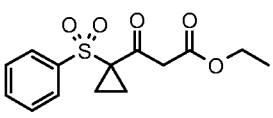


Ethyl 3-[1-(benzenesulfonyl)cyclopropyl]-3-oxopropanoate (5.4 g, 15.12 mmol), 4-aminobenzamidine dihydrochloride (3.78 g, 18.15 mmol) and potassium carbonate (3.83 mL, 63.52 mmol) were added to methanol (150 mL) and heated at reflux overnight. The solvent was evaporated to dryness and the remaining solid was acidified with 1.0N citric acid. The solid was filtered and then triturated with hot acetonitrile to give the desired material as a yellow solid (4.0 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) 1.58 (2H, q), 1.86 (2H, q), 5.86 (2H, s), 6.21 (1H, s), 6.50 (2H, d), 7.51 (2H, d), 7.60 (2H, t), 7.72 (1H, t), 7.82 (2H, d), 12.11 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=368; HPLC tR=1.23min

Ethyl 3-[1-(benzenesulfonyl)cyclopropyl]-3-oxopropanoate

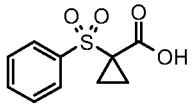


Triethylamine (20.70 mL, 148.51 mmol) and magnesium chloride (9.28 g, 97.46 mmol) were added to a stirred solution of potassium 3-ethoxy-3-oxopropanoate (15.80 g, 92.82 mmol) in acetonitrile (150 mL). The reaction was stirred for 2 hours. 1-(Benzenesulfonyl)cyclopropane-1-carboxylic acid (10.5 g, 46.41 mmol) and 1,1'-carbonyldiimidazole (9.03 g, 55.69 mmol) were dissolved in acetonitrile (30 mL) and stirred for 2 hours. This was then added to the

initial reaction and the system was stirred over the weekend at RT. 2M hydrochloric acid (150 mL) was added and the mixture extracted with diethyl ether (3 x 50 mL), the organics separated and evaporated to afford an orange oil. This oil was washed with a saturated solution of sodium hydrogen carbonate (100 mL) and extracted with diethyl ether (3 x 100 mL). The organics were dried over $MgSO_4$, filtered and evaporated to afford a yellow gum. This was passed through a plug of silica, eluting with DCM, to afford a colourless gum. The crude product was further purified by flash silica chromatography, eluting with DCM, to give the desired material as a colourless gum (5.6 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.23 (3H, t), 1.74 (2H, q), 1.99 (2H, q), 3.77 (2H, s), 4.12 (2H, q), 7.57 (2H, t), 7.67 (1H, t), 7.92 (2H, d).

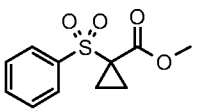
1-(Benzenesulfonyl)cyclopropane-1-carboxylic acid



Methyl 1-(benzenesulfonyl)cyclopropane-1-carboxylate (11 g, 45.78 mmol) was added to ethanol (50 mL) and water (50 mL), to this was added sodium hydroxide (1.904 mL, 48.07 mmol) and the reaction was stirred for 1 hour. The ethanol was carefully evaporated and the reaction mixture was extracted with diethyl ether (1 x 100 mL). The aqueous layer was quenched with 2M hydrochloric acid (50 mL), extracted with diethyl ether (3 x 100 mL) and the combined organics dried over MgSO4, filtered and evaporated to afford a white solid. The crude solid was triturated with ethyl acetate to give the desired material as a white solid (10.5 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.63 (2H, q), 1.85 (2H, q), 7.63 (2H, t), 7.73 (1H, t), 7.97 (2H, d).

Methyl 1-(benzenesulfonyl)cyclopropane-1-carboxylate



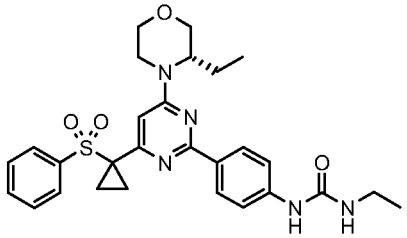
Methyl 2-(phenylsulfonyl)acetate (15 g, 70.02 mmol), benzyltriethylammonium chloride (4.77 g, 21.00 mmol), Potassium carbonate (29.0 g, 210.05 mmol) and 1,2-dibromoethane (12.07 mL, 140.03 mmol) were added to toluene (200 mL) and heated at 100°C over the

weekend. The reaction was filtered and solvent evaporated to afford a viscous gum. This reaction mixture was quenched with water (100 mL) and extracted with diethyl ether (3 x 100 mL). The organics were dried over $MgSO_4$, filtered and evaporated to afford an orange liquid. This liquid was passed through a plug of silica, eluting with diethyl ether, to afford an orange gum. The crude gum was triturated with ethanol to give the desired material as a white solid (11.0 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 11.70 (2H, q), 2.00 (2H, q), 3.63 (3H, s), 7.55 (2H, t), 7.64 (1H, t), 8.00 (2H, d).

LCMS Spectrum: m/z (ES+)(M+H)+=241; HPLC tR=1.84min

Example 70: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea



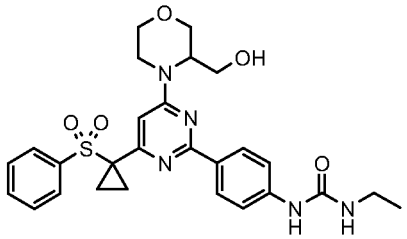
Triethylamine (0.062 mL, 0.45 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.102 g, 0.20 mmol), (*S*)-3-ethylmorpholine (0.047 g, 0.41 mmol) in dioxane (5 mL) and the resulting solution stirred at 50°C overnight. Ethyl isocyanate (0.564 mL, 7.12 mmol) was added and the solution allowed to stir at RT overnight. Methanol was added and then the solvent was removed. The crude product was purified by preparative HPLC, to give the desired material as a white solid (0.042 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.83-0.86(3H, t), 1.05-1.08(3H, t), 1.56-1.67(4H, m), 1.71-1.80(1H, m), 1.88-1.91(2H, m), 3.09-3.16(3H, m), 3.40-3.47(1H, td), 3.50-3.54(1H, dd), 3.84-3.87(1H, d), 3.90-3.94(1H, dd), 4.18(1H, bs), 6.12-6.15(1H, t), 6.61(1H, s), 7.37-7.40(2H, d), 7.57-7.61(2H, t), 7.69-7.74(1H, tt), 7.77-7.80(2H, dd), 7.84-7.86(2H, d), 8.61(1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=536; HPLC tR=2.43min.

The preparation of [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate was described earlier.

Example 71: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[3-(hydroxymethyl)morpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea

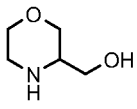


Triethylamine (0.112 mL, 0.80 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.100 g, 0.20 mmol), morpholin-3-ylmethanol hydrochloride (0.062 g, 0.40 mmol) in dioxane (5 mL) and the resulting solution stirred at 50°C overnight. Ethyl isocyanate (0.555 mL, 7.01 mmol) was added and the solution allowed to stir at RT overnight. The solvent was removed and the sludge was taken up in methanol. 30% Sodium methoxide in methanol solution was added and the reaction was allowed to stir overnight. Additional 30% sodium methoxide in methanol solution was added and the reaction refluxed overnight. Approximately 80% of the methanol was removed and the solution was quenched with saturated ammonium chloride solution. The mixture was extracted with DCM, the organics dried over $MgSO_4$, filtered and evaporated. The crude product was purified by preparative HPLC, to give the desired material as a cream solid (0.019 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.58-1.66 (2H, m), 1.86-1.92 (2H, m), 3.07-3.16 (3H, m), 3.42-3.53 (3H, m), 3.69-3.73 (1H, m), 3.92-3.95 1H, dd), 4.05-4.08 (1H, d), 4.18 (1H, bs), 4.93 (1H, bs), 6.14-6.17 (1H, t), 6.68 (1H, s), 7.36 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.84 (4H, m), 8.64 (1H, s) (1 peak under water or solvent peak).

LCMS Spectrum: m/z (ES+)(M+H)+=538; HPLC tR=1.95min.

Morpholin-3-ylmethanol

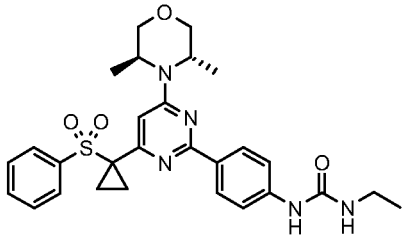


(4-Benzylmorpholin-3-yl)methanol (0.473 g, 2.28 mmol) and palladium (5% on carbon, 50%wet) (0.094 g, 0.02 mmol) in ethanol (50 mL) were stirred under an atmosphere of hydrogen at 5 bar and 25°C for 18 hours. The mixture was filtered and then hydrochloric acid (0.628 mL, 2.51 mmol) added. The reaction was stirred overnight at RT and then the solvent removed to give the desired material (as a hydrochloride salt) as an orangey brown gum (257 mg).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.43-1.46(1H, t), 3.14-3.67(3H, m), 3.81-4.18(4H, m), 4.62(1H, bs), 9.32(bs), 9.60(bs), 10.43(bs).

The preparation of [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate was described earlier.

Example 72: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea



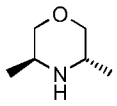
DIPEA (0.141 mL, 0.81 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.101 g, 0.20 mmol) and (3*S*,5*S*)-3,5-dimethylmorpholine (hydrochloride salt) (0.061 g, 0.40 mmol) in dioxane (5 mL) under nitrogen. The resulting solution was stirred at 70°C overnight then at 90ºC for several hours. Additional (3*S*,5*S*)-3,5-dimethylmorpholine (hydrochloride salt) was added and the reaction was allowed to stir at 90ºC overnight. Ethyl isocyanate (0.320 mL, 4.05 mmol) was added and the reaction allowed to stir at RT over the weekend. Methanol was added and then the solvent was removed. The crude product was purified by preparative HPLC, to give the desired material as a cream solid (0.029 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.27-1.29(6H, d), 1.61-1.71 (2H, m), 1.88-1.95 (2H, m), 3.09-3.16 (2H, m), 3.67-3.70 (2H, m), 4.10-4.16 (4H, m), 6.14-6.16 (1H, t), 6.60 (1H, s), 7.39-7.41 (2H, d), 7.57-7.61 (2H, t), 7.69-7.73 (1H, tt), 7.78-7.81 (2H, dd), 7.86-7.89 (2H, d), 8.62 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=536; HPLC tR=2.41min.

The preparation of [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate was described earlier.

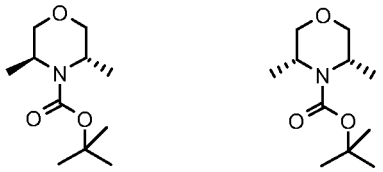
(3*S*,5*S*)-3,5-Dimethylmorpholine



Hydrogen chloride (4M solution in dioxane, 30.1 mL, 120.25 mmol) was added to *tert*-butyl (3*S*,5*S*)-3,5-dimethylmorpholine-4-carboxylate (5.23 g, 24.29 mmol) in dioxane (50 mL) and the resulting solution stirred at RT overnight. The solvent was removed and the solid was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a white solid (3.22 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.50-1.51(6H, d), 3.56-3.67 (4H, m), 3.97-4.00 (2H, dd), 9.96 (2H, bs).

tert-Butyl (3*S*,5*S*)-3,5-dimethylmorpholine-4-carboxylate and *tert*-butyl (3*S*,5*R*)-3,5-dimethylmorpholine-4-carboxylate



(3*S*)-3,5-Dimethylmorpholine (13.73 g, 90.55 mmol) was dissolved in a solution of sodium hydroxide (3.91 mL, 208.26 mmol) in water (100 mL) and di-tert-butyl dicarbonate (22.88 mL, 99.60 mmol) added portionwise. The resulting solution was stirred at RT overnight then extracted with diethyl ether and the organics dried over $MgSO_4$, filtered and evaporated to give a clear liquid. The crude material was purified and the diastereomers separated using silica chromatography, eluting with 0-10% ethyl acetate in isohexane, to give *tert*-butyl (3*S*,5*S*)-3,5-dimethylmorpholine-4-carboxylate (first product to elut) as a colourless liquid (5.93 g) and *tert*-butyl (3*S*,5*R*)-3,5-dimethylmorpholine-4-carboxylate (second product to elut) as a colourless liquid (5.03 g).

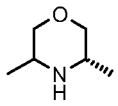
tert-butyl (3*S*,5*S*)-3,5-dimethylmorpholine-4-carboxylate:

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.28-1.29(6H, d), 1.47(9H, s), 3.43-3.48 (2H, m), 3.77-3.84 (4H, m).

tert-butyl (3*S*,5*R*)-3,5-dimethylmorpholine-4-carboxylate

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.30-1.31(6H, d), 1.47(9H, s), 3.52-3.56(2H, dd), 3.68-3.71(2H, d), 3.90-3.96(2H, m).

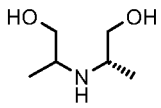
(3*S*)-3,5-Dimethylmorpholine



2-[[(2*S*)-1-Hydroxypropan-2-yl]amino]propan-1-ol (14.79 g, 111.01 mmol) was cooled to 0ºC with stirring and concentrated sulfuric acid (19.85 g, 202.39 mmol) added. The mixture was heated to 180ºC for 5 hours. Potassium hydroxide (23.95 g, 426.87 mmol) in water (120 mL) was added slowly then the mixture filtered to leave a dark black aqueous solution. This solution was distilled (distillate came off at 98ºC) and the distillate acidified with 2M hydrochloric acid. The water was removed to give the desired material (as the hydrochloride salt) as a white solid (13.73g). The material was used in the following step without further purification.

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.44-1.46 (3H, d), 1.48-1.50 (3H, d), 3.31-3.34 (1H, m), 3.56-3.59 (1H, m), 3.62-3.72 (2H, m), 3.84-3.88 (1H, m), 3.96-3.99 (1H, dd), 9.69-10.12 (2H, bt).

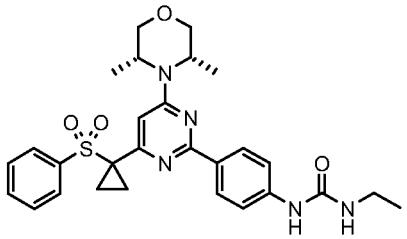
2-[[(2*S*)-1-Hydroxypropan-2-yl]amino]propan-1-ol



(*S*)-2-Aminopropan-1-ol (9 g, 119.82 mmol), platinum(IV) oxide (0.052 g, 0.23 mmol) and 1-hydroxypropan-2-one (11.54 g, 155.77 mmol) in methanol (100 mL) were stirred for 1 hour and then placed under an atmosphere of hydrogen at 1 bar and 25°C for 3 hours. The solution was filtered and evaporated to give a crude product that was purified by distillation at (0.55 mBar, 92°C) to give the desired material as a yellow oil (10.71 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.01-1.03 (3H, d), 1.07-1.09 (3H, d), 2.56 (1H, bs), 2.83-2.94 (2H, m), 3.27-3.32 (2H, m), 3.55-3.61 (2H, m).

Example 73: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*R*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea

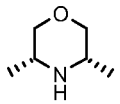


DIPEA (0.140 mL, 0.81 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.101 g, 0.20 mmol), (3*S*,5*R*)-3,5-dimethylmorpholine (as the hydrochloride salt) (0.052 g, 0.34 mmol) in dioxane (5 mL) under nitrogen. The reaction was heated to 90°C overnight. The reaction cooled and the solvent was removed. The residue was taken up in dioxane and ethyl isocyanate (0.319 mL, 4.03 mmol) added. The reaction was allowed to stir over the weekend. Methanol was added and the solvent was removed. The crude product was purified by preparative HPLC, to give the desired material as a white solid (9.00 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.05-1.09 (3H, t), 1.17-1.20(6H, m), 1.62-1.68 (2H, m), 1.89-1.92 (2H, m), 3.09-3.14 (2H, m), 3.43-3.48 (2H, m), 3.86-3.90 (1H, dd), 3.94-4.16 (1H, dd), 4.12-4.16 (1H, m), 4.29-4.31 (1H, m), 6.12-6.15 (1H, t), 6.60 (1H, s), 7.37-7.40 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.86 (4H, m), 8.61 (1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=536; HPLC tR=2.38min.

The preparation of [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate was described earlier.

(3*S*,5*R*)-3,5-Dimethylmorpholine



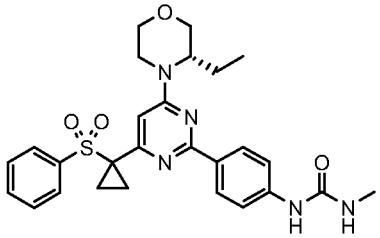
Hydrogen chloride (4M solution in dioxane, 9.98 mL, 39.92 mmol) was added to *tert*-butyl (3*S*,5*R*)-3,5-dimethylmorpholine-4-carboxylate (1.910 g, 8.87 mmol) in dioxane (15 mL) and

the resulting solution stirred at RT overnight. The solvent was removed and the solid was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a white solid (0.960 g).

NMR Spectrum:[1]H NMR (400MHz, $CDCl_3$) δ 1.47-1.48(6H, d), 3.31-3.40 (2H, m), 3.68-3.74 (2H, t), 3.86-3.90 (2H, dd), 9.77 (1H, bs), 10.22 (1H, bs).

The preparation of *tert*-butyl (3*S*,5*R*)-3,5-dimethylmorpholine-4-carboxylate was described earlier.

Example 74: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

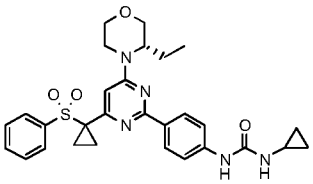
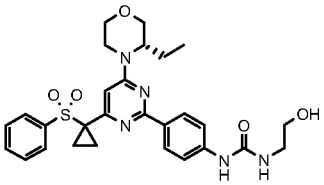
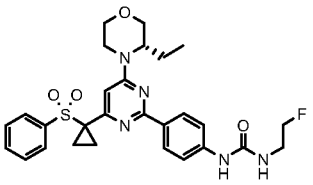
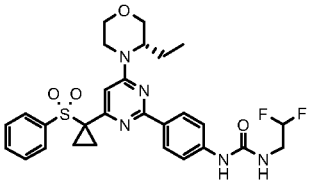
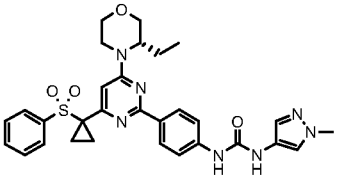


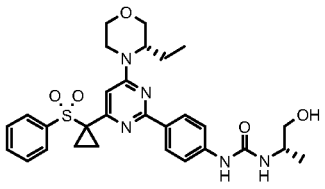
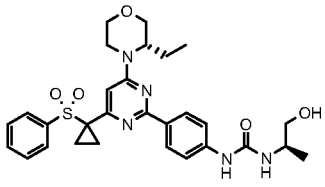
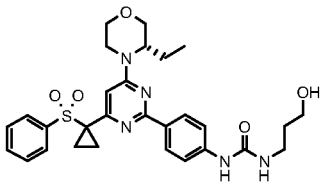
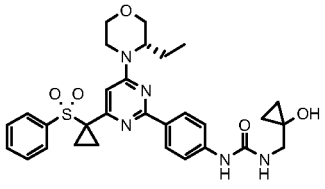
Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.1 g, 0.17 mmol), triethylamine (0.072 mL, 0.51 mmol) and methylamine (0.51 mmol) were dissolved in dioxane (10 mL) and heated at 50°C overnight. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid.

NMR Spectrum: [1]H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.65 - 1.56 (3H, m), 1.80 - 1.71 (1H, m), 1.91 - 1.87 (2H, m), 2.66 (3H, d), 3.12 (1H, ddd), 3.43 (1H, ddd), 3.51 (1H, dd), 3.85 (1H, d), 3.91 (1H, dd), 4.24 - 4.12 (2H, m), 6.04 (1H, q), 6.61 (1H, s), 7.39 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.84 (2H, d), 8.69 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+ = 522; HPLC tR= 2.31 min;

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
74a		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	548	2.46
74b		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	552	2.11
74c		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	554	1.95
74d		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	572	2.45
74e		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	588	2.33

Example	Structure	NAME	LCMS MH+	Retention time (min)
74f		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea	566	2.21
74g		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea	566	2.21
74h		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	578	2.28
74i		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea	578	2.29

Example 74a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.43 - 0.39 (2H, m), 0.67 - 0.62 (2H, m), 0.84 (3H, t), 1.64 - 1.58 (3H, m), 1.80 - 1.73 (1H, m), 1.92 - 1.85 (2H, m), 2.57 - 2.52 (1H, m), 3.12 (1H, ddd), 3.43 (1H, ddd), 3.51 (1H, dd), 3.85 (1H, d), 3.91 (1H, dd), 4.28 - 4.09 (2H, m), 6.40 (1H, s), 6.61 (1H, s), 7.39 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.85 (2H, d), 8.49 (1H, s);

Example 74b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.64 - 1.58 (3H, m), 1.80 - 1.73 (1H, m), 1.91 - 1.86 (2H, m), 3.19 - 3.09 (3H, m), 3.48 - 3.40 (3H, m), 3.51 (1H, dd),

3.85 (1H, d), 3.91 (1H, dd), 4.26 - 4.08 (2H, m), 4.72 (1H, t), 6.23 (1H, t), 6.61 (1H, s), 7.38 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.85 (2H, d), 8.75 (1H, s);

Example 74c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.64 - 1.58 (3H, m), 1.80 - 1.71 (1H, m), 1.91 - 1.87 (2H, m), 3.12 (1H, ddd), 3.47 - 3.36 (3H, m), 3.51 (1H, dd), 3.85 (1H, d), 3.91 (1H, dd), 4.28 - 4.09 (2H, m), 4.47 (2H, dt), 6.42 (1H, t), 6.62 (1H, s), 7.39 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.86 (2H, d), 8.77 (1H, s);

Example 74d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.65 - 1.58 (3H, m), 1.80 - 1.73 (1H, m), 1.91 - 1.87 (2H, m), 3.12 (1H, ddd), 3.43 (1H, ddd), 3.59 - 3.50 (3H, m), 3.85 (1H, d), 3.92 (1H, dd), 4.27 - 4.12 (2H, m), 6.07 (1H, tt), 6.51 (1H, t), 6.62 (1H, s), 7.40 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.87 (2H, d), 8.87 (1H, s);

Example 74e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.85 (3H, t), 1.68 - 1.59 (3H, m), 1.80 - 1.73 (1H, m), 1.92 - 1.87 (2H, m), 3.12 (1H, ddd), 3.43 (1H, ddd), 3.52 (1H, dd), 3.79 (3H, s), 3.86 (1H, d), 3.92 (1H, dd), 4.30 - 4.18 (2H, m), 6.62 (1H, s), 7.38 (1H, s), 7.43 (2H, d), 7.59 (2H, t), 7.72 (1H, t), 7.76 (1H, s), 7.78 (2H, d), 7.88 (2H, d), 8.36 (1H, s), 8.78 (1H, s);

Example 74f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.08 (3H, d), 1.65 - 1.58 (3H, m), 1.82 - 1.73 (1H, m), 1.90 - 1.88 (2H, m), 3.12 (1H, ddd), 3.39 - 3.33 (2H, m), 3.43 (1H, ddd), 3.51 (1H, dd), 3.73 - 3.67 (1H, m), 3.85 (1H, d), 3.91 (1H, dd), 4.25 - 4.13 (2H, m), 4.78 (1H, t), 6.07 (1H, d), 6.61 (1H, s), 7.36 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.85 (2H, d), 8.66 (1H, s);

Example 74g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.08 (3H, d), 1.67 - 1.58 (3H, m), 1.80 - 1.73 (1H, m), 1.90 - 1.88 (2H, m), 3.12 (1H, ddd), 3.40 - 3.32 (2H, m), 3.44 (1H, ddd), 3.51 (1H, dd), 3.73 - 3.67 (1H, m), 3.85 (1H, d), 3.91 (1H, dd), 4.27 - 4.08 (2H, m), 4.78 (1H, t), 6.07 (1H, d), 6.61 (1H, s), 7.36 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.85 (2H, d), 8.66 (1H, s);

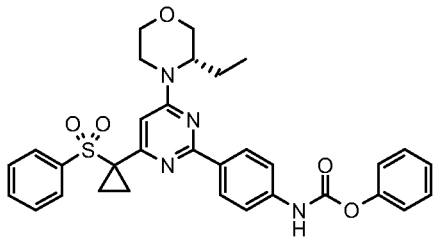
Example 74h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.64 - 1.56 (5H, m), 1.82 - 1.69 (1H, m), 1.91 - 1.87 (2H, m), 3.19 - 3.08 (3H, m), 3.53 - 3.40 (4H, m), 3.85 (1H, d), 3.91 (1H, dd), 4.26 - 4.08 (2H, m), 4.47 (1H, t), 6.18 (1H, t), 6.61 (1H, s), 7.38 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.85 (2H, d), 8.66 (1H, s);

Example 74i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.53 - 0.48 (2H, m), 0.59 - 0.56 (2H, m), 0.84 (3H, t), 1.64 - 1.58 (3H, m), 1.80 - 1.73 (1H, m), 1.92 - 1.88 (2H, m), 3.12 (1H, ddd), 3.21 (2H, d), 3.46 - 3.38 (1H, m), 3.51 (1H, dd), 3.85 (1H, d), 3.91 (1H, dd), 4.27 - 4.05 (2H,

m), 6.30 (1H, t), 6.61 (1H, s), 7.38 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.85 (2H, d), 8.76 (1H, s), hydroxy missing

The preparation of phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

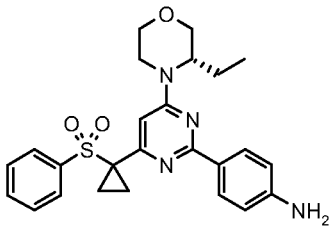


4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]aniline (as the hydrochloride salt) (1.418 g, 2.83 mmol) and sodium bicarbonate (2.377 g, 28.30 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.462 mL, 3.68 mmol) was added slowly and the reaction stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.22 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.68 - 1.59 (3H, m), 1.80 - 1.73 (1H, m), 1.92 - 1.89 (2H, m), 3.13 (1H, ddd), 3.43 (1H, ddd), 3.52 (1H, dd), 3.85 (1H, d), 3.92 (1H, dd), 4.18 (2H, s), 6.66 (1H, s), 7.29 - 7.24 (3H, m), 7.45 (2H, t), 7.54 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.79 (2H, d), 7.95 (2H, d), 10.39 (1H, s);

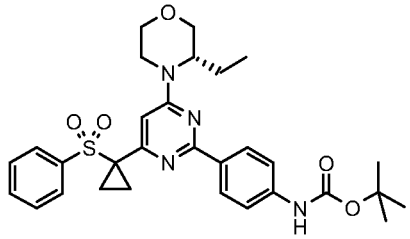
LCMS Spectrum: m/z (ES+) (M+H)+ = 585; HPLC tR= 3.12 min;

4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]aniline



tert-Butyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (1.6 g, 2.83 mmol) was added to 6.0 N hydrogen chloride in propan-2-ol (20 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a yellow solid (1.40 g). NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.81 - 0.71 (3H, m), 1.78 - 1.60 (5H, m), 1.96 - 1.87 (2H, m), 3.20 (1H, ddd), 3.41 (1H, ddd), 3.50 (1H, dd), 3.84 (1H, d), 3.93 (1H, dd), 6.56 (1H, s), 7.01 (2H, s), 7.61 (2H, t), 7.79 - 7.75 (4H, m), 7.95 (2H, d);
LCMS Spectrum: m/z (ES+) (M+H)+ = 465; HPLC tR= 2.54 min;

tert-Butyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



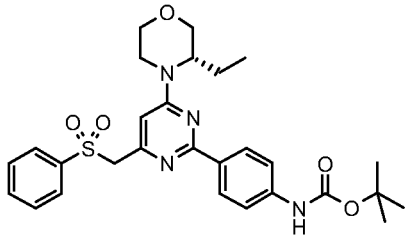
Sodium hydride (0.724 g, 15.07 mmol) was added rapidly to *tert*-butyl *N*-[4-[4-(benzenesulfonylmethyl)-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.03 g, 3.77 mmol) in DMF (30 mL) and the mixture stirred at RT for 10 minutes before the slow addition 1,2-dibromoethane (1.299 mL, 15.07 mmol) in DMF (30 mL). The resulting suspension was stirred at RT for 1 hour. Additional sodium hydride (0.36 g, 7.53 mmol) and 1,2 dibromoethane (0.65 mL, 7.53 mmol) were rapidly added and the reaction was stirred for a further 30 minutes. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to afford yellow foam. This was dissolved in

40% ethyl acetate in isohexane and stirred resulting in the desired material precipitating out as a white solid (1.65 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.49 (9H, s), 1.65 - 1.58 (3H, m), 1.80 - 1.73 (1H, m), 1.90 - 1.87 (2H, m), 3.12 (1H, ddd), 3.43 (1H, ddd), 3.51 (1H, dd), 3.85 (1H, d), 3.91 (1H, dd), 4.18 (2H, s), 6.63 (1H, s), 7.45 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.87 (2H, d), 9.49 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 565; HPLC tR= 3.23 min;

tert-Butyl *N*-[4-[4-(benzenesulfonylmethyl)-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

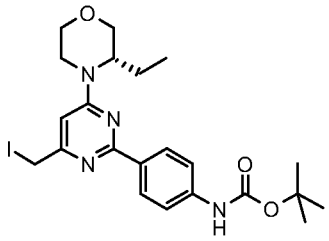


Sodium benzenesulfinate (0.626 g, 3.81 mmol) and *tert*-butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(iodomethyl)pyrimidin-2-yl]phenyl]carbamate (2.0 g, 3.81 mmol) were dissolved in DMF (25 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a yellow solid which was partitioned between aqueous sodium thiosulphate solution (50 mL) and DCM (75 mL). The organics were purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane., to give the desired material as a white foam (1.99 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.86 (3H, t), 1.49 (9H, s), 1.66 - 1.57 (1H, m), 1.82 - 1.74 (1H, m), 3.14 (1H, ddd), 3.45 (1H, ddd), 3.53 (1H, dd), 3.87 (1H, d), 3.93 (1H, dd), 4.16 (2H, s), 4.69 (2H, s), 6.61 (1H, s), 7.45 (2H, d), 7.61 (2H, t), 7.74 (1H, t), 7.85 - 7.80 (4H, m), 9.49 (1H, s);

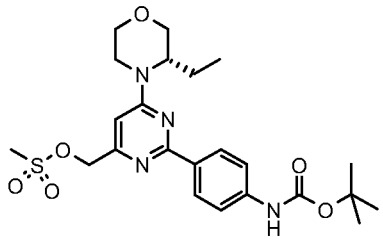
LCMS Spectrum: m/z (ES+) (M+H)+ = 539; HPLC tR= 3.00 min;

tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(iodomethyl)pyrimidin-2-yl]phenyl]carbamate



[6-[(3*S*)-3-Ethylmorpholin-4-yl]-2-[4-[(2-methylpropan-2-yl)oxycarbonylamino]phenyl]pyrimidin-4-yl]methyl methanesulfonate (10.34 g, 20.99 mmol) and lithium iodide (1.208 mL, 31.49 mmol) were added to dioxane (250 mL) and heated at 60°C for 1 hour and then at RT overnight. The solvent was evaporated and the reaction mixture quenched with saturated ammonium chloride solution (100 mL) then extracted with DCM (3 x 75 mL). The organic extracts were flushed through a 2 inch silica plug, eluting with ethyl acetate, to give a brown foam. This was dissolved in diethyl ether and isohexane carefully added until a cloudy solution was observed. Upon cooling to 0°C, the desired material precipitated out as a white solid and was isolated by filtration (9.80 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (3H, t), 1.50 (9H, s), 1.72 - 1.63 (1H, m), 1.83 - 1.76 (1H, m), 3.17 (1H, ddd), 3.47 (1H, ddd), 3.55 (1H, dd), 3.87 (1H, d), 3.93 (1H, dd), 4.29 (2H, s), 4.38 (2H, s), 6.81 (1H, s), 7.56 (2H, d), 8.22 (2H, d), 9.53 (1H, s);
LCMS Spectrum: m/z (ES+) (M+H)+ = 525; HPLC tR= 3.17 min;

[6-[(3*S*)-3-Ethylmorpholin-4-yl]-2-[4-[(2-methylpropan-2-yl)oxycarbonylamino]phenyl]pyrimidin-4-yl]methyl methanesulfonate

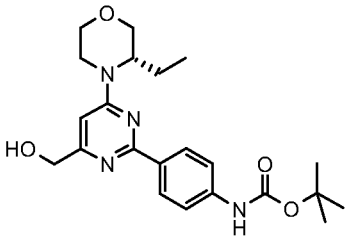


tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(hydroxymethyl)pyrimidin-2-yl]phenyl]carbamate (8.7 g, 20.99 mmol) and DIPEA (4.40 mL, 25.19 mmol) were added to DCM (80 mL), to this was slowly added methane sulphonyl chloride(1.636 mL, 20.99 mmol) and the reaction was stirred for 30 minutes. The reaction mixture was quenched with saturated

ammonium chloride solution (100 mL), extracted with DCM (2 x 100 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as a brown gum (10.2 g). This was used without any further purification.

LCMS Spectrum: m/z (ES+) (M+H)+ = 493; HPLC tR= 2.90 min;

tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(hydroxymethyl)pyrimidin-2-yl]phenyl]carbamate

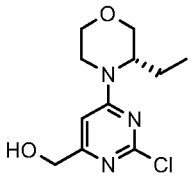


[2-Chloro-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-4-yl]methanol (12 g, 46.56 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (14.86 g, 46.56 mmol), sodium carbonate (24.68 g, 232.81 mmol) and 1,1'-bis(diphenyl phosphino)ferrocenedichloropalladium(II) (3.37 g, 4.66 mmol) were added to DME (150 mL) and water (37.5 mL) and heated to 90°C overnight under nitrogen. The solvent was evaporated and the residue was quenched with water (100 mL), extracted with ethyl acetate (3 x 100 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford black gum. The residue was filtered through a plug of silica, eluting with ethyl acetate, to give a very dark gum. This was purified by flash silica chromatography, elution gradient 40 to 100% ethyl acetate in isohexane, to give an orange gum. The gum was dissolved in diethyl ether and isohexane carefully added until a cloudy solution was observed, further stirring gave the desired material as a white solid precipitate which was isolated by filtration (8.7 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.49 (9H, s), 1.73 - 1.64 (1H, m), 1.84 - 1.77 (1H, m), 3.19 (1H, ddd), 3.47 (1H, ddd), 3.55 (1H, dd), 3.88 (1H, d), 3.94 (1H, dd), 4.33 - 4.23 (2H, m), 4.45 (2H, d), 5.38 (1H, t), 6.67 (1H, s), 7.53 (2H, d), 8.21 (2H, d), 9.50 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 415; HPLC tR= 2.49 min;

[2-Chloro-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-4-yl]methanol

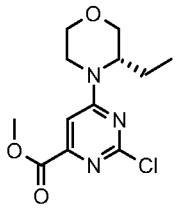


Lithium borohydride, 2M in THF (17.63 mL, 35.26 mmol) was added dropwise to methyl 2-chloro-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidine-4-carboxylate te (15.5 g, 54.25 mmol) in THF (100 mL) at 0ºC over a period of 30 minutes under nitrogen. The resulting solution was stirred at 0°C for 30 minutes then allowed to warm to RT. Water (250 mL) was added and the THF evaporated. The aqueous residues were extracted with ethyl acetate (2 x 500 mL) and the combined organics were washed with water (2 x 300 mL). The organic layer was dried over $MgSO_4$ then evaporated to dryness to afford a viscous oil, this was triturated with hot diethyl ether to give the desired material as a white solid (13.4 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.80 - 1.66 (2H, m), 3.19 - 3.14 (1H, m), 3.42 (1H, ddd), 3.51 (1H, dd), 3.82 (1H, d), 3.89 (1H, dd), 4.15 - 4.06 (2H, m), 4.34 (2H, d), 5.50 (1H, t), 6.74 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 258; HPLC tR= 1.45 min;

Methyl 2-chloro-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidine-4-carboxylate



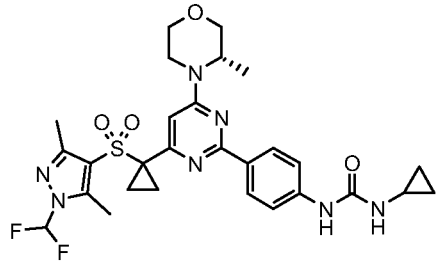
A solution of (S)-3-ethylmorpholine (10 g, 86.83 mmol) in DCM (75 mL) was added dropwise to a stirred solution of methyl 2,6-dichloropyrimidine-4-carboxylate (19.77 g, 95.51 mmol) and triethylamine (24.20 ml, 173.65 mmol) in DCM (200 mL) at RT, over a period of 2 hours under air. The resulting solution was stirred at RT overnight. The reaction mixture was quenched with water (250 mL), extracted with DCM (300 mL) and the solvent was removed to 30% the initial volume. The dark solution was passed through a 2 inch plug of silica, eluting with ethyl acetate, to give an orange gum which was dissolved in ethyl acetate (40 mL). To this was added diethyl ether (120 mL) and then isohexane until a cloudy solution was observed. The reaction was seeded with 15 mg of methyl 2-chloro-6-[(3*S*)-3-

methylmorpholin-4-yl]pyrimidine-4-carboxylate and stirred for 15 minutes to afford the desired material as a white solid (15.8 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.83 (3H, t), 1.75 (2H, septet), 3.22 (1H, s), 3.44 (1H, ddd), 3.53 (1H, dd), 3.82 (1H, d), 3.91 - 3.87 (4H, m), 4.22 (2H, m), 7.32 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 286; HPLC tR= 1.81 min;

Example 75: 3-Cyclopropyl-1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

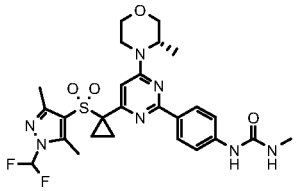
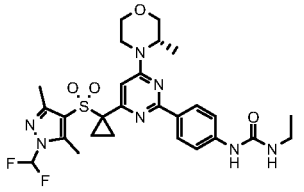
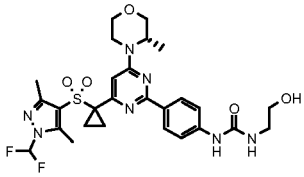
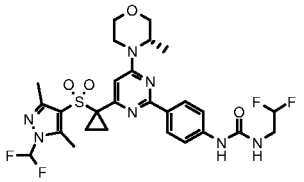
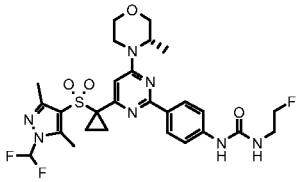


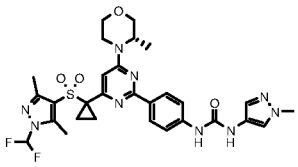
Cyclopropylamine (0.038 mL, 0.54 mmol) was added to a solution of phenyl *N*-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.115g, 0.18mmol) in NMP (2 mL) followed by triethylamine (0.076 mL, 0.54 mmol) and the reaction was heated at 50°C overnight. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as an off white solid (88 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 1.19 - 1.21 (3H, d), 1.46 - 1.54 (2H, m), 1.75 - 1.78 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 2.53 - 2.58 (1H, m), 3.12 - 3.20 (1H, m), 3.44 - 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.13 (1H, d), 4.51 (1H, s), 6.42 (1H, d), 6.69 (1H, s), 7.42 - 7.45 (2H, m), 7.64 - 7.93 (1H, t), 7.91 - 7.94 (2H, m), 8.53 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 602; HPLC tR = 2.20 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
75a		1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	576	2.05
75b		3-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	590	2.19
75c		1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	606	1.89
75d		3-(2,2-difluoroethyl)-1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	626	2.31
75e		1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	608	2.18

Example	Structure	NAME	LCMS MH+	Retention time (min)
75f*		1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	642	2.08

* In addition to the reaction conditions described above this reaction was subsequently subjected to the addition of DIPEA (3 equivalents) and heating at 95°C for 90 minutes.

Example 75a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.46 - 1.54 (2H, m), 1.75 - 1.78 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 2.68 (3H, d), 3.12 - 3.17 (1H, m), 3.44 - 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.13 (1H, d), 4.51 (1H, s), 6.05 (1H, q), 6.69 (1H, s), 7.42 - 7.44 (2H, m), 7.64 - 7.92 (1H, t), 7.90 - 7.93 (2H, m), 8.73 (1H, s).

Example 75b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.20 (3H, d), 1.49 - 1.51 (2H, m), 1.75 - 1.78 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 3.10 - 3.20 (3H, m), 3.44 - 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.11 - 4.15 (1H, m), 4.51 (1H, s), 6.14 (1H, t), 6.69 (1H, s), 7.41 - 7.44 (2H, m), 7.64 - 7.92 (1H, t), 7.91 - 7.93 (2H, d), 8.65 (1H, s).

Example 75c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, s), 1.46 - 1.54 (2H, m), 1.75 - 1.78 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 3.12 - 3.20 (3H, m), 3.45 - 3.50 (3H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.13 (1H, d), 4.51 (1H, s), 4.74 (1H, t), 6.24 (1H, t), 6.69 (1H, s), 7.42 (2H, d), 7.64 - 7.92 (1H, t), 7.92 (2H, d), 8.79 (1H, s).

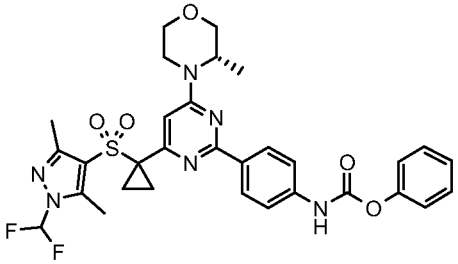
Example 75d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.46 - 1.54 (2H, m), 1.75 - 1.78 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 3.16 - 3.19 (1H, m), 3.44 - 3.64 (4H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.12 - 4.15 (1H, m), 4.51 (1H, s), 5.93 - 6.23 (1H, m), 6.52 (1H, t), 6.70 (1H, s), 7.44 (2H, d), 7.64 - 7.92 (1H, t), 7.95 (2H, d), 8.92 (1H, s).

Example 75e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.46 - 1.54 (2H, m), 1.73 - 1.78 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 3.14 - 3.20 (1H, m), 3.36 - 3.50 (3H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.13 (1H, d), 4.42 (1H, t), 4.54 (2H, t), 6.42 (1H, t), 6.70 (1H, s), 7.43 (2H, d), 7.64 - 7.93 (1H, t), 7.93 (2H, d), 8.80 (1H, s).

Example 75f: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 - 1.21 (3H, m), 1.47 - 1.54 (2H, m), 1.74 - 1.79 (2H, m), 2.07 (3H, s), 2.35 (3H, s), 3.13 - 3.21 (1H, m), 3.44 - 3.51 (1H, m), 3.61 - 3.64 (1H, m), 3.75 - 3.78 (1H, m), 3.80 (3H, s), 3.95 - 3.99 (1H, m), 4.14 (1H, d), 4.52 (1H, s), 6.70 (1H, s), 7.39 - 7.39 (1H, m), 7.46 - 7.49 (2H, m), 7.78 (1H, s), 7.65 - 7.94 (1H, t), 7.96 (2H, d), 8.37 (1H, s), 8.84 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

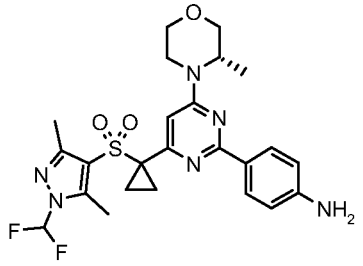


Phenyl chloroformate (0.176 mL, 1.40 mmol) was added dropwise to a mixture of 4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.726 g, 1.4 mmol) and sodium hydrogen carbonate (0.176 g, 2.10 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The precipitate was collected by filtration, washed with a mixture of isohexane (4 mL) and diethyl ether (2 mL), then suspended in water (20 mL) and stirred for 20 minutes. The precipitate was collected by filtration, washed with water (5 mL) then with a mixture of isohexane (10 mL) and diethyl ether (5 mL) and dried under vacuum to afford the desired material as a white solid (0.826 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.48 - 1.55 (2H, m), 1.74 - 1.79 (2H, m), 2.07 (3H, s), 2.35 (3H, s), 3.14 - 3.17 (1H, m), 3.39 - 3.50 (1H, m), 3.61 - 3.64 (1H, m), 3.77 (1H, m), 3.95 - 3.99 (1H, m), 4.16 (1H, d), 4.53 (1H, s), 6.75 (1H, s), 7.24 - 7.31 (3H, m), 7.44 - 7.48 (2H, m), 7.57 (2H, d), 7.64 - 7.93 (1H, t), 8.00 - 8.03 (2H, m), 10.42 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 639; HPLC tR = 2.92 min.

4-[4-[1-[1-(Difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

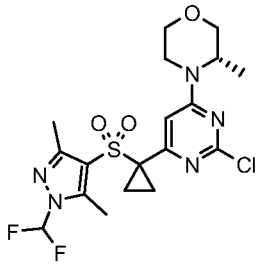


Dichlorobis(triphenylphosphine)palladium(II) (0.412 g, 0.59 mmol) was added in one portion to a mixture of sodium carbonate (1.867 g, 17.61 mmol), 2-chloro-4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.712 g, 5.87 mmol) and (4-aminophenyl)boronic acid pinacol ester (1.351 g, 6.16 mmol) in DME (50 mL)and water (12.5 mL) under nitrogen. The mixture was stirred at 80°C for 2 hours, cooled to RT then diluted with DCM (100 mL) and water (50 mL). The organic layer was washed with saturated brine (50 mL) then dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give a residue which was further purified by trituration with isohexane (25 mL) and diethyl ether (25 mL), to give the desired material as a yellow solid (2.84 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.18 (3H, m), 1.43 - 1.51 (2H, m), 1.73 - 1.76 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 3.09 - 3.17 (1H, m), 3.42 - 3.49 (1H, m), 3.59 - 3.63 (1H, m), 3.75 (1H, d), 3.94 - 3.97 (1H, m), 4.48 (1H, s), 5.52 (2H, m), 6.52 - 6.55 (2H, m), 6.58 (1H, s), 7.75 - 7.78 (2H, m), 7.64 - 7.93 (1H, t).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 519; HPLC tR = 1.91 min.

2-Chloro-4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

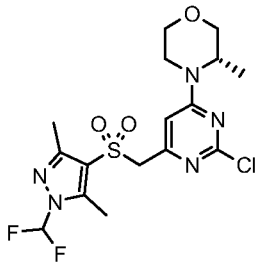


Sodium hydroxide (33.0 mL, 412.50 mmol) was added to 2-chloro-4-[[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.27 g, 7.5 mmol), 1,2-dibromoethane (1.939 mL, 22.50 mmol) and tetrabutylammonium bromide (0.242 g, 0.75 mmol) in toluene (132 mL). The resulting solution was stirred at 60°C for 1 hour. The reaction mixture was diluted with DCM (200 mL), and washed twice with water (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a white solid (2.77 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.45 - 1.52 (2H, m), 1.69 - 1.76 (2H, m), 2.13 (3H, s), 2.37 (3H, s), 3.12 - 3.19 (1H, m), 3.37 - 3.44 (1H, m), 3.53 - 3.57 (1H, m), 3.71 (1H, d), 3.90 - 3.94 (2H, m), 4.35 (1H, s), 6.80 (1H, s), 7.71 - 8.00 (1H, t).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 462; HPLC tR = 2.26 min.

2-Chloro-4-[[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



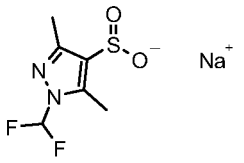
Sodium 1-(difluoromethyl)-3,5-dimethylpyrazole-4-sulfinate (3.44 g, 14.83 mmol) was added to a solution of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.37 g, 12.36 mmol) in DMF (20 mL). The resulting mixture was stirred at RT for 1 hour. The reaction mixture was evaporated to dryness, redissolved in DCM (150 mL), and washed

sequentially with water (100 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 60% ethyl acetate in isohexane, to give the desired material as a white solid (5.22 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.19 (3H, d), 2.21 (3H, s), 2.42 (3H, s), 3.15 - 3.22 (1H, m), 3.40 - 3.47 (1H, m), 3.57 - 3.60 (1H, m), 3.73 (1H, d), 3.92 - 3.96 (2H, m), 4.25 (1H, s), 4.57 (2H, s), 6.82 (1H, s), 7.73 - 8.02 (1H, t).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 436; HPLC tR = 2.13 min.

Sodium 1-(difluoromethyl)-3,5-dimethylpyrazole-4-sulfinate

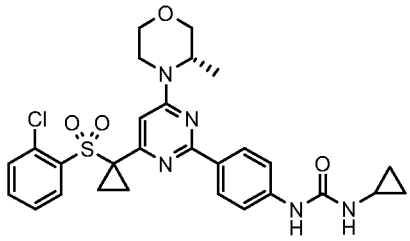


Sodium hydrogen carbonate (3.43 g, 40.88 mmol) was added to a solution of sodium sulfite (2.58 g, 20.44 mmol) in water (25 mL) and the resulting solution was stirred at 50°C for 1 hour. 1-(Difluoromethyl)-3,5-dimethyl-1H-pyrazole-4-sulfonyl chloride (5 g, 20.44 mmol) was added portionwise and the solution was stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and methanol (75 mL) was added. The suspension was allowed to stir at RT for 20 minutes, filtered and the filtrate was evaporated. The residue was dissolved in ethanol (50 mL) at 50°C, filtered and evaporated to afford the desired material as a white solid (4.59 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 2.24 (3H, s), 2.46 (3H, s), 7.44 - 7.74 (1H, t).

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 76: 1-[4-[4-[1-(2-Chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea

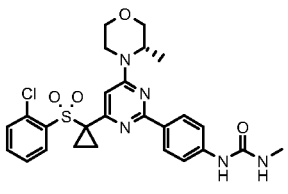


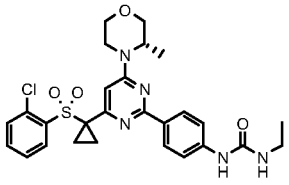
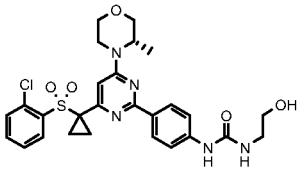
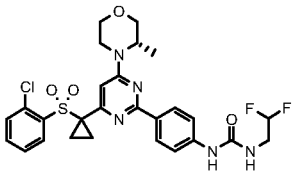
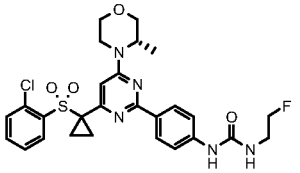
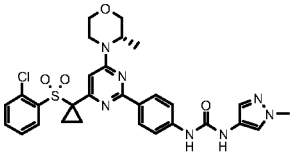
Cyclopropylamine (0.037 mL, 0.51 mmol) was added to a solution of phenyl *N*-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.103g, 0.17mmol) in NMP (2 mL) followed by triethylamine (0.072 mL, 0.51 mmol) and the reaction was heated at 50°C overnight. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as an off- white solid (82mg, 80%).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 1.16 (3H, d), 1.71 - 1.75 (2H, m), 1.97 - 2.01 (2H, m), 2.53 - 2.57 (1H, m), 3.12 - 3.16 (1H, m), 3.41 - 3.48 (1H, m), 3.58 - 3.61 (1H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.10 (1H, d), 4.41 (1H, s), 6.42 (1H, d), 6.63 (1H, s), 7.37 - 7.40 (2H, m), 7.43 - 7.46 (1H, m), 7.60 - 7.64 (1H, m), 7.67 - 7.69 (1H, m), 7.78 - 7.82 (2H, m), 7.90 - 7.92 (1H, m), 8.50 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 568; HPLC tR = 2.30 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
76a		1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	542	2.16

Example	Structure	NAME	LCMS MH+	Retention time (min)
76b		3-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	556	2.30
76c		1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	572	1.99
76d		1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	592	2.40
76e		1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	574	2.27
76f*		1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	608	2.12

* In addition to the reaction conditions described above this reaction was subsequently subjected to the addition of DIPEA (3 equivalents) and heating at 95°C for 90 minutes.

Example 76a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.15 - 1.16 (3H, m), 1.73 2H, m), 1.97 - 2.01 (2H, m), 2.66 (3H, d), 3.12 (1H, d), 3.40 – 3.48 (1H, m), 3.58 - 3.61 (1H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.08 (1H, m), 4.41 (1H, s), 6.06 (1H, d), 6.62 (1H, s), 7.38 (2H, d), 7.46 (1H, m), 7.60 - 7.62 (1H, m), 7.67 - 7.69 (1H, m), 7.79 (2H, d), 7.90 - 7.92 (1H, d), 8.70 (1H, s).

Example 76b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.16 (3H, d), 1.72 - 1.75 (2H, m), 1.97 - 2.01 (2H, m), 3.10 - 3.16 (3H, m), 3.42 - 3.45 (1H, m), 3.58 - 3.61 (1H, m), 3.73 - 3.75 (1H, m), 3.93 – 3.98 (1H, m), 4.10 (1H, d), 4.41 (1H, s), 6.15 (1H, t), 6.63 (1H, s), 7.35 - 7.39 (2H, m), 7.43 - 7.47 (1H, m), 7.60 - 7.64 (1H, m), 7.67 - 7.70 (1H, m), 7.78 - 7.81 (2H, d), 7.90 - 7.92 (1H, m), 8.62 (1H, s).

Example 76c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.15 - 1.16 (3H, m), 1.73 (2H, m), 1.97 - 2.01 (2H, m), 3.16 (1H, m), 3.17 - 3.19 (2H, m), 3.46 (3H, m), 3.58 - 3.61 (1H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.10 (1H, m), 4.42 (1H, s), 4.74 (1H, t), 6.24 (1H, t), 6.63 (1H, s), 7.36 (2H, d), 7.42 - 7.47 (1H, m), 7.60 - 7.62 (1H, m), 7.67 - 7.70 (1H, m), 7.80 (2H, d), 7.90 - 7.92 (1H, m), 8.76 (1H, s).

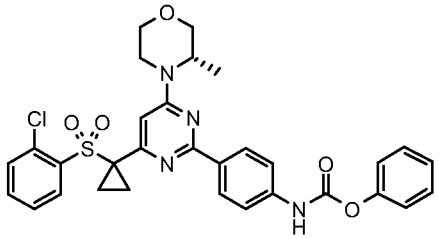
Example 76d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.70 - 1.77 (2H, m), 1.96 - 2.03 (2H, m), 3.09 - 3.16 (1H, m), 3.41 - 3.48 (1H, m), 3.49 - 3.62 (3H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.08 - 4.12 (1H, d), 4.41 (1H, s), 5.92 - 6.22 (1H, m), 6.52 (1H, t), 6.64 (1H, s), 7.37 - 7.41 (2H, d), 7.44 - 7.47 (1H, m), 7.60 - 7.62 (1H, m), 7.67 - 7.70 (1H, m), 7.82 (2H, d), 7.90 - 7.92 (1H, m), 8.88 (1H, s).

Example 76e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.69 - 1.77 (2H, m), 1.95 - 2.03 (2H, m), 3.09 - 3.16 (1H, m), 3.36 - 3.48 (3H, m), 3.58 - 3.62 (1H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.10 (1H, d), 4.42 (2H, m), 4.54 (1H, t), 6.42 (1H, t), 6.63 (1H, s), 7.36 - 7.40 (2H, m), 7.43 - 7.47 (1H, m), 7.60 - 7.66 (1H, m), 7.67 - 7.70 (1H, m), 7.80 - 7.82 (2H, m), 7.90 - 7.92 (1H, m), 8.77 (1H, s).

Example 76f: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.10 - 1.17 (3H, d), 1.72 - 1.75 (2H, m), 1.98 - 2.01 (2H, m), 3.13 - 3.16 (1H, m), 3.42 - 3.48 (1H, m), 3.58 - 3.62 (1H, m), 3.75 (1H, d), 3.80 (3H, s), 3.94 - 3.97 (1H, m), 4.12 (1H, m), 4.42 (1H, s), 6.64 (1H, s), 7.40 - 7.47 (4H, m), 7.61 - 7.63 (1H, m), 7.68 - 7.71 (1H, m), 7.77 (1H, s), 7.83 (2H, d), 7.90 - 7.93 (1H, m), 8.38 (1H, s), 8.80 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

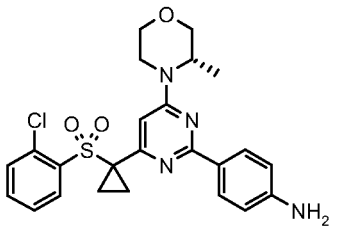


Phenyl chloroformate (0.189 mL, 1.50 mmol) was added dropwise to a mixture of 4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.727 g, 1.5 mmol) and sodium hydrogen carbonate (0.189 g, 2.25 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The precipitate was collected by filtration, washed with diethyl ether (10 mL), suspended in water (20 mL), stirred for 20 minutes, collected by filtration, washed with water (10 mL) then ether (2 mL) and dried under vacuum to afford the desired material as a white solid (0.735 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.72 - 1.77 (2H, m), 1.98 - 2.01 (2H, m), 3.10 - 3.18 (1H, m), 3.44 - 3.62 (2H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.12 (1H, d), 4.43 (1H, s), 6.67 (1H, s), 7.24 - 7.31 (3H, m), 7.43 - 7.48 (3H, m), 7.51 - 7.53 (2H, m), 7.60 - 7.63 (1H, m), 7.67 - 7.70 (1H, m), 7.88 - 7.92 (3H, m), 10.40 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 605; HPLC tR = 3.02 min.

4-[4-[1-(2-Chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



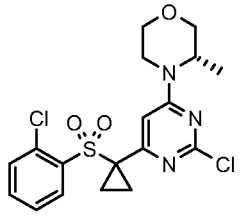
Dichlorobis(triphenylphosphine)palladium(II) (0.519 g, 0.74 mmol) was added in one portion to a mixture of sodium carbonate (2.352 g, 22.20 mmol), 2-chloro-4-[1-(2-

chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.169 g, 7.40 mmol) and (4-aminophenyl)boronic acid pinacol ester (1.702 g, 7.77 mmol) in DME (56 mL)and water (14 mL) under nitrogen. The mixture was stirred at 80°C for 2 hours, cooled to RT then diluted with DCM (100 mL) and water (50 mL). The organic layer was washed with saturated brine (50 mL) then dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give a residue which was further purified by trituration with isohexane (25 mL) and diethyl ether (25 mL), to give the desired material as a yellow solid (3.21 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.08 - 1.19 (3H, m), 1.67 - 1.75 (2H, m), 1.97 - 2.00 (2H, m), 3.05 - 3.13 (1H, m), 3.39 - 3.43 (1H, m), 3.56 - 3.60 (1H, m), 3.73 (1H, d), 3.91 - 3.96 (1H, m), 4.04 (1H, q), 4.37 (1H, s), 5.49 (2H, m), 6.47 - 6.49 (2H, m), 6.52 (1H, s), 7.43 - 7.47 (1H, m), 7.59 - 7.68 (4H, m), 7.90 - 7.93 (1H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 485; HPLC tR = 1.94 min.

2-Chloro-4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



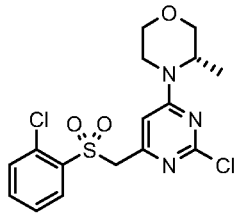
Sodium hydroxide (50%w/w solution) (35.2 mL, 440.00 mmol) was added to 2-chloro-4-[(2-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.22 g, 8mmol), 1,2-dibromoethane (2.068 mL, 24.00 mmol) and tetrabutylammonium bromide (0.258 g, 0.80 mmol) in toluene (141 mL). The resulting solution was stirred at 60°C for 18 hours. The reaction mixture was diluted with DCM (150 mL), and washed twice with water (150 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% ethyl acetate in DCM, to give the desired material as a colourless dry film (3.23 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.64 - 1.67 (2H, m), 1.92 - 1.95 (2H, m), 3.07 - 3.15 (1H, m), 3.35 - 3.41 (1H, m), 3.51 - 3.55 (1H, m), 3.69 (1H, d), 3.88

- 3.92 (2H, m), 4.24 (1H, s), 6.72 (1H, s), 7.52 - 7.56 (1H, m), 7.66 - 7.73 (2H, m), 7.88 - 7.91 (1H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 428; HPLC tR = 2.42 min.

2-Chloro-4-[(2-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



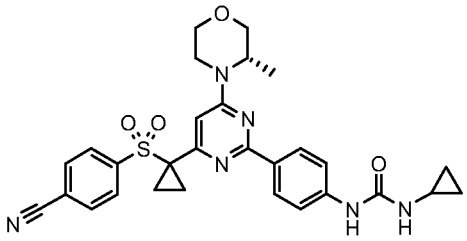
Sodium 2-chlorobenzenesulfinate (3.19 g, 16.07 mmol) was added to a solution of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.37 g, 12.36 mmol) in DMF (20 mL). The resulting mixture was stirred at RT for 1 hour. The reaction mixture was evaporated to dryness and redissolved in DCM (150 mL) and washed sequentially with water (100 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 60% ethyl acetate in isohexane, to give the desired material as a white solid (4.34 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.16 - 1.18 (3H, d), 3.13 - 3.20 (1H, m), 3.39 - 3.46 (1H, m), 3.56 - 3.59 (1H, m), 3.72 (1H, d), 3.91 - 3.95 (2H, m), 4.22 (1H, s), 4.78 (2H, s), 6.79 (1H, s), 7.56 - 7.59 (1H, m), 7.74 - 7.79 (2H, m), 7.82 - 7.84 (1H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 402; HPLC tR = 2.26 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 77: 1-[4-[4-[1-(4-Cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea

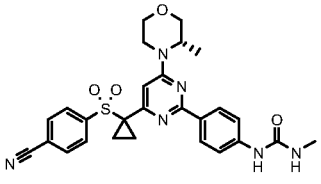


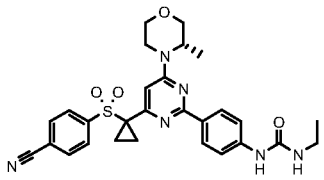
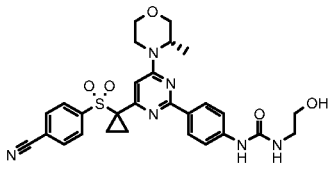
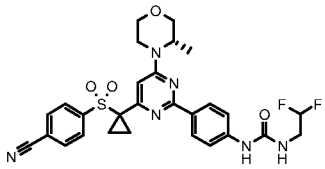
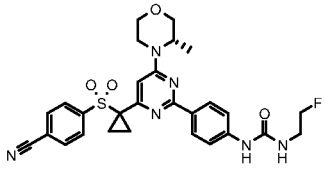
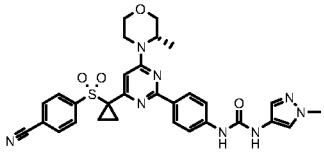
Cyclopropylamine (32 mg, 0.564 mmol) was added to phenyl *N*-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (112 mg, 0.188 mmol) and triethylamine (0.080 mL, 0.564 mmol) in NMP (2 mL). The resulting solution was stirred at 50°C for 16 hours then cooled to RT and purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a solid (81 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.42 (2H, m), 0.65 (2H, m), 1.19 (3H, d), 1.65 (2H, m), 1.96 (2H, m), 2.56 (1H, m), 3.17 (1H, m), 3.47 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.46 (1H, m), 6.41 (1H, d), 6.67 (1H, s), 7.39 (2H, d), 7.68 (2H, d), 7.98 (2H, d), 8.08 (2H, d), 8.53 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 559; HPLC tR = 2.36 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
77a		1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	533	2.20

Example	Structure	NAME	LCMS MH+	Retention time (min)
77b		3-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	547	2.34
77c		1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	563	2.00
77d		1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	583	2.46
77e		1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	565	2.34
77f		1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	599	2.22

* In addition to the reaction conditions described above this sample was further subjected to the addition of more triethylamine (3 equivalents) and stirred for an additional 7 hours at 80°C.

Example 77a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.65 (2H, m), 1.95 (2H, m), 2.66 (3H, d), 3.16 (1H, m), 3.47 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.46 (1H, m), 6.06 (1H, q), 6.66 (1H, s), 7.39 (2H, d), 7.68 (2H, d), 7.98 (2H, d), 8.08 (2H, d), 8.73 (1H, s).

Example 77b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.19 (3H, d), 1.65 (2H, m), 1.95 (2H, m), 3.09 - 3.20 (3H, m), 3.47 (1H, m), 3.62 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.46 (1H, m), 6.15 (1H, t), 6.66 (1H, s), 7.38 (2H, d), 7.67 (2H, d), 7.98 (2H, d), 8.08 (2H, d), 8.65 (1H, s).

Example 77c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.65 (2H, m), 1.96 (2H, m), 3.18 (3H, m), 3.47 (3H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.46 (1H, m), 4.74 (1H, t), 6.25 (1H, t), 6.66 (1H, s), 7.37 (2H, d), 7.67 (2H, d), 7.98 (2H, d), 8.09 (2H, d), 8.79 (1H, s).

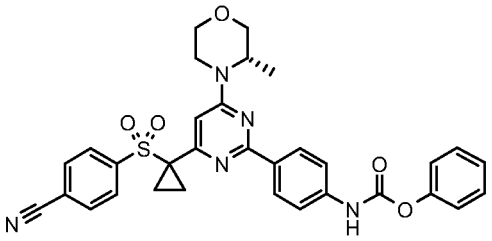
Example 77d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.65 (2H, m), 1.96 (2H, m), 3.17 (1H, m), 3.43 - 3.63 (4H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.46 (1H, m), 5.92 - 6.22 (1H, m), 6.52 (1H, t), 6.67 (1H, s), 7.39 (2H, d), 7.70 (2H, d), 7.98 (2H, d), 8.08 (2H, d), 8.91 (1H, s).

Example 77e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.65 (2H, m), 1.96 (2H, m), 3.16 (1H, m), 3.39 (1H, m), 3.47 (2H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.41 - 4.55 (3H, m), 6.43 (1H, t), 6.67 (1H, s), 7.39 (2H, d), 7.69 (2H, d), 7.98 (2H, d), 8.09 (2H, d), 8.80 (1H, s).

Example 77f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (4H, d), 1.65 (2H, m), 1.96 (3H, m), 3.17 (2H, m), 3.47 (1H, m), 3.62 (1H, m), 3.74 - 3.80 (4H, m), 3.97 (1H, m), 4.17 (1H, m), 4.47 (1H, m), 6.68 (1H, s), 7.38 (2H, s), 7.43 (3H, d), 7.71 (3H, d), 7.77 (2H, s), 7.98 (2H, d), 8.09 (2H, d), 8.38 (1H, s), 8.83 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

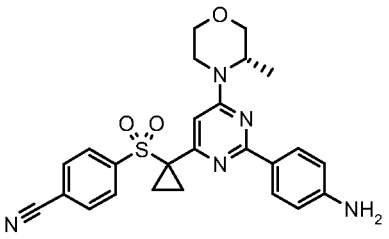


Phenyl chloroformate (0.185 mL, 1.47 mmol) was added dropwise to 4-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzonitrile (700 mg, 1.47 mmol) and sodium bicarbonate (185 mg, 2.21 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The precipitate was collected by filtration, washed with diethyl ether (2 mL) and suspended in water (20 mL) and stirred for 20 minutes. The precipitate was collected by filtration, washed with water (5 mL) then diethyl ether (5 mL) and dried under vacuum to afford the desired material as a white solid (786 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.67 (2H, m), 1.97 (2H, m), 3.18 (1H, m), 3.45 (1H, m), 3.62 (1H, m), 3.76 (1H, m), 3.97 (1H, m), 4.18 (1H, m), 4.47 (1H, m), 6.71 (1H, s), 7.27 (3H, m), 7.46 (2H, m), 7.53 (2H, d), 7.78 (2H, d), 7.98 (2H, d), 8.09 (2H, d), 10.44 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 596; HPLC tR = 3.01 min.

4-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzonitrile



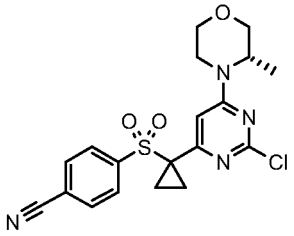
Sodium carbonate (1.693 g, 15.97 mmol) was added to 4-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzonitrile (2.23 g, 5.32 mmol) and (4-aminophenyl)boronic acid pinacol ester (1.225 g, 5.59 mmol) in a mixture of DME (40 mL) and water (10.00 mL). The mixture was bubbled with nitrogen for 10 minutes then

dichlorobis(triphenylphosphine)palladium(II) (0.374 g, 0.53 mmol) was added and the mixture stirred at 80°C for 2 hours. The reaction mixture was cooled to RT then diluted with DCM (100 mL) and water (50 mL). The organic layer was washed with saturated brine (50 mL) then dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 40% ethyl acetate in isohexane followed by 40% ethyl acetate in isohexane, to give the desired material as an orange solid (2.31 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.62 (2H, m), 1.93 (2H, m), 3.14 (1H, m), 3.45 (1H, m), 3.60 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.12 (1H, m), 4.42 (1H, m), 5.55 (2H, s), 6.48 (2H, d), 6.56 (1H, s), 7.50 (2H, d), 7.97 (2H, d), 8.08 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 476; HPLC tR = 2.37 min.

4-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzonitrile



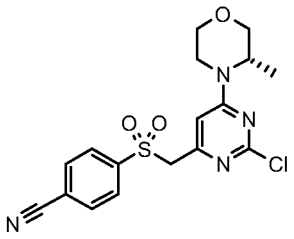
Sodium hydride, 60% dispersion in mineral oil (0.316 g, 7.91 mmol) was added in one portion to 4-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]benzonitrile (2.96 g, 7.53 mmol) in DMF (20 mL) at 0°C under nitrogen. The resulting suspension was stirred for 10 minutes then 1,2-dibromoethane (0.682 mL, 7.91 mmol) was added. The mixture was warmed to 10°C for 10 minutes then cooled back to 0°C and a further portion of sodium hydride, 60% dispersion in mineral oil (0.316 g, 7.91 mmol) added. The mixture was warmed to 50°C and stirred at 50°C for 2 hours. A further portion of sodium hydride, 60% dispersion in mineral oil (0.158 g, 3.95 mmol) and 1,2-dibromoethane (0.341 ml, 3.95 mmol) was added and stirred for a further 2 hours. The reaction mixture was cooled to RT, quenched with saturated aqueous ammonium chloride (2 mL) and the solvents evaporated. The residues were stirred in water (50 mL) for 15 minutes then the resulting solid collected by filtration. The solid was dissolved in DCM (50 mL), washed with water (20 mL), then saturated brine (20 mL), dried over $MgSO_4$, filtered and evaporated to give the crude

product. The crude product was purified by flash silica chromatography, elution gradient 20 to 40% ethyl acetate in isohexane, to give the desired material as a white solid (2.33 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.60 (2H, m), 1.90 (2H, m), 3.15 (1H, m), 3.40 (1H, m), 3.55 (1H, m), 3.70 (1H, m), 3.90 - 3.99 (2H, m), 4.27 (1H, m), 6.72 (1H, s), 7.96 (2H, d), 8.11 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 419; HPLC tR = 2.19 min.

4-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]benzonitrile

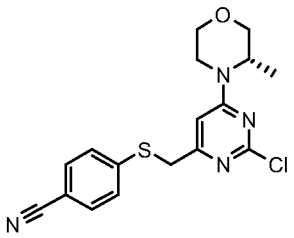


2N Sulfuric acid (0.4 mL) was added to a stirred solution of 4-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]benzonitrile (5.18 g, 14.35 mmol) in dioxane (125 mL) and the solution heated to 55ºC. Sodium tungstate dihydrate (0.095 g, 0.29 mmol) in water (3.5 mL) was added and the solution was allowed to stir for 5 minutes. Hydrogen peroxide, 30% by wt solution in water (8.80 mL, 86.13 mmol) was added dropwise and the solution stirred at 55°C for 3 hours. The reaction was cooled to RT then water added until precipitation ceased. The precipitate was collected by filtration, washed with water and dried under vacuum to afford the desired material as a white solid (5.0 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 3.18 (1H, m), 3.43 (1H, m), 3.58 (1H, m), 3.73 (1H, m), 3.91 (2H, m), 4.18 (1H, m), 4.77 (2H, s), 6.76 (1H, s), 7.99 (2H, d), 8.15 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 393; HPLC tR = 1.99 min.

4-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]benzonitrile



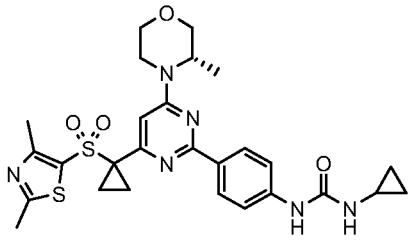
4-Mercaptobenzonitrile (3.48 g, 25.74 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7 g, 19.80 mmol) and DIPEA (5.32 mL, 29.70 mmol) in THF (50 mL). The resulting slurry was stirred at RT for 16 hours then the temperature was increased to 70ºC for a further 16 hours. The reaction mixture was cooled to RT then diluted with DCM (200 mL), and washed sequentially with water (200 mL) then saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 30% ethyl acetate in isohexane, to give the desired material as a yellow solid (5.18 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (3H, d), 3.16 (1H, m), 3.42 (1H, m), 3.57 (1H, m), 3.71 (1H, m), 3.90 - 3.99 (2H, m), 4.26 (3H, m), 6.88 (1H, s), 7.55 (2H, d), 7.75 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 361; HPLC tR = 2.33 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 78: 3-Cyclopropyl-1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



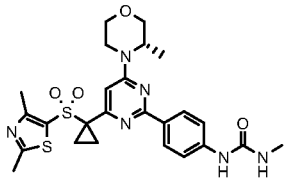
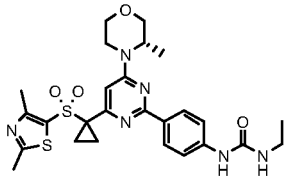
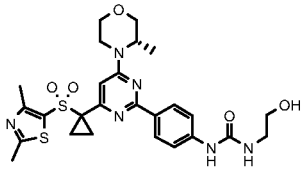
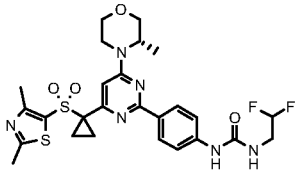
Cyclopropylamine (26 mg, 0.450 mmol) was added to phenyl *N*-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (91 mg, 0.150 mmol) and triethylamine (0.063 mL, 0.450 mmol) in NMP (2 mL). The resulting solution was stirred at 50°C for 16 hours then cooled to RT and purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (64 mg).

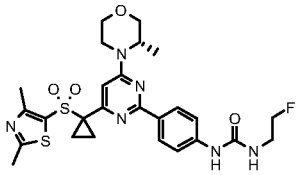
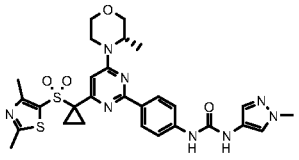
NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.42 (2H, m), 0.66 (2H, m), 1.21 (3H, d), 1.62 (2H, m), 1.79 (2H, m), 2.22 (3H, s), 2.56 (1H, m), 2.62 (3H, s), 3.18 (1H, m), 3.48

(1H, m), 3.63 (1H, m), 3.76 (1H, m), 3.97 (1H, m), 4.16 (1H, m), 4.49 (1H, m), 6.43 (1H, d), 6.73 (1H, s), 7.45 (2H, d), 7.93 (2H, d), 8.53 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 569; HPLC tR = 2.27 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
78a		1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	543	2.08
78b		3-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	557	2.25
78c		1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	573	1.91
78d		3-(2,2-difluoroethyl)-1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	593	2.38

Example	Structure	NAME	LCMS MH+	Retention time (min)
78e		1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	575	2.24
78f*		1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	609	2.13

* Stirred for an additional 4 hours at 80°C

Example 78a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.61 (2H, m), 1.79 (2H, m), 2.22 (3H, s), 2.62 (3H, s), 2.67 (3H, d), 3.18 (1H, m), 3.48 (1H, m), 3.63 (1H, m), 3.76 (1H, m), 3.97 (1H, m), 4.16 (1H, m), 4.49 (1H, m), 6.06 (1H, q), 6.72 (1H, s), 7.44 (2H, d), 7.92 (2H, d), 8.74 (1H, s).

Example 78b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.21 (3H, d), 1.62 (2H, m), 1.79 (2H, m), 2.22 (3H, s), 2.62 (3H, s), 3.10 - 3.22 (3H, m), 3.48 (1H, m), 3.63 (1H, m), 3.76 (1H, m), 3.98 (1H, m), 4.16 (1H, m), 4.49 (1H, m), 6.15 (1H, t), 6.72 (1H, s), 7.43 (2H, d), 7.92 (2H, d), 8.66 (1H, s).

Example 78c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.62 (2H, m), 1.79 (2H, m), 2.22 (3H, s), 2.62 (3H, s), 3.14 - 3.22 (3H, m), 3.44 - 3.51 (3H, m), 3.63 (1H, m), 3.76 (1H, m), 3.97 (1H, m), 4.16 (1H, m), 4.49 (1H, m), 4.74 (1H, t), 6.24 (1H, t), 6.73 (1H, s), 7.43 (2H, d), 7.93 (2H, d), 8.80 (1H, s).

Example 78d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.62 (2H, m), 1.79 (2H, m), 2.22 (3H, s), 2.62 (3H, s), 3.18 (1H, m), 3.45 - 3.65 (4H, m), 3.76 (1H, m), 3.97 (1H, m), 4.16 (1H, m), 4.49 (1H, m), 5.93 - 6.23 (1H, m), 6.53 (1H, t), 6.74 (1H, s), 7.45 (2H, d), 7.95 (2H, d), 8.92 (1H, s).

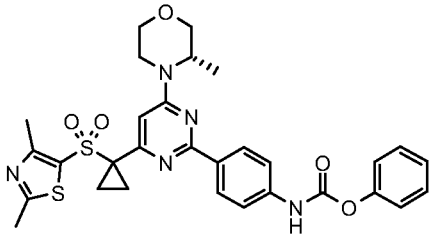
Example 78e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.62 (2H, m), 1.79 (2H, m), 2.22 (3H, s), 2.62 (3H, s), 3.18 (1H, m), 3.37 - 3.51 (3H, m), 3.63 (1H, m), 3.77 (1H, m),

3.98 (1H, m), 4.16 (1H, m), 4.41 - 4.55 (3H, m), 6.43 (1H, t), 6.73 (1H, s), 7.44 (2H, d), 7.93 (2H, d), 8.81 (1H, s).

Example 78f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.62 (2H, m), 1.80 (2H, m), 2.23 (3H, s), 2.63 (3H, s), 3.19 (1H, m), 3.48 (1H, m), 3.64 (1H, m), 3.77 (1H, m), 3.80 (3H, s), 3.98 (1H, m), 4.17 (1H, m), 4.49 (1H, m), 6.74 (1H, s), 7.39 (1H, s), 7.49 (2H, d), 7.78 (1H, s), 7.96 (2H, d), 8.38 (1H, s), 8.83 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

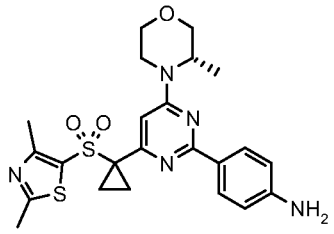


Phenyl chloroformate (0.181 mL, 1.44 mmol) was added dropwise to 4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (700 mg, 1.44 mmol) and sodium bicarbonate (182 mg, 2.16 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The precipitate was collected by filtration, washed with diethyl ether (2 mL) and suspended in water (20 mL) and stirred for 20 minutes. The precipitate was collected by filtration, washed with water (5 mL) then diethyl ether (5 mL) and dried under vacuum to afford the desired material as a beige solid (637 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.63 (2H, m), 1.81 (2H, m), 2.24 (3H, s), 2.61 (3H, s), 3.20 (1H, m), 3.49 (1H, m), 3.63 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.17 (1H, m), 4.51 (1H, m), 6.78 (1H, s), 7.28 (3H, m), 7.46 (2H, m), 7.58 (2H, d), 8.02 (2H, d), 10.43 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 606; HPLC tR = 2.91 min.

4-[4-[1-[(2,4-Dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

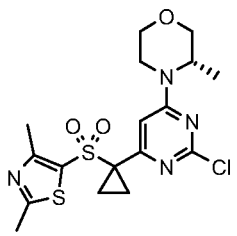


Sodium carbonate (2.105 g, 19.86 mmol) was added to 2-chloro-4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.84 g, 6.62 mmol) and (4-aminophenyl)boronic acid pinacol ester (1.523 g, 6.95 mmol) in a mixture of DME (40 mL) and water (10 mL). The mixture was bubbled with nitrogen for 10 minutes then dichlorobis(triphenylphosphine)palladium(II) (0.465 g, 0.66 mmol) was added and the mixture stirred at 80°C for 2 hours. Further dichlorobis(triphenylphosphine)palladium(II) (0.232 g, 0.33 mmol) was added and the mixture was stirred at 80°C for a further 4 hours. The reaction mixture was cooled to RT then diluted with DCM (250 mL) and water (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 40 to 50% ethyl acetate in isohexane followed by 50% ethyl acetate in isohexane, to give a material which was further purified by ion exchange chromatography using an SCX column, eluting with 2M ammonia in methanol, to give the desired material as an orange solid (2.59 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.59 (2H, m), 1.77 (2H, m), 2.22 (3H, s), 2.62 (3H, s), 3.15 (1H, m), 3.47 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.12 (1H, m), 4.45 (1H, m), 5.54 (2H, s), 6.54 (2H, d), 6.62 (1H, s), 7.76 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 486; HPLC tR = 2.17 min.

2-Chloro-4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

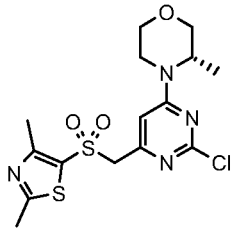


Sodium hydroxide (15.94 g, 398.59 mmol) in water (16 mL) was added to a stirred solution of 2-chloro-4-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.92 g, 7.25 mmol), 1,2-dibromoethane (1.874 mL, 21.74 mmol) and tetrabutylammonium bromide (0.234 g, 0.72 mmol) in toluene (100 mL). The resulting solution was stirred at RT for 90 minutes then at 60°C for 1 hour. The reaction mixture was diluted with water (300 mL), the organic layer separated and washed with saturated brine (100 mL) then dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to give the desired material as a white solid (2.84 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 (2H, m), 1.76 (2H, m), 2.29 (3H, s), 2.68 (3H, s), 3.17 (1H, m), 3.42 (1H, m), 3.56 (1H, m), 3.72 (1H, m), 3.91 - 4.00 (2H, m), 4.33 (1H, m), 6.82 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 429; HPLC tR = 2.09 min.

2-Chloro-4-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

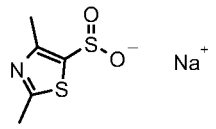


Sodium 2,4-dimethylthiazole-5-sulfinate (5.2 g, 26.10 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.01 g, 11.35 mmol) in DMF (50 mL). The resulting mixture was stirred at RT for 1 hour. The reaction mixture was evaporated to dryness and redissolved in DCM (250 mL), and washed sequentially with water (150 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane followed by 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (4.77 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 2.40 (3H, s), 2.67 (3H, s), 3.19 (1H, m), 3.44 (1H, m), 3.59 (1H, m), 3.73 (1H, m), 3.93 (2H, m), 4.23 (1H, m), 4.69 (2H, s), 6.83 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 403; HPLC tR = 1.82 min.

Sodium 2,4-dimethylthiazole-5-sulfinate

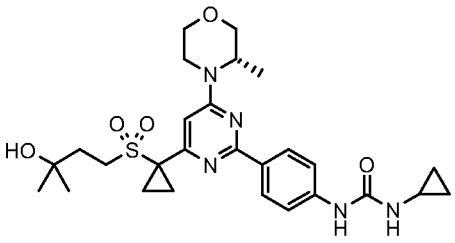


A solution of sodium sulfite (2.98 g, 23.62 mmol) in water (25 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (3.97 g, 47.24 mmol) was added and the resulting solution was stirred at 50°C for 1 hour. 2,4-Dimethylthiazole-5-sulfonyl chloride (5 g, 23.62 mmol) was added portion wise to the solution and stirring was continued at 50°C for 18 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (75 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford the desired material as a yellow solid (5.21 g), which was dried under vacuum and used without further purification.

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 2.28 (3H, s).

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 79: 3-Cyclopropyl-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

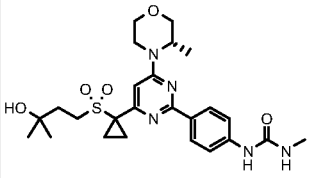
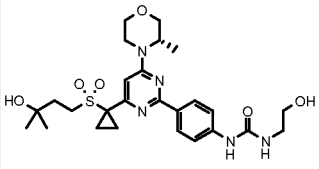
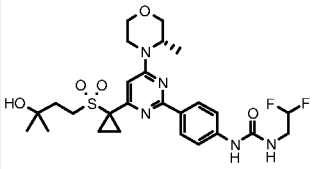
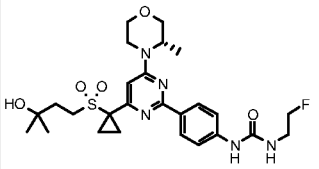


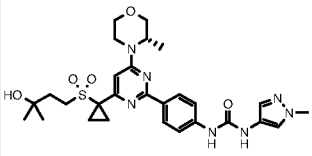
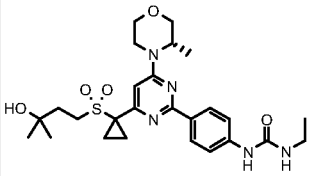
Cyclopropylamine (33 mg, 0.573 mmol) was added to phenyl *N*-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (111 mg, 0.191 mmol) and triethylamine (0.080 mL, 0.573 mmol) in NMP (2 mL). The resulting solution was stirred at 50°C for 16 hours then cooled to RT and purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (83 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.43 (2H, m), 0.65 (2H, m), 1.12 (6H, s), 1.24 (3H, d), 1.56 (2H, m), 1.65 (2H, m), 1.85 (2H, m), 2.56 (1H, m), 3.21 (1H, m), 3.49 (1H, m), 3.56 (2H, m), 3.63 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.22 (1H, m), 4.49 (1H, s), 4.56 (1H, m), 6.44 (1H, d), 6.76 (1H, s), 7.50 (2H, d), 8.24 (2H, d), 8.57 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 544; HPLC tR = 2.10 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
79a		1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	518	1.93
79b		3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.78
79c		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	568	2.18
79d		3-(2-fluoroethyl)-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	550	2.06

Example	Structure	NAME	LCMS MH+	Retention time (min)
79e*		1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	584	1.98
79f		1-ethyl-3-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	532	2.07

* 6 Equivalents of triethylamine were used.

Example 79a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.23 (3H, d), 1.55 (2H, m), 1.65 (2H, m), 1.85 (2H, m), 2.67 (3H, d), 3.21 (1H, m), 3.45 - 3.58 (3H, m), 3.63 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.22 (1H, m), 4.49 (1H, s), 4.57 (1H, m), 6.07 (1H, m), 6.75 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.77 (1H, s).

Example 79b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.24 (3H, d), 1.55 (2H, m), 1.65 (2H, m), 1.85 (2H, m), 3.16 - 3.24 (3H, m), 3.45 - 3.49 (3H, m), 3.56 (2H, m), 3.63 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.22 (1H, m), 4.49 (1H, s), 4.56 (1H, m), 4.74 (1H, t), 6.25 (1H, t), 6.76 (1H, s), 7.48 (2H, d), 8.23 (2H, d), 8.82 (1H, s).

Example 79c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.24 (3H, d), 1.56 (2H, m), 1.65 (2H, m), 1.85 (2H, m), 3.21 (1H, m), 3.45 - 3.65 (6H, m), 3.77 (1H, m), 3.98 (1H, m), 4.23 (1H, m), 4.49 (1H, s), 4.57 (1H, m), 5.93 - 6.23 (1H, m), 6.53 (1H, t), 6.77 (1H, s), 7.50 (2H, d), 8.26 (2H, d), 8.95 (1H, s).

Example 79d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.12 (6H, s), 1.24 (3H, d), 1.55 (2H, m), 1.65 (2H, m), 1.85 (2H, m), 3.21 (1H, m), 3.36 - 3.58 (5H, m), 3.64 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.22 (1H, m), 4.41 - 4.58 (4H, m), 6.43 (1H, t), 6.76 (1H, s), 7.49 (2H, d), 8.25 (2H, d), 8.83 (1H, s).

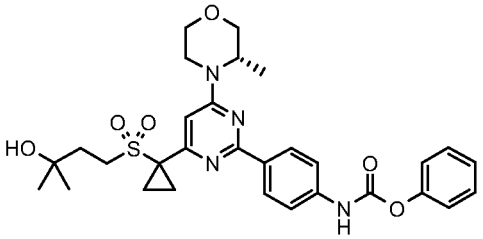
Example 79e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.24 (3H, d), 1.56 (2H, m), 1.66 (2H, m), 1.86 (2H, m), 3.22 (1H, m), 3.49 (1H, m), 3.57 (2H, m), 3.64 (1H, m), 3.78

(4H, m), 3.98 (1H, m), 4.23 (1H, m), 4.50 (1H, s), 4.57 (1H, m), 6.77 (1H, s), 7.39 (1H, s), 7.54 (2H, d), 7.78 (1H, s), 8.27 (2H, d), 8.38 (1H, s), 8.86 (1H, s)

Example 79f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.12 (6H, s), 1.23 (3H, d), 1.59 (4H, m), 1.84 (2H, m), 3.17 (3H, m), 3.54 (4H, m), 3.76 (1H, m), 3.98 (1H, m), 4.23 (1H, m), 4.56 (2H, m), 6.17 (1H, m), 6.75 (1H, s), 7.48 (2H, d), 8.23 (2H, d), 8.72 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

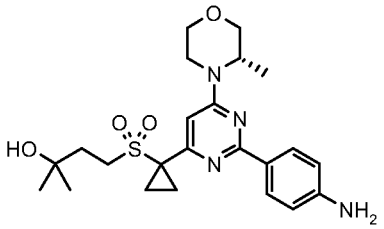


Phenyl chloroformate (0.191 mL, 1.52 mmol) was added dropwise to 4-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-2-methylbutan-2-ol (700 mg, 1.52 mmol) and sodium bicarbonate (192 mg, 2.28 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The precipitate was collected by filtration then washed with diethyl ether (2 mL). The precipitate was suspended in water (20 mL) then extracted into DCM (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as a yellow solid (774 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.12 (6H, s), 1.24 (3H, d), 1.57 (2H, m), 1.66 (2H, m), 1.85 (2H, m), 3.22 (1H, m), 3.46 - 3.57 (3H, m), 3.64 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.24 (1H, m), 4.58 (1H, m), 6.80 (1H, s), 7.28 (3H, m), 7.46 (2H, m), 7.62 (2H, d), 8.33 (2H, d), 10.43 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 581; HPLC tR = 2.63 min.

4-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-2-methylbutan-2-ol

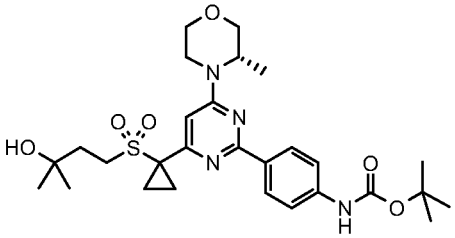


TFA (5 mL) was added to *tert*-butyl *N*-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.08 g, 3.71 mmol) in DCM (5 mL). The resulting solution was stirred at RT for 1 hour then added to an SCX column. The crude product was eluted from the column using 2M ammonia in methanol the further purified by flash silica chromatography, elution gradient 40 to 50% ethyl acetate in isohexane, to give the desired material as a white solid (1.15 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.22 (3H, d), 1.52 (2H, m), 1.63 (2H, m), 1.85 (2H, m), 3.18 (1H, m), 3.48 (1H, m), 3.55 (2H, m), 3.62 (1H, m), 3.76 (1H, m), 3.97 (1H, m), 4.19 (1H, m), 4.48 (1H, s), 4.53 (1H, m), 5.57 (2H, s), 6.59 (2H, d), 6.65 (1H, s), 8.07 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 461; HPLC tR = 1.96 min.

tert-Butyl *N*-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

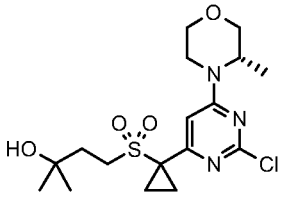


Sodium carbonate (1.299 g, 12.25 mmol) was added to 4-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-2-methylbutan-2-ol (1.65 g, 4.08 mmol) and (4-boc-aminophenyl)boronic acid pinacol ester (1.369 g, 4.29 mmol) in a mixture of DME (40 mL) and water (10 mL). The mixture was bubbled with nitrogen for 10 minutes then 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.296 g, 0.41 mmol) was

added and the mixture stirred at 80°C for 8 hours. The reaction mixture was cooled to RT then diluted with DCM (150 mL), and washed with water (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to give the desired material as a yellow gum (2.08 g).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 561; HPLC tR = 2.69 min.

4-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-2-methylbutan-2-ol

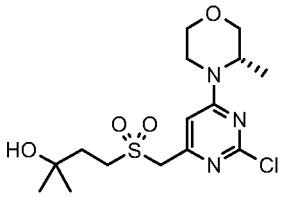


Sodium hydroxide (11.93 g, 298.37 mmol) in water (12 mL) was added to a stirred solution of 4-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-2-methylbutan-2-ol (2.05 g, 5.42 mmol), 1,2-dibromoethane (1.402 mL, 16.27 mmol) and tetrabutylammonium bromide (0.175 g, 0.54 mmol) in toluene (75 mL). The resulting solution was stirred at RT for 5 hours then at 45°C for 3 hours. The reaction mixture was diluted with water (100 mL), the organic layer separated and dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to give the desired material as a yellow dry film (1.75 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.22 (3H, d), 1.52 (2H, m), 1.61 (2H, m), 1.80 (2H, m), 3.21 (1H, m), 3.36 - 3.47 (3H, m), 3.58 (1H, m), 3.72 (1H, m), 3.93 (1H, m), 4.05 (1H, m), 4.40 (1H, m), 4.46 (1H, s), 6.94 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 404; HPLC tR = 1.83 min.

4-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-2-methylbutan-2-ol

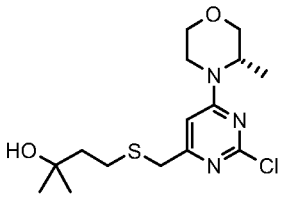


2N Sulfuric Acid (0.307 mL) was added to a stirred solution of 4-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]-2-methylbutan-2-ol (3.78 g, 10.93 mmol) in dioxane (100 mL) and the solution heated to 55ºC. Sodium tungstate dihydrate (0.072 g, 0.22 mmol) in water (3 mL) was added and the solution was allowed to stir for 5 minutes. Hydrogen peroxide, 30% by wt solution in water (6.7 mL, 65.57 mmol) was added dropwise and the solution stirred at 55°C for 2.5 hours. The reaction mixture was cooled to RT and diluted with water (100 mL), and extracted with DCM (2 x 200 mL). The organic layer was washed with brine (50 mL) then dried over $MgSO_4$, filtered and evaporated to afford the desired material as a cream solid (4.39 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (6H, s), 1.23 (3H, d), 1.82 (2H, m), 3.19 - 3.30 (3H, m), 3.46 (1H, m), 3.61 (1H, m), 3.74 (1H, m), 3.93 - 4.02 (2H, m), 4.31 (1H, m), 4.46 (2H, s), 4.48 (1H, s), 6.95 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 378; HPLC tR = 1.64 min.

4-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]-2-methylbutan-2-ol



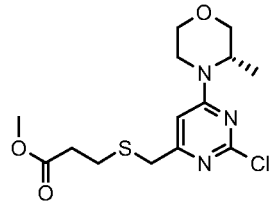
Methylmagnesium bromide, 3M in diethyl ether (13.17 mL, 39.50 mmol) was added dropwise to methyl 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]propanoate (4.14 g, 11.97 mmol) in THF (50 mL) at 0ºC over a period of 10 minutes under nitrogen. The resulting solution was stirred at 0°C for 30 minutes then at RT for 90 minutes. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (1 mL), diluted with water (100 mL) then extracted with DCM (3 x 100

mL), the organic layer was washed with brine (100 mL) then dried over $MgSO_4$, filtered and evaporated to afford the desired material as a yellow gum (3.96 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.08 (6H, s), 1.21 (3H, d), 1.61 (2H, m), 2.54 (2H, m), 3.18 (1H, m), 3.44 (1H, m), 3.57 (2H, s), 3.61 (1H, m), 3.72 (1H, m), 3.91 - 4.01 (2H, m), 4.23 (1H, s), 4.32 (1H, m), 6.78 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 346; HPLC tR = 1.79 min.

Methyl 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]propanoate



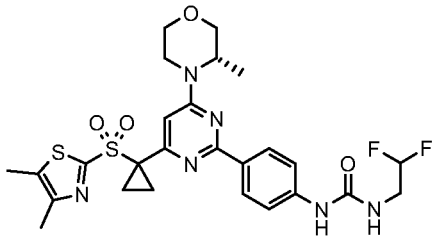
Methyl 3-mercaptopropionate (2.55 g, 21.21 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (5 g, 14.14 mmol) and DIPEA (3.80 mL, 21.21 mmol) in THF (50 mL). The resulting slurry was stirred at RT for 16 hours. The reaction mixture was diluted with DCM (150 mL), and washed sequentially with water (100 mL) then saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 30% ethyl acetate in isohexane, to give the desired material as a colourless liquid (4.6 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 2.65 (2H, t), 2.76 (2H, t), 3.19 (1H, m), 3.45 (1H, m), 3.56 - 3.64 (6H, m), 3.72 (1H, m), 3.91 - 4.00 (2H, m), 4.33 (1H, m), 6.81 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 346; HPLC tR = 2.05 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 80: 3-(2,2-Difluoroethyl)-1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

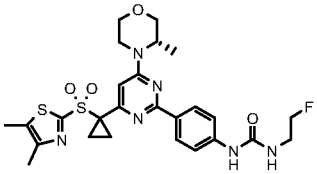


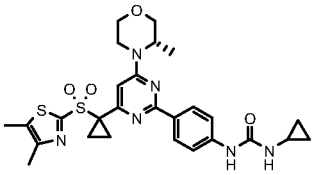
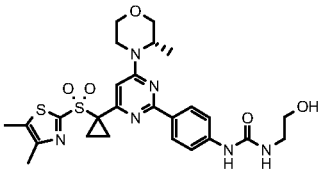
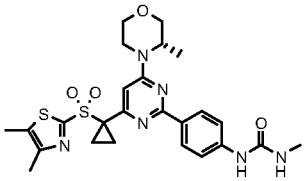
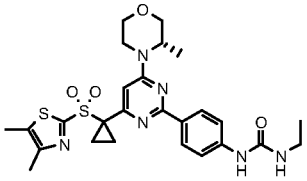
Phenyl *N*-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.25 mmol), triethylamine (0.104 mL, 0.74 mmol) and 2,2-difluoroethanamine (60.2 mg, 0.74 mmol) were added to dioxane (10 mL) and heated at 50°C for 72 hours. The reaction mixture was evaporated under reduced pressure to a gum which was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (83 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.77 - 1.72 (2H, m), 1.95 - 1.88 (2H, m), 2.37 (3H, s), 2.40 (3H, s), 3.23 - 3.13 (1H, m), 3.66 - 3.41 (4H, m), 3.80 - 3.73 (1H, m), 3.97 (1H, d), 4.17 (1H, d), 4.51 - 4.41 (1H, m), 6.23 - 5.91 (1H, m), 6.51 (1H, t), 6.79 (1H, s), 7.44 (2H, d), 7.90 (2H, d), 8.91 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 493; HPLC tR = 2.42 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
80a		1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	576	2.25

Example	Structure	NAME	LCMS MH+	Retention time (min)
80b		3-cyclopropyl-1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	569	2.23
80c		1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	573	1.90
80d*		1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	543	2.06
80e*		3-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	557	2.21

* Stirred at RT for 16 hours

Example 80a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.78 - 1.71 (2H, m), 1.94 - 1.89 (2H, m), 2.37 (3H, s), 2.40 (3H, s), 3.24 - 3.13 (1H, m), 3.51 - 3.35 (4H, m), 3.65 - 3.59 (1H, m), 3.79 - 3.74 (1H, m), 4.01 - 3.94 (1H, m), 4.17 (1H, d), 4.56 - 4.38 (3H, m), 6.41 (1H, t), 7.43 (2H, d), 7.89 (2H, d), 8.80 (1H, s)

Example 80b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.45 - 0.38 (2H, m), 0.69 - 0.61 (2H, m), 1.21 (3H, d), 1.76 - 1.72 (2H, m), 1.94 - 1.89 (2H, m), 2.37 (3H, s), 2.41 (3H, s), 2.59 - 2.53 (1H, m), 3.24 - 3.13 (1H, m), 3.47 (1H, t), 3.64 - 3.59 (1H, m), 3.80 - 3.72 (1H, m), 3.98

(1H, d), 4.17 (1H, d), 4.50 - 4.41 (1H, m), 6.41 (1H, d), 6.78 (1H, s), 7.43 (2H, d), 7.88 (2H, d), 8.53 (1H, s)

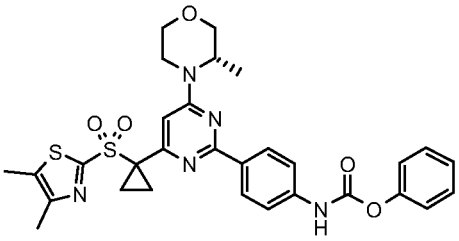
Example 80c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.77 - 1.72 (2H, m), 1.94 - 1.89 (2H, m), 2.37 (3H, s), 2.40 (4H, s), 3.51 - 3.42 (3H, m), 3.65 - 3.59 (1H, m), 3.79 - 3.74 (1H, m), 3.97 (1H, d), 4.06 (2H, q), 4.17 (1H, d), 4.50 - 4.41 (1H, m), 4.72 (1H, t), 6.23 (1H, t), 6.78 (1H, s), 7.41 (2H, d), 7.88 (2H, d), 8.79 (1H, s)

Example 80d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.78 - 1.72 (2H, m), 1.94 - 1.89 (2H, m), 2.37 (3H, s), 2.40 (3H, s), 2.66 (3H, d), 3.23 - 3.13 (1H, m), 3.52 - 3.42 (1H, m), 3.65 - 3.59 (1H, m), 3.79 - 3.74 (1H, m), 3.97 (1H, d), 4.20 - 4.13 (1H, m), 4.49 - 4.41 (1H, m), 6.07 - 6.03 (1H, m), 6.78 (1H, s), 7.43 (2H, d), 7.87 (2H, d), 8.73 (1H, s)

Example 80e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.21 (3H, d), 1.77 - 1.71 (2H, m), 1.95 - 1.88 (2H, m), 2.37 (3H, s), 2.41 (3H, s), 3.23 - 3.07 (3H, m), 3.47 (1H, t), 3.65 - 3.59 (1H, m), 3.79 - 3.73 (1H, m), 3.98 (1H, d), 4.16 (1H, d), 4.51 - 4.40 (1H, m), 6.14 (1H, t), 6.78 (1H, s), 7.42 (2H, d), 7.88 (2H, d), 8.65 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

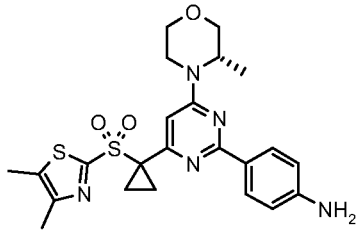


Phenyl chloroformate (0.866 mL, 6.91 mmol) was added dropwise to 4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (2.58 g, 5.31 mmol) and sodium hydrogencarbonate (8.93 g, 106.26 mmol) in DCM (52.3 mL) at RT under nitrogen. The resulting suspension was stirred at RT for 90 minutes, saturated ammonium chloride solution added followed by DCM (40 mL). The organics were separated, washed with water (50 mL) and saturated brine (50 mL), dried over $MgSO_4$ and evaporated to give the desired material (2.91 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.87 - 1.77 (2H, m), 2.14 - 2.10 (2H, m), 2.34 (3H, s), 2.36 (3H, s), 3.32 (1H, t), 3.60 (1H, t), 3.77 - 3.72 (1H, m), 3.85 - 3.81 (1H, m), 4.04 (1H, d), 4.20 (1H, d), 4.53 - 4.44 (1H, m), 7.04 (1H, s), 7.10 (1H, s), 7.28 - 7.17 (3H, m), 7.40 (2H, t), 7.46 (2H, d), 8.16 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 606; HPLC tR = 2.90 min.

4-[4-[1-[(4,5-Dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

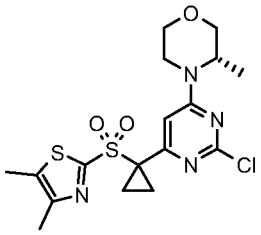


Dichlorobis(triphenylphosphine)palladium(II) (0.219 g, 0.31 mmol) was added in one portion to 2-chloro-4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.68 g, 6.25 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.369 g, 6.25 mmol) and sodium bicarbonate (15.62 mL, 31.24 mmol) in a mix of solvents (18% DMF, 82% of a 7:3:2 mixture of DME:water:ethanol) (75 mL) and the resulting mixture stirred at 80°C for 16 hours under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (2 x 150 mL) and saturated brine (3 x 100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a yellow foam (2.85 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.88 - 1.75 (2H, m), 2.16 - 2.06 (2H, m), 2.34 (3H, s), 2.36 (3H, s), 3.33 - 3.24 (1H, m), 3.63 - 3.55 (1H, m), 3.88 - 3.71 (4H, m), 4.03 (1H, d), 4.18 (1H, d), 4.51 - 4.43 (1H, m), 6.64 (2H, d), 7.04 (1H, s), 8.01 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 486; HPLC tR = 1.65 min.

2-Chloro-4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

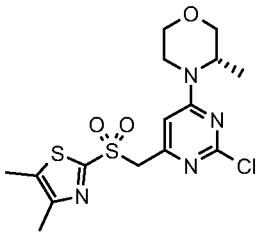


Sodium hydroxide (50% w/w) (45.9 g, 573.32 mmol) was added in one portion to 2-chloro-4-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.2 g, 10.42 mmol), tetrabutylammonium bromide (0.336 g, 1.04 mmol) and 1,2-dibromoethane (2.69 mL, 31.27 mmol) in toluene (52.1 mL) and the resulting mixture stirred at 60°C for 5 hours. The reaction mixture was diluted with toluene (50 mL) and water (100 mL) and washed sequentially with water (2 x 100 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a white foam (3.42 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.83 - 1.72 (2H, m), 2.11 - 2.02 (2H, m), 2.37 (3H, s), 2.44 (3H, s), 3.29 (1H, t), 3.54 (1H, t), 3.72 - 3.66 (1H, m), 3.82 - 3.76 (1H, m), 4.13 - 3.97 (2H, m), 4.35 (1H, s), 7.29 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 429; HPLC tR = 2.35 min.

2-Chloro-4-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



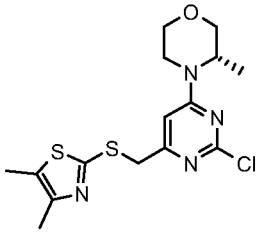
3-Chloroperoxybenzoic acid (11.18 g, 49.88 mmol) was added portionwise to (2-chloro-4-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7.4 g, 19.95 mmol) in DCM (100 mL) at 5ºC over a period of 15 minutes under nitrogen. The resulting suspension was stirred at 5ºC for 1 hour then allowed to warm to RT and stirred for

3 hours. A saturated solution of sodium hydrogen carbonate (100 mL) was added and the organics separated and washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in DCM, to give the desired material as a white solid (4.2 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.32 (3H, d), 2.42 (3H, s), 2.46 (3H, s), 3.28 (1H, t), 3.54 (1H, t), 3.71 - 3.66 (1H, m), 3.81 - 3.76 (1H, m), 4.09 - 3.96 (2H, m), 4.35 - 4.23 (1H, m), 4.51 (2H, s), 6.59 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 403; HPLC tR = 2.02 min.

2-Chloro-4-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



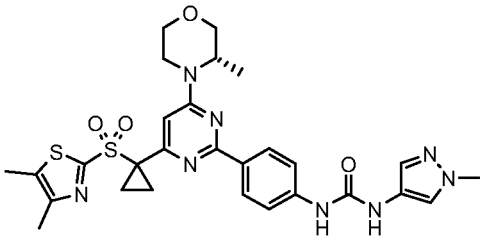
2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7 g, 19.80 mmol) was added to 4,5-dimethylthiazole-2-thiol (3.16 g, 21.78 mmol) and DIPEA (5.17 mL, 29.70 mmol) in THF (10 mL) and the slurry stirred at RT for 7 hours. The solvent was removed under reduced pressure and the residue diluted with DCM and washed sequentially with water and saturated brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a yellow gum (7.95 g).

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16 - 1.19 (3H, m), 2.23 (3H, d), 2.29 (3H, d), 3.16 - 3.20 (1H, td), 3.39 - 3.46 (1H, td), 3.55 - 3.59 (1H, dd), 3.71 (1H, d), 3.91 - 3.94 (2H, dd), 4.21 - 4.29 (3H, m), 6.80 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 371; HPLC tR = 2.31 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 81: 1-[4-[4-[1-[(4,5-Dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea



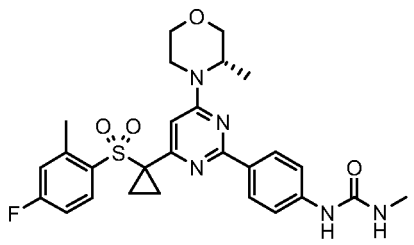
Phenyl *N*-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.25 mmol), 1-methyl-1H-pyrazol-4-amine dihydrochloride (126 mg, 0.74 mmol) and DIPEA (0.428 mL, 2.48 mmol) were dissolved in dioxane (10 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 150 minutes in the microwave reactor and cooled to RT. The solvent was evaporated under reduced pressure, and the crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (70 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.77 - 1.72 (2H, m), 1.95 - 1.89 (2H, m), 2.37 (3H, s), 2.41 (3H, s), 3.24 - 3.14 (1H, m), 3.52 - 3.43 (1H, m), 3.65 - 3.59 (1H, m), 3.81 - 3.75 (4H, m), 4.00 - 3.95 (1H, m), 4.22 - 4.11 (1H, m), 4.51 - 4.41 (1H, m), 6.79 (1H, s), 7.38 (1H, s), 7.47 (2H, d), 7.77 (1H, s), 7.92 (2H, d), 8.36 (1H, s), 8.83 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 609; HPLC tR = 2.09 min.

The preparation of phenyl *N*-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 82: 1-[4-[4-[1-(4-Fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

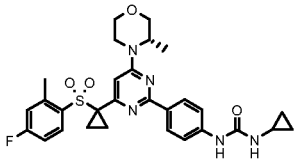
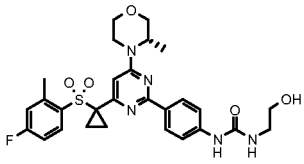
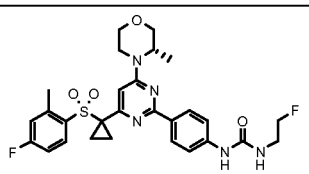


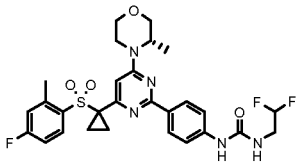
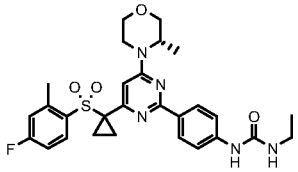
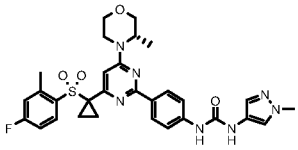
Phenyl *N*-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.150 g, 0.25 mmol), triethylamine (0.104 mL, 0.75 mmol) and methylamine (0.75 mmol) were dissolved in dioxane (10 mL) and heated at 50°C overnight. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.63 - 1.60 (2H, m), 1.85 - 1.83 (2H, m), 2.44 (3H, s), 2.66 (3H, d), 3.13 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.42 (1H, s), 6.04 (1H, q), 6.62 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.40 (2H, d), 7.84 - 7.81 (3H, m), 8.71 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 540; HPLC tR= 2.34 min

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
82a		3-cyclopropyl-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	566	2.51
82b		1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	570	2.15
82c		3-(2-fluoroethyl)-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	572	2.50

Example	Structure	NAME	LCMS MH+	Retention time (min)
82d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	590	2.62
82e		3-ethyl-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	554	2.50
82f		1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	606	2.36

Example 82a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.63 - 1.60 (2H, m), 1.85 - 1.83 (2H, m), 2.44 (3H, s), 2.66 (3H, d), 3.13 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.42 (1H, s), 6.04 (1H, q), 6.62 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.40 (2H, d), 7.84 - 7.81 (3H, m), 8.71 (1H, s);

Example 82b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.63 - 1.60 (2H, m), 1.85 - 1.83 (2H, m), 2.44 (3H, s), 3.20 - 3.09 (3H, m), 3.48 - 3.42 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.42 (1H, s), 4.73 (1H, t), 6.23 (1H, t), 6.62 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.39 (2H, d), 7.85 - 7.80 (3H, m), 8.77 (1H, s);

Example 82c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.63 - 1.60 (2H, m), 1.85 - 1.83 (2H, m), 2.44 (3H, s), 3.13 (1H, ddd), 3.47 - 3.36 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.55 - 4.40 (3H, m), 6.41 (1H, t), 6.63 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.40 (2H, d), 7.86 - 7.81 (3H, m), 8.78 (1H, s);

Example 82d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.63 - 1.60 (2H, m), 1.86 - 1.83 (2H, m), 2.44 (3H, s), 3.13 (1H, ddd), 3.62 - 3.42 (4H, m), 3.74 (1H, d), 3.95 (1H, dd),

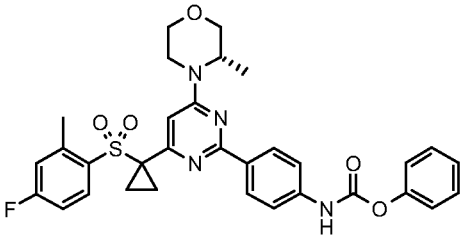
4.10 (1H, d), 4.42 (1H, s), 6.07 (1H, ddt), 6.50 (1H, t), 6.63 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.41 (2H, d), 7.86 - 7.80 (3H, m), 8.90 (1H, s);

Example 82e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.16 (3H, d), 1.63 - 1.60 (2H, m), 1.85 - 1.83 (2H, m), 2.44 (3H, s), 3.18 - 3.09 (3H, m), 3.44 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, ddd), 4.42 (1H, s), 6.13 (1H, t), 6.62 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.39 (2H, d), 7.84 - 7.81 (3H, m), 8.63 (1H, s);

Example 82f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.64 - 1.61 (2H, m), 1.86 - 1.83 (2H, m), 2.45 (3H, s), 3.14 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.79 (3H, s), 3.96 (1H, dd), 4.11 (1H, d), 4.43 (1H, s), 6.64 (1H, s), 7.18 (1H, ddd), 7.25 (1H, dd), 7.38 (1H, s), 7.45 (2H, d), 7.77 (1H, s), 7.88 - 7.81 (3H, m), 8.36 (1H, s), 8.81 (1H, s);

The preparation of phenyl *N*-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

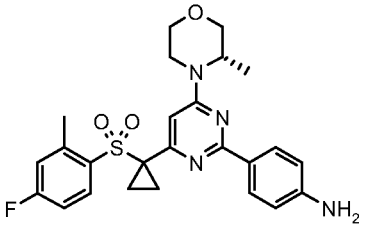


4-[4-[1-(4-Fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (as the hydrochloride salt) (1.80 g, 3.47 mmol) and sodium bicarbonate (2.91 g, 34.68 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.566 mL, 4.51 mmol) was added slowly and the reaction stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.73 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.65 - 1.62 (2H, m), 1.87 - 1.84 (2H, m), 2.45 (3H, s), 3.14 (1H, ddd), 3.49 - 3.42 (1H, m), 3.60 (1H, dd), 3.74

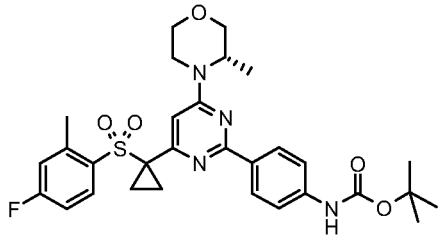
(1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.45 (1H, s), 6.67 (1H, s), 7.17 (1H, ddd), 7.30 - 7.23 (4H, m), 7.45 (2H, t), 7.54 (2H, d), 7.83 (1H, dd), 7.93 (2H, d), 10.40 (1H, s);
LCMS Spectrum: m/z (ES+) (M+H)+ = 603; HPLC tR= 3.15 min

4-[4-[1-(4-Fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



tert-Butyl *N*-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.03 g, 3.48 mmol) was added to 6.0 N hydrogen chloride in propan-2-ol (30 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a white solid (1.80 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.04 (3H, d), 1.70 - 1.65 (2H, m), 1.89 - 1.86 (2H, m), 2.45 (3H, s), 3.22 (1H, ddd), 3.44 (1H, ddd), 3.59 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.21 (1H, s), 4.50 (1H, s), 6.14 (2H, s), 6.70 (1H, s), 7.14 - 7.03 (2H, m), 7.21 (1H, t), 7.31 (1H, d), 7.82 (1H, dd), 7.93 (2H, d);
LCMS Spectrum: m/z (ES+) (M+H)+ = 483; HPLC tR= 2.67 min

tert-Butyl *N*-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



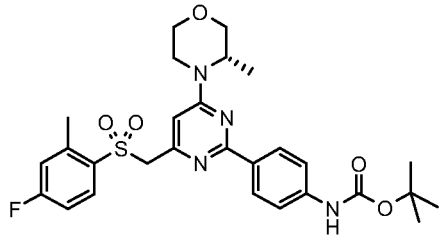
To *tert*-butyl *N*-[4-[4-[(4-fluoro-2-methylphenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3.36 g, 6.04 mmol) in DMF (30 mL) was added rapidly sodium hydride (1.159 g, 24.14 mmol), this was stirred at RT for 10 minutes before

the slow addition 1,2-dibromoethane (2.081 mL, 24.14 mmol) in DMF (30 mL). The resulting suspension was stirred at RT for 1 hour. A further portion of sodium hydride (0.58 g, 12.07 mmol) and 1,2 dibromoethane (1.04 mL, 12.07 mmol) were rapidly added and the reaction was stirred for a further 30 minutes. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give the desired material as a white foam (2.05 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.49 (9H, s), 1.63 - 1.60 (2H, m), 1.86 - 1.83 (2H, m), 2.44 (3H, s), 3.13 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.11 (1H, d), 4.43 (1H, s), 6.65 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.47 (2H, d), 7.82 (1H, dd), 7.86 (2H, d), 9.50 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 583; HPLC tR= 3.17 min

tert-Butyl *N*-[4-[4-[(4-fluoro-2-methylphenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

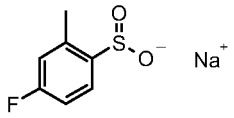


Sodium 4-fluoro-2-methylbenzenesulfinate (1.663 g, 7.84 mmol) and *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (4.0 g, 7.84 mmol) were dissolved in DMF (25 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a yellow solid. This was partitioned between aqueous sodium thiosulphate solution (50 mL) and DCM (75 mL). The organics were purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a white foam (4.20 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.49 (9H, s), 2.65 (3H, s), 3.16 (1H, ddd), 3.48 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.39 (1H, s), 4.67 (2H, s), 6.67 (1H, s), 7.15 (1H, ddd), 7.39 (1H, dd), 7.45 (2H, d), 7.68 (1H, dd), 7.80 (2H, d), 9.50 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 557; HPLC tR= 3.06 min

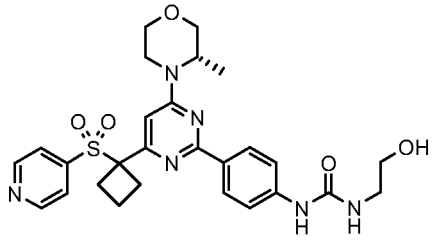
Sodium 4-fluoro-2-methylbenzenesulfinate



A solution of sodium sulfate (15.10 g, 119.82 mmol) in water (100 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (20.13 g, 239.65 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 10 minutes. 4-Fluoro-2-methylbenzene-1-sulfonyl chloride (25 g, 119.82 mmol) was added portionwise to the solution and was stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and re-dissolved in ethanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (17.5 g). NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.46 (3H, s), 6.86 (1H, dd), 6.95 (1H, ddd), 7.66 (1H, dd);

The preparation of *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 83: 3-(2-Hydroxyethyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea



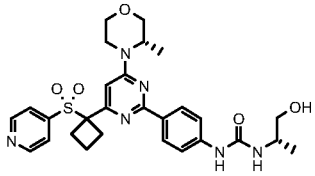
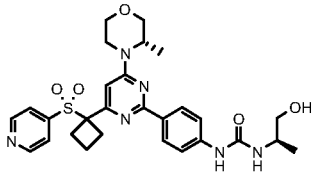
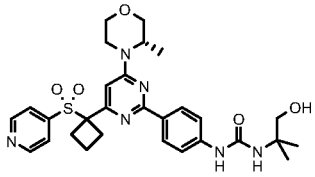
A solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) in NMP (2 mL) was treated with ethanolamine (11 mg, 0.18 mmol) and triethylamine (51 mg, 0.5 mmol) and stirred at RT overnight. The crude reaction mixture was purified by preparative HPLC, eluting

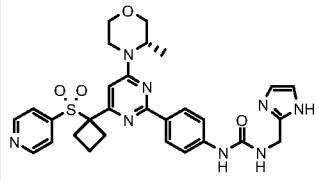
with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material (66mg).

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20 - 1.22 (3H, m), 1.93 (1H, t), 2.11 - 2.16 (1H, m), 2.78 - 2.85 (2H, m), 3.09 - 3.19 (5H, m), 3.45 - 3.52 (3H, m), 3.63 - 3.66 (1H, m), 3.75 - 3.78 (1H, m), 3.97 (1H, d), 4.15 - 4.19 (1H, m), 4.51 (1H, s), 4.78 (1H, s), 6.26 (1H, t), 6.63 (1H, s), 7.35 (2H, d), 7.46 (2H, d), 7.68 (2H, d), 8.72 (2H, d), 8.80 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 553.48; HPLC tR = 1.93 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
83a		3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	567.5	2.02
83b		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	567.5	2.02
83c		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	581.6	2.22

Example	Structure	NAME	LCMS MH+	Retention time (min)
83d		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	589.5	1.43

Example 83a: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.07 - 1.09 (3H, m), 1.20 (3H, d), 1.91 - 1.93 (1H, m), 2.13 (1H, t), 2.78 - 2.85 (2H, m), 3.08 - 3.19 (3H, m), 3.38 - 3.41 (2H, m), 3.45 - 3.54 (1H, td), 3.60 - 3.82 (3H, m), 3.96 (1H, dd), 4.16 (1H, d), 4.50 (1H, s), 4.83 (1H, t), 6.09 - 6.11 (1H, m), 6.63 (1H, s), 7.34 (2H, d), 7.46 - 7.47 (2H, m), 7.68 (2H, d), 8.70 - 8.72 (3H, m)

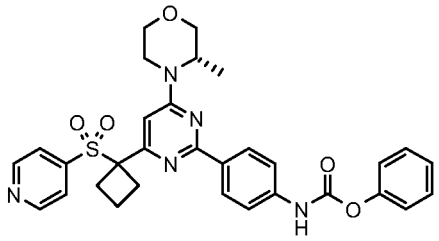
Example 83b: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.07 - 1.09 (3H, m), 1.20 (3H, d), 1.91 - 1.93 (1H, m), 2.13 (1H, t), 2.78 - 2.85 (2H, m), 3.08 - 3.19 (3H, m), 3.38 - 3.41 (2H, m), 3.45 - 3.54 (1H, td), 3.60 - 3.82 (3H, m), 3.96 (1H, dd), 4.16 (1H, d), 4.50 (1H, s), 4.83 (1H, t), 6.09 - 6.11 (1H, m), 6.63 (1H, s), 7.34 (2H, d), 7.46 - 7.47 (2H, m), 7.68 (2H, d), 8.70 - 8.72 (3H, m)

Example 83c: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.24 (6H, s), 1.91 - 1.93 (1H, m), 2.11 - 2.16 (1H, m), 2.77 - 2.84 (2H, m), 3.08 - 3.20 (3H, m), 3.39 (2H, d), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 (1H, d), 4.51 (1H, s), 5.00 (1H, t), 6.00 (1H, s), 6.63 (1H, s), 7.29 - 7.32 (2H, m), 7.46 - 7.47 (2H, m), 7.65 - 7.67 (2H, m), 8.71 - 8.72 (3H, m)

Example 83d: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.92 (1H, q), 2.11 - 2.16 (1H, m), 2.81 (2H, s), 3.09 - 3.18 (3H, m), 3.49 (1H, t), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.17 (1H, d), 4.32 (2H, d), 4.51 (1H, s), 6.64 (2H, s), 6.84 (1H, s), 7.04 (1H, s), 7.38 (2H, d), 7.46 (2H, d), 7.69 (2H, d), 8.72 (2H, d), 8.92 (1H, s), 11.87 (1H, s)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate



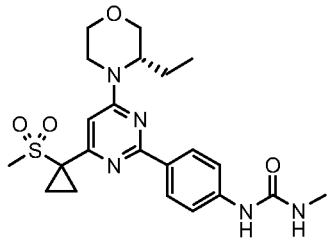
Phenyl chloroformate (0.241 mL, 1.92 mmol) was added dropwise to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline (894 mg, 1.92 mmol) and sodium bicarbonate (161 mg, 1.92 mmol) in dioxane (10 mL) at RT under air. The resulting solution was stirred at RT for 2hours. The reaction was evaporated to dryness and the residue was taken up in water (100 mL) and extracted with ethyl acetate (200 mL). The organic layer was washed with water, brine and then dried ($MgSO_4$). The solution was evaporated to dryness and the crude material was chromatographed on a silica, eluting with 50% ethyl acetate in isohexane, to give the desired material as a cream coloured solid (690 mg).

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17 - 1.23 (3H, m), 1.90 - 1.92 (1H, m), 2.00 (1H, s), 2.12 (1H, t), 2.77 - 2.83 (2H, m), 3.06 - 3.17 (3H, m), 3.47 - 3.50 (1H, m), 3.61 - 3.65 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.15 (1H, d), 4.50 (1H, s), 5.54 (1H, d), 6.46 (1H, d), 6.53 (1H, s), 6.75 - 6.79 (2H, m), 7.15 - 7.19 (1H, m), 7.43 - 7.49 (2H, m), 7.49 (1H, d), 7.53 (1H, s), 8.70 - 8.72 (2H, m), 9.34 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 586.18; HPLC tR = 2.87 min.

The preparation of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline was described earlier.

Example 84: 1-[4-[4-[(3*S*)-3-Ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-methylurea

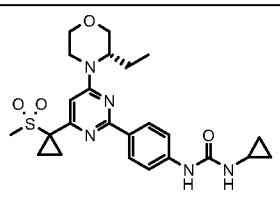


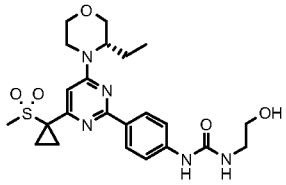
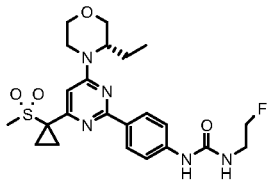
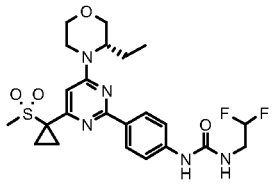
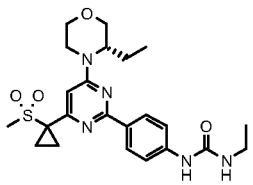
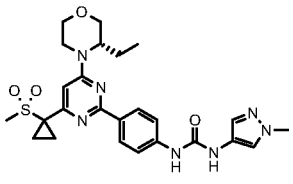
Phenyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (54.0 mg, 0.10 mmol), triethylamine (0.043 mL, 0.31 mmol) and methyl amine (-, 0.31 mmol) were dissolved in dioxane (10 mL) and heated at 50 °C over the weekend. The reaction was evaporated to dryness and was purified by preparative HPLC (Waters XTerra C18 column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford (S)-1-(4-(4-(3-ethylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)phenyl)-3-methylurea as a white solid.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.56 - 1.54 (2H, m), 1.69 - 1.64 (2H, m), 1.83 - 1.69 (2H, m), 2.66 (3H, d), 3.22 - 3.14 (1H, m), 3.27 (3H, s), 3.47 (1H, ddd), 3.55 (1H, dd), 3.87 (1H, d), 3.93 (1H, dd), 4.41 - 4.27 (2H, m), 6.07 (1H, q), 6.78 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.74 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 460; HPLC tR = 1.98 min.

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
84a		3-cyclopropyl-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	486	2.15

Example	Structure	NAME	LCMS MH+	Retention time (min)
84b		1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	490	1.8
84c		1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	492	2.13
84d		3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	510	2.27
84e		3-ethyl-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	474	2.13
84f		1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	526	2.03

Example 84a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.44 - 0.40 (2H, m), 0.65 - 0.64 (2H, m), 0.89 (3H, t), 1.57 - 1.53 (2H, m), 1.66 (2H, m), 1.68 - 1.64 (2H, m), 3.23 - 3.14 (1H, m), 3.50 - 3.44 (1H, m), 3.55 (1H, dd), 3.87 (1H, d), 3.94 - 3.92 (1H, m), 4.47 - 4.22 (2H, m), 6.44 (1H, s), 6.78 (1H, s), 7.51 (2H, d), 8.19 (2H, d), 8.54 (1H, s); 4 protons missing due to very weak sample!!

Example 84b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.57 - 1.53 (2H, m), 1.69 - 1.64 (2H, m), 1.83 - 1.71 (2H, m), 3.22 - 3.16 (3H, m), 3.27 (3H, s), 3.49 - 3.44 (3H, m), 3.55

(1H, dd), 3.87 (1H, d), 3.94 - 3.92 (1H, m), 4.39 - 4.24 (2H, m), 4.73 (1H, t), 6.25 (1H, t), 6.78 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.80 (1H, s);

Example 84c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.58 - 1.54 (2H, m), 1.69 - 1.64 (2H, m), 1.83 - 1.69 (2H, m), 3.22 - 3.17 (1H, m), 3.29 (s, 3H), 3.49 - 3.37 (3H, m), 3.55 (1H, dd), 3.87 (1H, d), 3.94 - 3.92 (1H, m), 4.40 - 4.16 (2H, m), 4.48 (2H, dt), 6.44 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.81 (1H, s);

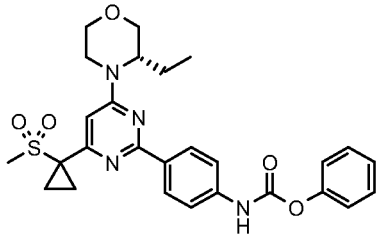
Example 84d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.57 - 1.54 (2H, m), 1.67 - 1.64 (2H, m), 1.83 - 1.69 (2H, m), 3.22 - 3.16 (1H, m), 3.29 (3H, s), 3.60 - 3.44 (4H, m), 3.87 (1H, d), 3.93 (1H, dd), 4.48 - 4.21 (2H, m), 6.07 (1H, tt), 6.53 (1H, t), 6.79 (1H, s), 7.51 (2H, d), 8.21 (2H, d), 8.92 (1H, s);

Example 84e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.07 (3H, t), 1.56 - 1.54 (2H, m), 1.68 - 1.65 (2H, m), 1.83 - 1.69 (2H, m), 3.22 - 3.09 (3H, m), 3.29 (3H, s), 3.47 (1H, ddd), 3.55 (1H, dd), 3.87 (1H, d), 3.93 (1H, dd), 4.40 - 4.24 (2H, m), 6.16 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.66 (1H, s);

Example 84f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.57 - 1.54 (2H, m), 1.69 - 1.65 (2H, m), 1.84 - 1.70 (2H, m), 3.23 - 3.17 (1H, m), 3.47 (1H, ddd), 3.56 (1H, dd), 3.79 (3H, s), 3.88 (1H, d), 3.94 (1H, dd), 4.41 - 4.23 (2H, m), 6.80 (1H, s), 7.38 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.23 (2H, d), 8.39 (1H, s), 8.84 (1H, s); Methyl sulfone hidden under water peak (3H missing).

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate



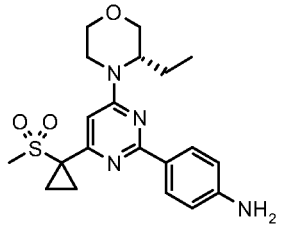
4-[4-[(3*S*)-3-Ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (as the hydrochloride salt) (0.43 g, 0.98 mmol) and sodium bicarbonate (0.823 g, 9.80 mmol)

were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.160 mL, 1.27 mmol) was added slowly and the reaction stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a yellow solid (0.46 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.58 - 1.55 (2H, m), 1.69 - 1.65 (2H, m), 1.84 - 1.70 (2H, m), 3.20 (1H, ddd), 3.27 (3H, s), 3.47 (1H, ddd), 3.56 (1H, dd), 3.87 (1H, d), 3.93 (1H, dd), 4.41 - 4.24 (2H, m), 6.82 (1H, s), 7.30 - 7.24 (3H, m), 7.45 (2H, t), 7.64 (2H, d), 8.29 (2H, d), 10.44 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 523; HPLC tR = 2.85 min.

4-[4-[(3*S*)-3-Ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline

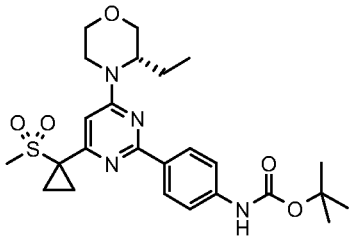


tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (0.5 g, 0.99 mmol) was added to 6.0 N hydrogen chloride in propan-2-ol (30 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a yellow solid (0.43 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.65 - 1.60 (2H, m), 1.75 - 1.67 (2H, m), 1.83 - 1.80 (2H, m), 3.24 (3H, s), 3.38 - 3.28 (1H, m), 3.52 - 3.46 (1H, m), 3.58 (1H, dd), 3.89 (1H, d), 3.96 (1H, dd), 4.48 - 4.33 (2H, m), 7.09 - 6.98 (3H, m), 8.21 - 8.08 (2H, m); NH2 missing;

LCMS Spectrum: m/z (ESI+) (M+H)+ = 403; HPLC tR = 2.23 min.

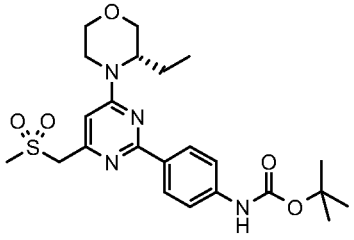
tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate



Sodium hydride (0.705 g, 14.69 mmol) was added rapidly to *tert*-butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate (1.75 g, 3.67 mmol) in DMF (30 mL) and the mixture stirred at RT for 10 minutes before the slow addition 1,2-dibromoethane (1.266 mL, 14.69 mmol) in DMF (30 mL). The resulting suspension was stirred at RT for 1 hour. The reaction was heated to 40°C and a further portion of sodium hydride (2.0 eq) and 1,2 dibromoethane (2.0 eq) were rapidly added and the reaction was stirred for a further 30 minutes. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give the desired material as a yellow foam (0.30 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.50 (9H, s), 1.57 - 1.54 (2H, m), 1.68 - 1.66 (2H, m), 1.83 - 1.70 (2H, m), 3.22 - 3.16 (1H, m), 3.50 - 3.44 (1H, m), 3.57 - 3.53 (1H, m), 3.87 (1H, d), 3.94 - 3.92 (1H, m), 4.38 - 4.24 (2H, m), 6.80 (1H, s), 7.57 (2H, d), 8.21 (2H, d), 9.55 (1H, s); methyl peak under water (3H missing).

tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate



tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(iodomethyl)pyrimidin-2-yl]phenyl]carbamate (2.0 g, 3.81 mmol) and sodium methanesulfinate (0.389 g, 3.81 mmol)

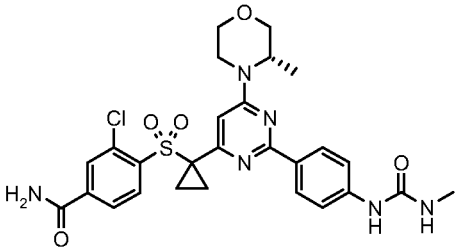
were dissolved in DMF (25 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a yellow solid which was partitioned between aqueous sodium thiosulphate solution (50 mL) and DCM (75 mL). The layers were separated, the aquoes layer further extracted with DCM (75 mL), the combined organics purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a white foam (1.7 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90 (3H, t), 1.50 (9H, s), 1.73 - 1.64 (1H, m), 1.85 - 1.78 (1H, m), 3.24 - 3.18 (4H, m), 3.48 (1H, ddd), 3.57 (1H, dd), 3.89 (1H, d), 3.95 (1H, dd), 4.30 (2H, s), 4.48 (2H, s), 6.80 (1H, s), 7.57 (2H, d), 8.23 (2H, d), 9.55 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 477; HPLC tR = 2.67 min.

The preparation of *tert*-butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(iodomethyl)pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 85: 3-Chloro-4-[1-[2-[4-(methylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide

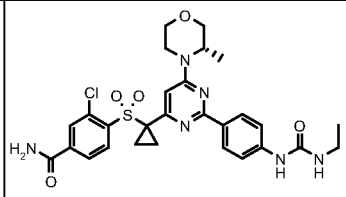
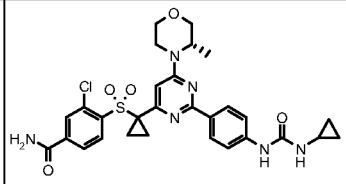
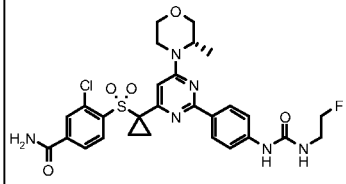
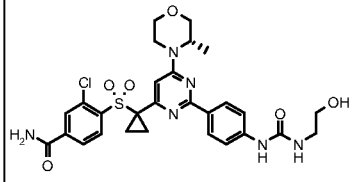
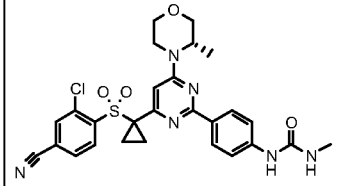


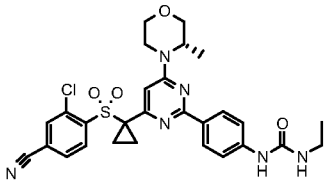
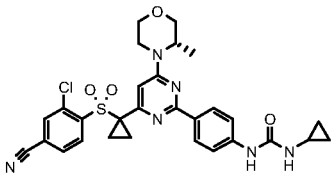
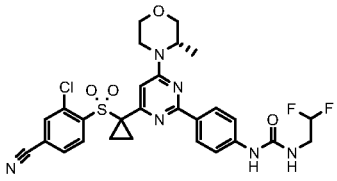
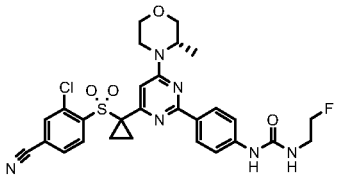
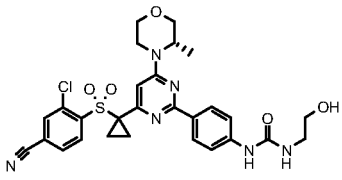
Methylamine (0.347 mL, 0.69 mmol) was added to phenyl *N*-[4-[4-[1-(4-carbamoyl-2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.23 mmol) and triethylamine (0.096 mL, 0.69 mmol) in DMF (0.714 mL) and resulting solution was stirred at 50°C for 2 hours. The crude mixture was purified by prep HPLC to give the desired material.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.72 - 1.76 (2H, m), 1.99 - 2.02 (2H, m), 2.65 (3H, d), 3.09 - 3.17 (1H, m), 3.44 (1H, dt), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, d), 4.09 (1H, d), 4.41 (1H, s), 6.03 - 6.07 (1H, m), 6.61 (1H, s), 7.35 (2H, d), 7.67 (1H, s), 7.74 (2H, d), 7.88 (1H, dd), 7.99 (1H, d), 8.12 (1H, d), 8.20 (1H, s), 8.68 (1H, s)

LCMS Spectrum: m/z (ES+) (M+H)+ = 586; HPLC tR= 1.86 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(4-carbamoyl-2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
85a		3-chloro-4-[1-[2-[4-(ethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide	598 $(M-H)^-$	1.98
85b		3-chloro-4-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide	610 $(M-H)^-$	2.00
85c		3-chloro-4-[1-[2-[4-(2-fluoroethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide	616 $(M-H)^-$	1.98
85d		3-chloro-4-[1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide	615	1.76
85e		1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	568	2.25

Example	Structure	NAME	LCMS MH+	Retention time (min)
85f		3-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	582	2.39
85g		1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	592 (M-H)	2.40
85h		1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	618	2.51
85i		1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	598 $(M-H)^-$	2.39
85j		1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	598	2.06

Example 85a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.15 (3H, d), 1.72 - 1.76 (2H, m), 1.99 - 2.02 (2H, m), 3.09 - 3.18 (3H, m), 3.44 (1H, dt), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, d), 4.09 (1H, d), 4.41 (1H, s), 6.13 (1H, t), 6.61 (1H, s), 7.34 (2H, d), 7.67 (1H, s), 7.74 (2H, d), 7.88 (1H, dd), 7.99 (1H, d), 8.12 (1H, d), 8.21 (1H, s), 8.60 (1H, s)

Example 85b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.15 (3H, d), 1.72 - 1.76 (2H, m), 1.99 - 2.02 (2H, m), 2.54 - 2.55 (1H, m), 3.13 (1H, dt), 3.44 (1H, dt), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.41 (1H, s), 6.40 (1H, d), 6.62 (1H, s), 7.35 (2H, d), 7.67 (1H, s), 7.74 (2H, d), 7.88 (1H, dd), 7.99 (1H, d), 8.12 (1H, d), 8.21 (1H, s), 8.48 (1H, s)

Example 85c: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.29 (3H, d), 1.54 - 1.56 (2H, m), 2.15 - 2.19 (2H, m), 3.27 (1H, dt), 3.51 - 3.62 (2H, m), 3.72 (1H, dd), 3.81 (1H, d), 4.02 (1H, dd), 4.08 (1H, d), 4.40 (1H, s), 4.46 (1H, t), 4.58 (1H, t), 5.63 (1H, t), 6.58 (1H, s), 7.17 (1H, s), 7.17 (1H, s), 7.24 (2H, d), 7.45 - 7.56 (2H, m), 7.64 - 7.69 (1H, m), 7.84 - 7.88 (2H, m), 7.90 (2H, d)

Example 85d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.72 - 1.76 (2H, m), 1.99 - 2.02 (2H, m), 3.09 - 3.12 (1H, m), 3.15 - 3.19 (2H, m), 3.43 - 3.48 (3H, m), 3.59 (1H, dd), 3.73 (1H, d), 3.93 (1H, dd), 4.09 (1H, d), 4.41 (1H, s), 4.72 (1H, t), 6.24 (1H, t), 6.61 (1H, s), 7.33 (2H, d), 7.66 (1H, s), 7.74 (2H, d), 7.88 (1H, dd), 7.99 (1H, d), 8.12 (1H, d), 8.21 (1H, s), 8.74 (1H, s)

Example 85e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.72 - 1.78 (2H, m), 2.00 - 2.03 (2H, m), 2.66 (3H, d), 3.10 - 3.15 (1H, m), 3.45 (1H, dt), 3.60 (1H, dd), 3.74 (1H, d), 4.06 (1H, q), 4.14 (1H, d), 4.47 (1H, s), 6.04 - 6.09 (1H, m), 6.66 (1H, s), 7.38 (2H, d), 7.66 (2H, d), 7.90 (1H, d), 8.02 (1H, d), 8.34 (1H, d), 8.71 (1H, s)

Example 85f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.18 (3H, d), 1.73 - 1.77 (2H, m), 1.99 - 2.03 (2H, m), 3.09 - 3.16 (2H, m), 3.16 - 3.19 (1H, m), 3.45 (1H, dt), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.14 (1H, d), 4.47 (1H, s), 6.16 (1H, t), 6.66 (1H, s), 7.37 (2H, d), 7.66 (2H, d), 7.90 (1H, dd), 8.02 (1H, d), 8.35 (1H, d), 8.62 (1H, s)

Example 85g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.18 (3H, d), 1.73 - 1.77 (2H, m), 2.00 - 2.03 (2H, m), 2.53 - 2.59 (1H, m), 3.11 - 3.18 (1H, m), 3.45 (1H, dt), 3.58 - 3.62 (1H, m), 3.74 (1H, d), 3.95 (1H, dd), 4.14 (1H, d), 4.47 (1H, s), 6.42 (1H, d), 6.66 (1H, s), 7.38 (2H, d), 7.66 (2H, d), 7.90 (1H, dd), 8.02 (1H, d), 8.35 (1H, d), 8.50 (1H, s)

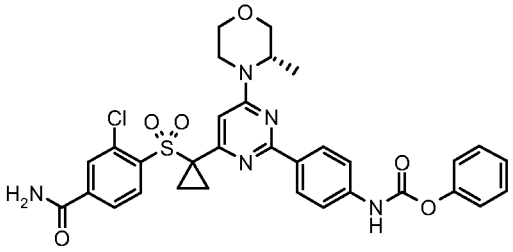
Example 85h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.73 - 1.77 (2H, m), 2.00 - 2.03 (2H, m), 3.15 (1H, dt), 3.42 - 3.51 (1H, m), 3.54 - 3.62 (3H, m), 3.74 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.47 (1H, s), 6.07 (1H, app t), 6.53 (1H, t), 6.67 (1H, s), 7.39 (2H, d), 7.68 (2H, d), 7.90 (1H, dd), 8.02 (1H, d), 8.35 (1H, d), 8.89 (1H, s)

Example 85i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.73 - 1.77 (2H, m), 2.00 - 2.03 (2H, m), 3.15 (1H, dt), 3.39 (1H, q), 3.42 - 3.48 (2H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.42 (1H, t), 4.48 (1H, s), 4.53 (1H, t), 6.44 (1H, t), 6.66 (1H, s), 7.38 (2H, d), 7.67 (2H, d), 7.90 (1H, dd), 8.02 (1H, d), 8.35 (1H, d), 8.77 (1H, s)

Example 85j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.73 - 1.77 (2H, m), 2.00 - 2.03 (2H, m), 3.14 - 3.20 (3H, m), 3.43 - 3.48 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.14 (1H, d), 4.48 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.66 (1H, s), 7.37 (2H, d), 7.66 (2H, d), 7.90 (1H, dd), 8.02 (1H, d), 8.35 (1H, d), 8.77 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-(4-carbamoyl-2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(4-carbamoyl-2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

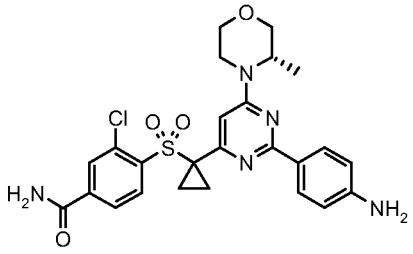


Sodium bicarbonate (0.263 g, 3.12 mmol) was added to 4-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-3-chlorobenzamide (1.1 g, 2.08 mmol), in 1,4-dioxane (10.15 mL) and to the resulting suspension was added phenyl chloroformate (0.262 mL, 2.08 mmol) dropwise over 2 minutes. The reaction was stirred at RT for 2 hours then evaporated to dryness and the residue redissolved in DCM (20 mL), and washed with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford a solid which was triturated with diethyl ether to give the desired material as a beige solid (0.9 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.73 - 1.77 (2H, m), 1.99 - 2.03 (2H, m), 3.12 - 3.17 (1H, m), 3.40 - 3.47 (1H, m), 3.57 - 3.61 (1H, m), 3.73 (1H, d), 3.91 - 3.96 (1H, m), 4.06 - 4.10 (1H, m), 4.44 (1H, s), 6.67 (1H, s), 7.24 - 7.30 (2H, m), 7.45 (2H, t), 7.50 (2H, d), 7.85 (2H, d), 7.88 - 7.90 (1H, m), 8.00 (1H, d), 8.13 (1H, d), 8.22 (1H, s), 10.40 (1H, s)

LCMS Spectrum: m/z (ES+) (M+H)+ = 648; HPLC tR= 2.62 min.

4-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-3-chlorobenzamide

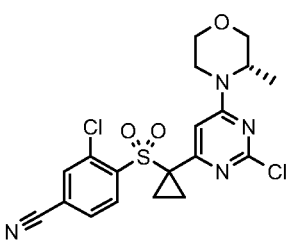


Bis(triphenylphosphine)palladium(II) chloride (0.271 g, 0.39 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.199 g, 10.04 mmol) and 3-chloro-4-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzonitrile (3.5 g, 7.72 mmol) and 2M aqueous solution of sodium carbonate (11.58 mL, 23.16 mmol) in a solvent mixture of DME (20 mL), ethanol (10 mL) and water (10 mL) and the resulting mixture stirred at 95°C for 16 hours. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (2 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give the desired material as a brown solid (1.1 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.71 - 1.73 (2H, m), 1.97 - 2.01 (2H, m), 3.06 - 3.13 (1H, m), 3.37 - 3.45 (1H, m), 3.58 (1H, dd), 3.72 (1H, d), 3.92 - 3.94 (1H, m), 4.04 - 4.08 (1H, m), 4.37 (1H, s), 5.48 (2H, s), 6.50 (1H, s), 7.58 (2H, d), 7.89 (1H, dd), 8.00 (2H, d), 8.11 (1H, d), 8.21 (1H, s)

LCMS Spectrum: m/z (ES+) (M+H)+ = 528; HPLC tR= 1.99 min.

3-Chloro-4-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzonitrile

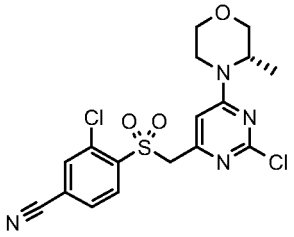


1,2-Dibromoethane (1.654 ml, 19.19 mmol) was added to 3-chloro-4-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]benzonitrile (4.1 g, 9.60 mmol), sodium hydroxide (50% w/w) (9.60 mL, 95.95 mmol) and tetrabutylammonium bromide (0.619 g, 1.92 mmol) in DCM and the resulting solution stirred at 40°C for 5 hours. The reaction mixture was washed sequentially with water (200 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 50% ethyl acetate in DCM, to give the desired material as a cream solid (3.50 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.68 - 1.72 (2H, m), 1.95 - 1.98 (2H, m), 3.11 - 3.17 (1H, m), 3.29 - 3.30 (1H, m), 3.39 (1H, dt), 3.54 (1H, dd), 3.69 (1H, d), 3.91 (1H, dd), 4.30 (1H, s), 6.76 (1H, s), 8.03 (2H, s), 8.33 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 453; HPLC tR = 2.41 min.

3-Chloro-4-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]benzonitrile

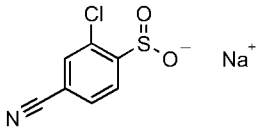


Sodium 2-chloro-4-cyanobenzenesulfinate (4.43 g, 19.80 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7 g, 19.80 mmol) in acetonitrile (99 mL) and the resulting suspension stirred at 80°C for 6 hours. The reaction mixture was evaporated to dryness, redissolved in DCM (200 mL) and washed with water (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a cream solid (6.20 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 3.15 - 3.21 (1H, m), 3.43 (1H, dt), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (2H, m), 4.24 (1H, s), 4.86 (2H, s), 6.87 (1H, s), 7.96 (1H, d), 8.06 (1H, dd), 8.43 (1H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 427; HPLC tR = 2.28 min.

Sodium 2-chloro-4-cyanobenzenesulfinate



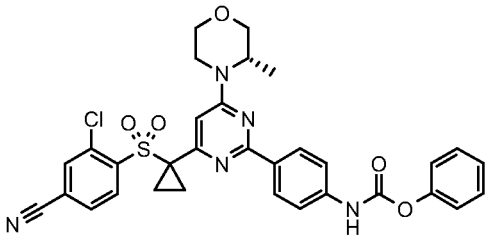
A solution of sodium sulfite (6.02 g, 47.74 mmol) in water (100 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (8.02 g, 95.48 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 10 minutes. 2-Chloro-4-cyanobenzene-1-sulfonyl chloride (11.27 g, 47.74 mmol) was added dropwise to the solution and was stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in ethanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (10.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.80 - 7.77 (2H, m), 7.84 (1H, d)

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



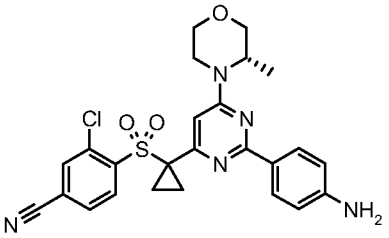
Sodium bicarbonate (1.400 g, 16.67 mmol) was added to 4-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-3-chlorobenzonitrile (1.7 g, 3.33 mmol), in 1,4-dioxane (16.25 mL) and to the resulting suspension was added phenyl chloroformate (0.42 mL, 3.33 mmol) dropwise over 2 minutes. The reaction was stirred at RT for 2 hours then evaporated to dryness, the residue redissolved in DCM (20 mL), and washed

with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford a solid which was triturated with diethyl ether to give the desired material as a cream solid (1.4 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.76 - 1.80 (2H, m), 2.01 - 2.04 (2H, m), 3.14 - 3.19 (1H, m), 3.43 - 3.48 (1H, m), 3.59 - 3.62 (1H, m), 3.74 (1H, d), 3.94 - 3.97 (1H, m), 4.16 (1H, d), 4.49 (1H, s), 6.71 (1H, s), 7.24 - 7.30 (3H, m), 7.45 (2H, t), 7.53 (2H, d), 7.77 (2H, d), 7.90 - 7.92 (1H, m), 8.02 (1H, d), 8.35 (1H, d), 10.44 (1H, s)

LCMS Spectrum: m/z (ES+) (M+H)+ = 630; HPLC tR= 3.02 min.

4-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-3-chlorobenzonitrile

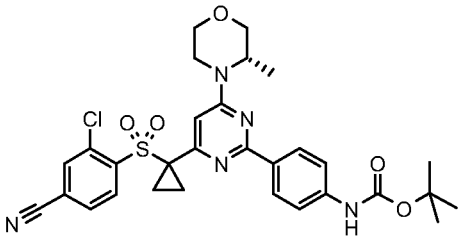


tert-Butyl *N*-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3.4 g, 5.57 mmol) was dissolved in methanol (17.86 mL) and to this was added 6 N hydrogen chloride in propan-2-ol (10 mL) and the reaction stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material as a white solid (3.50 g). The material was used without further purification.

MR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.76 - 1.79 (2H, m), 2.01 - 2.04 (2H, m), 3.18 - 3.24 (1H, m), 3.42 - 3.48 (1H, m), 3.60 (1H, dd), 3.74 - 3.77 (1H, m), 3.94 - 3.98 (1H, m), 4.20 (1H, s), 4.51 (1H, s), 6.76 (1H, s), 7.11 - 7.14 (2H, m), 7.86 (2H, d), 7.95 - 7.97 (2H, m), 8.07 (1H, d), 8.37 (1H, d)

LCMS Spectrum: m/z (ES+) (M+H)+ = 510; HPLC tR= 2.49 min.

tert-Butyl *N*-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

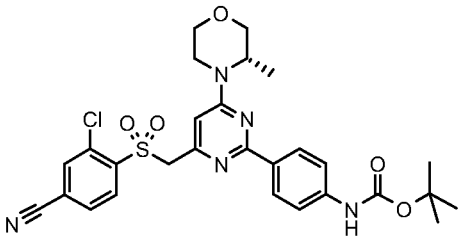


Sodium hydride (1.282 g, 26.71 mmol) was added rapidly to *tert*-butyl *N*-[4-[4-[(2-chloro-4-cyanophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3.9 g, 6.68 mmol) in DMF (70 mL) and the mixture stirred at RT for 10 minutes before the slow addition 1,2-dibromoethane (2.302 mL, 26.71 mmol) in DMF (70 mL) at RT. The resulting suspension was stirred at RT for 90 minutes. A further portion of sodium hydride (1.0 eq) and 1,2 dibromoethane (1.0 eq) were rapidly added and the reaction was stirred for a further 30 minutes. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (3.40 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.50 (9H, s), 1.73 - 1.78 (2H, m), 1.99 - 2.05 (2H, m), 3.12 - 3.18 (1H, m), 3.45 (1H, t), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.15 (1H, d), 4.48 (1H, s), 6.68 (1H, s), 7.45 (2H, d), 7.69 (2H, d), 7.90 (1H, d), 8.01 (1H, d), 8.35 (1H, s), 9.52 (1H, s)

LCMS Spectrum: m/z (ES+) (M+H)+ = 610; HPLC tR= 3.10 min.

tert-Butyl *N*-[4-[4-[(2-chloro-4-cyanophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



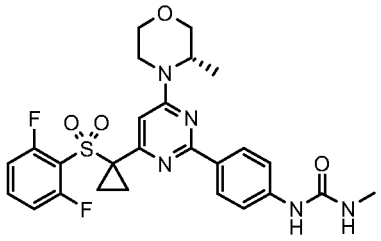
Sodium 2-chloro-4-cyanobenzenesulfinate (1.753 g, 7.84 mmol) and *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (4 g, 7.84 mmol) were dissolved in DMF (50 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a yellow solid which was partitioned between water (50 mL) and DCM (75 mL). The layers were separated, the aqueous layer extracted with DCM (75 mL) and the combined organics concentrated *in vacuo* to give a yellow solid. This was rapidly stirred with ether (100 mL), to afford the desired material as an off white solid (3.90 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.49 (9H, s), 3.19 (1H, dt), 3.48 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.13 (1H, d), 4.41 (1H, s), 4.97 (2H, s), 6.79 (1H, s), 7.43 (2H, d), 7.61 (2H, d), 7.86 (1H, d), 7.91 (1H, dd), 8.53 (1H, d), 9.54 (1H, s)

LCMS Spectrum: m/z (ES+) (M+H)+ = 583.94; HPLC tR= 3.07 min.

The preparation of *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 86: 1-[4-[4-[1-(2,6-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea



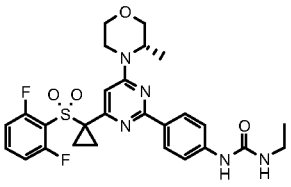
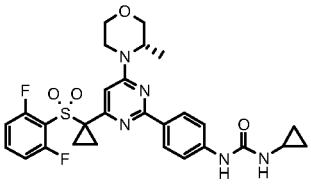
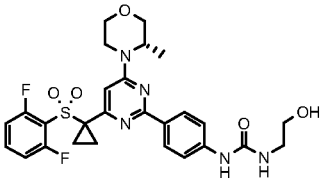
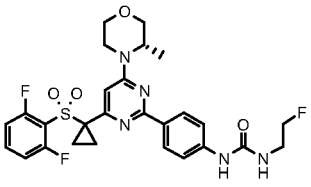
Phenyl *N*-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.15 g, 0.25 mmol), triethylamine (0.103 mL, 0.74 mmol) and methylamine (0.74 mmol) were dissolved in dioxane (10 mL) and stirred at RT overnight. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid.

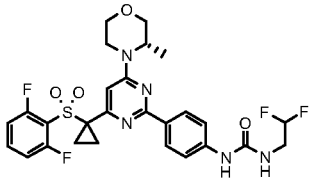
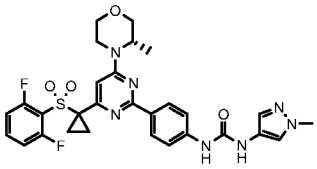
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.69 - 1.67 (2H, m), 1.94 - 1.91 (2H, m), 2.66 (3H, d), 3.17 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.75 (1H, d),

3.96 (1H, dd), 4.16 (1H, d), 4.49 (1H, s), 6.04 (1H, q), 6.74 (1H, s), 7.25 (2H, t), 7.35 (2H, d), 7.80 - 7.73 (3H, m), 8.69 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 544; HPLC tR = 1.82 min

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
86a		1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea	558	2.43
86b*		3-cyclopropyl-1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	570	2.44
86c*		1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	574	2.07
86d*		1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	576	2.42

Example	Structure	NAME	LCMS MH+	Retention time (min)
86e*		3-(2,2-difluoroethyl)-1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	594	2.55
86f*		1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	610	2.28

* No triethylamine added

Example 86a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.20 (3H, d), 1.71 - 1.65 (2H, m), 1.93 - 1.89 (2H, m), 3.20 - 3.09 (3H, m), 3.47 (1H, ddd), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (2H, ddd), 4.48 (1H, s), 6.14 (1H, t), 6.74 (1H, s), 7.25 (2H, t), 7.35 (2H, d), 7.80 - 7.73 (3H, m), 8.61 (1H, s);

Example 86b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.43 - 0.39 (2H, m), 0.67 - 0.62 (2H, m), 1.20 (3H, d), 1.71 - 1.65 (2H, m), 1.92 - 1.91 (2H, m), 2.57 - 2.54 (1H, m), 3.17 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 6.40 (1H, s), 6.75 (1H, s), 7.25 (2H, t), 7.36 (2H, d), 7.80 - 7.73 (3H, m), 8.49 (1H, s);

Example 86c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.71 - 1.65 (2H, m), 1.94 - 1.88 (2H, m), 3.21 - 3.14 (3H, m), 3.50 - 3.44 (3H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.74 (1H, s), 7.25 (2H, t), 7.34 (2H, d), 7.80 - 7.73 (3H, m), 8.75 (1H, s);

Example 86d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.69 - 1.67 (2H, m), 1.93 - 1.89 (2H, m), 3.17 (1H, ddd), 3.50 - 3.36 (3H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.16 (1H, d), 4.47 (2H, tt), 4.49 (1H, s), 6.41 (1H, t), 6.75 (1H, s), 7.25 (2H, t), 7.36 (2H, d), 7.80 - 7.74 (3H, m), 8.76 (1H, s);

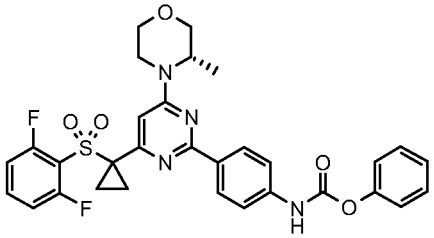
Example 86e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.69 - 1.67 (2H, m), 1.93 - 1.89 (2H, m), 3.17 (1H, ddd), 3.59 - 3.44 (3H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd),

4.16 (1H, d), 4.48 (1H, s), 6.07 (1H, tt), 6.51 (1H, t), 6.75 (1H, s), 7.25 (2H, t), 7.37 (2H, d), 7.80 - 7.72 (3H, m), 8.87 (1H, s);

Example 86f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.70 - 1.68 (2H, m), 1.94 - 1.89 (2H, m), 3.18 (1H, ddd), 3.47 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.79 (3H, s), 3.97 (1H, dd), 4.16 (1H, d), 4.49 (1H, s), 6.76 (1H, s), 7.26 (2H, t), 7.41 - 7.38 (3H, m), 7.80 - 7.73 (4H, m), 8.36 (1H, s), 8.79 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

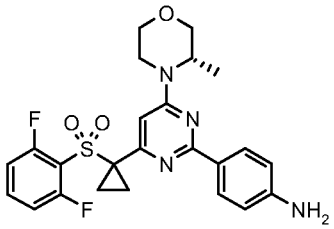


4-[4-[1-(2,6-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (as the hydrochloride salt) (1.67 g, 3.19 mmol) and sodium bicarbonate (2.68 g, 31.93 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.521 mL, 4.15 mmol) was added slowly and the reaction stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.4 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.72 - 1.66 (2H, m), 1.93 - 1.92 (2H, m), 3.18 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.76 (1H, d), 3.96 (1H, dd), 4.18 (1H, d), 4.50 (1H, s), 6.79 (1H, s), 7.30 - 7.23 (5H, m), 7.45 (2H, t), 7.49 (2H, d), 7.79 - 7.72 (1H, m), 7.84 (2H, d), 10.38 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 607; HPLC tR = 3.02 min.

4-[4-[1-(2,6-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

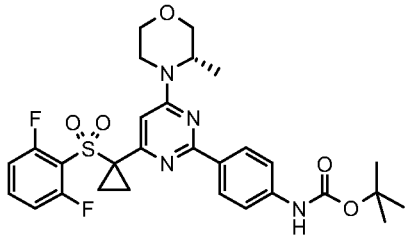


tert-Butyl *N*-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.15 g, 3.66 mmol) was added to 6.0 N hydrogen chloride in propan-2-ol (30 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a white solid (1.67 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.04 (3H, d), 1.76 - 1.72 (2H, m), 1.98 - 1.90 (2H, m), 3.24 (1H, ddd), 3.46 (1H, ddd), 3.60 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.25 (1H, s), 4.53 (1H, s), 6.85 (1H, s), 7.15 - 7.02 (2H, m), 7.29 (2H, t), 7.84 - 7.77 (1H, m), 7.91 (2H, d); NH2 not visible)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 487; HPLC tR = 2.45 min.

tert-Butyl *N*-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



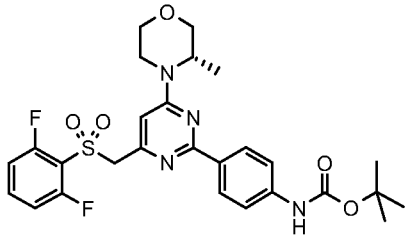
Sodium hydride (1.027 g, 21.41 mmol) was added rapidly to *tert*-butyl *N*-[4-[4-[(2,6-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3.0 g, 5.35 mmol) in DMF (70 mL) and stirred at RT for 10 minutes before the slow addition 1,2-dibromoethane (1.845 mL, 21.41 mmol) in DMF (70 mL). The resulting suspension was stirred at RT for 1.5 hours. A further portion of sodium hydride (2.0 eq) and 1,2 dibromoethane (2.0 eq) were rapidly added and the reaction was stirred for a further 30 minutes. The reaction mixture was quenched with water (50 mL), extracted with

ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to afford a yellow foam. This was dissolved in 40% ethyl acetate in isohexane and upon stirring the desired material precipitated as a white solid (2.15 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.49 (9H, s), 1.71 - 1.65 (2H, m), 1.93 - 1.90 (2H, m), 3.17 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 6.76 (1H, s), 7.25 (2H, t), 7.42 (2H, d), 7.80 - 7.72 (3H, m), 9.49 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 587; HPLC tR = 3.12 min.

tert-Butyl *N*-[4-[4-[(2,6-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



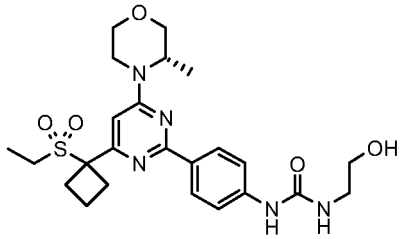
Sodium 2,6-difluorobenzenesulfonate (1.270 g, 5.88 mmol) and *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3 g, 5.88 mmol) were dissolved in DMF (50 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a yellow solid which was partitioned between water (50 mL) and DCM (75 mL). The layers were separated, the aqueous layer extracted with DCM (75 mL) and the combined organics concentrated *in vacuo* to give a yellow solid. The solid was rapidly stirred with ether (100 mL), to afford a solid which was collected by filtration and dried under vacuum to give the desired material as an off white solid (3.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.49 (9H, s), 3.20 (1H, ddd), 3.49 (1H, ddd), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.14 (1H, d), 4.42 (1H, s), 4.78 (2H, s), 6.81 (1H, s), 7.32 (2H, t), 7.42 (2H, d), 7.73 (2H, d), 7.85 - 7.78 (1H, m), 9.50 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 561; HPLC tR = 2.84 min.

The preparation of *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 87: 1-[4-[4-(1-Ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea

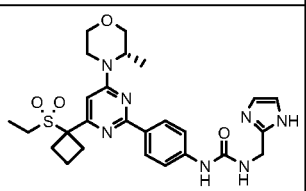


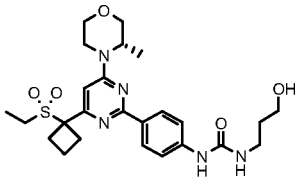
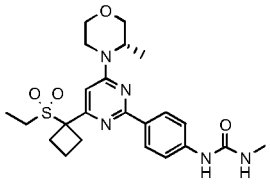
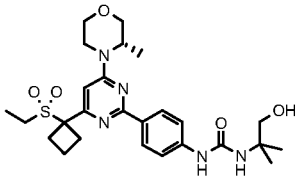
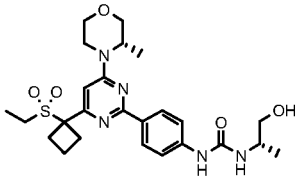
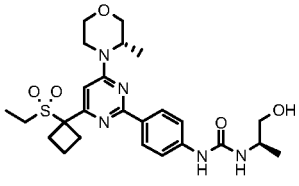
Ethanolamine (0.023 mL, 0.37 mmol) was added in one portion to phenyl *N*-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (101 mg, 0.19 mmol) and triethylamine (0.078 mL, 0.56 mmol) in NMP (2 mL) at RT and stirred for a period of 16 hours. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to afford desired material as a cream solid (71 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.23 (d, 3H), 1.86 - 1.97 (m, 1H), 2.01 - 2.11 (m, 1H), 2.77 - 2.87 (m, 2H), 2.90 - 2.99 (m, 4H), 3.16 - 3.25 (m, 2H), 3.46 (q, 1H), 3.52 (dd, 3H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.20 - 4.28 (m, 1H), 4.52 - 4.61 (m, 1H), 4.77 (t, 1H), 6.28 (t, 1H), 6.72 (s, 1H), 7.50 (d, 2H), 8.22 (d, 2H), 8.84 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 504; HPLC tR = 1.79 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
87a		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	540	1.87

Example	Structure	NAME	LCMS MH+	Retention time (min)
87b		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	518	1.83
87c		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	474	1.95
87d		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	532	2.08
87e		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea	518	1.88
87f		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea	518	1.89

Example 87a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.23 (d, 3H), 1.87 - 1.97 (m, 1H), 2.02 - 2.10 (m, 1H), 2.77 - 2.87 (m, 2H), 2.90 - 3.01 (m, 4H), 3.17 - 3.25 (m, 1H), 3.50 (td, 1H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.21 - 4.29 (m, 1H), 4.33 (d, 2H), 4.52 - 4.61 (m, 1H), 6.65 (t, 1H), 6.73 (s, 1H), 6.82 - 6.86 (m, 1H), 7.02 - 7.07 (m, 1H), 7.52 (d, 2H), 8.24 (d, 2H), 8.97 (s, 1H), 11.87 (s, 1H)

Example 87b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.23 (d, 3H), 1.60 (quintet, 2H), 1.86 - 1.97 (m, 1H), 2.01 - 2.11 (m, 1H), 2.77 - 2.87 (m, 2H), 2.90 - 2.99 (m, 4H), 3.14 - 3.25 (m, 3H), 3.47 (q, 2H), 3.49 - 3.54 (m, 1H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H),

4.20 - 4.30 (m, 1H), 4.51 - 4.61 (m, 1H), 4.52 (t, 1H), 6.23 (t, 1H), 6.72 (s, 1H), 7.50 (d, 2H), 8.22 (d, 2H), 8.75 (s, 1H)

Example 87c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.23 (d, 3H), 1.85 - 1.97 (m, 1H), 2.00 - 2.10 (m, 1H), 2.66 (d, 3H), 2.77 - 2.87 (m, 2H), 2.90 - 3.00 (m, 4H), 3.21 (td, 1H), 3.50 (td, 1H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.20 - 4.29 (m, 1H), 4.52 - 4.60 (m, 1H), 6.09 (q, 1H), 6.72 (s, 1H), 7.51 (d, 2H), 8.22 (d, 2H), 8.79 (s, 1H)

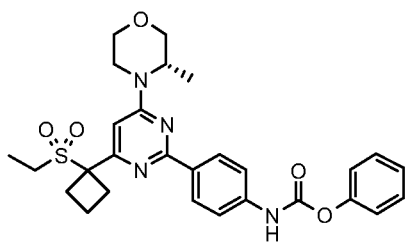
Example 87d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.23 (d, 3H), 1.24 (s, 6H), 1.86 - 1.97 (m, 1H), 2.01 - 2.11 (m, 1H), 2.76 - 2.87 (m, 2H), 2.90 - 3.01 (m, 4H), 3.22 (dd, 1H), 3.39 (d, 2H), 3.50 (td, 1H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.19 - 4.30 (m, 1H), 4.51 - 4.61 (m, 1H), 5.00 (t, 1H), 6.02 (s, 1H), 6.72 (s, 1H), 7.46 (d, 2H), 8.21 (d, 2H), 8.77 (s, 1H)

Example 87e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.09 (d, 3H), 1.15 (t, 3H), 1.23 (d, 3H), 1.86 - 1.97 (m, 1H), 2.01 - 2.11 (m, 1H), 2.77 - 2.87 (m, 2H), 2.90 - 3.00 (m, 4H), 3.21 (td, 1H), 3.32 - 3.42 (m, 2H), 3.50 (td, 1H), 3.65 (dd, 1H), 3.68 - 3.74 (m, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.20 - 4.29 (m, 1H), 4.52 - 4.61 (m, 1H), 4.83 (t, 1H), 6.12 (d, 1H), 6.72 (s, 1H), 7.49 (d, 2H), 8.22 (d, 2H), 8.75 (s, 1H)

Example 87f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.08 (d, 3H), 1.15 (t, 3H), 1.23 (d, 3H), 1.86 - 1.97 (m, 1H), 2.01 - 2.11 (m, 1H), 2.77 - 2.87 (m, 2H), 2.90 - 3.00 (m, 4H), 3.21 (td, 1H), 3.32 - 3.42 (m, 2H), 3.50 (td, 1H), 3.65 (dd, 1H), 3.68 - 3.74 (m, 1H), 3.76 - 3.79 (m, 1H), 3.98 (dd, 1H), 4.20 - 4.29 (m, 1H), 4.52 - 4.61 (m, 1H), 4.83 (t, 1H), 6.12 (d, 1H), 6.72 (s, 1H), 7.48 (d, 2H), 8.22 (d, 2H), 8.75 (s, 1H)

The preparation of phenyl *N*-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

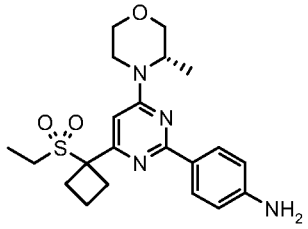


Phenyl chloroformate (0.211 mL, 1.68 mmol) was added dropwise to 4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (700 mg, 1.68 mmol) and sodium hydrogen carbonate (141 mg, 1.68 mmol) in dioxane (20 mL) and the resulting suspension stirred at RT for 3 hours. The reaction mixture was evaporated and DCM (50 mL) added and washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford desired material as a yellow oil which solidified on standing. (930 mg)

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.16 (t, 3H), 1.25 (d, 3H), 1.87 - 1.98 (m, 1H), 2.02 - 2.12 (m, 1H), 2.78 - 2.88 (m, 2H), 2.92 - 3.00 (m, 4H), 3.23 (td, 1H), 3.48 - 3.55 (m, 1H), 3.66 (dd, 1H), 3.78 (d, 1H), 3.99 (dd, 1H), 4.21 - 4.32 (m, 1H), 4.53 - 4.64 (m, 1H), 6.76 (s, 1H), 7.24 - 7.32 (m, 3H), 7.46 (dt, 2H), 7.64 (d, 2H), 8.32 (d, 2H), 10.44 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 537.15; HPLC tR = 2.95 min.

4-[4-(1-Ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



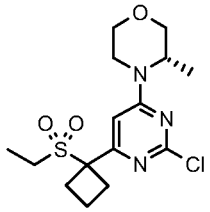
Bis(triphenylphosphine)palladium(II) chloride (0.137 g, 0.19 mmol) was added in one portion to 2-chloro-4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.4 g, 3.89 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.852 g, 3.89 mmol) and sodium carbonate (9.73 ml, 19.45 mmol) in a DMF / DME / water / ethanol solution at RT under nitrogen. The reaction mixture was thoroughly degassed and was stirred at 80°C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL), and washed sequentially with water (50 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 100% ethyl acetate in DCM, to afford desired material as a yellow dry film (1.536 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.22 (d, 3H), 1.85 - 1.96 (m, 1H), 2.02 - 2.11 (m, 1H), 2.75 - 2.86 (m, 2H), 2.89 - 2.99 (m, 4H), 3.19 (td, 1H), 3.50 (td,

1H), 3.64 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 2H), 4.16 - 4.25 (m, 1H), 5.56 (s, 2H), 6.59 - 6.63 (m, 3H), 8.06 (d, 2H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 417.25; HPLC tR = 2.03 min.

2-Chloro-4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



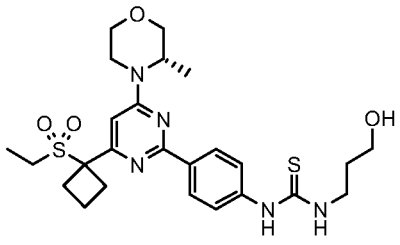
Sodium hydroxide (50% w/w solution) (27.4 g, 683.96 mmol) was added to 2-chloro-4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.977 g, 12.44 mmol), 1,3-dibromopropane (3.79 mL, 37.31 mmol) and tetrabutylammonium bromide (0.401 g, 1.24 mmol) in toluene (200 mL) and the resulting suspension stirred at 45°C for 3 hours. The organics were washed with water twice, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in DCM, to afford desired material as a colourless dry film (1.47 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 - 1.19 (m, 3H), 1.22 (d, 3H), 1.84 - 1.95 (m, 1H), 1.98 - 2.10 (m, 1H), 2.65 - 2.77 (m, 2H), 2.82 - 2.92 (m, 2H), 2.96 (q, 2H), 3.18 - 3.25 (m, 1H), 3.45 (td, 1H), 3.60 (dd, 1H), 3.73 (d, 1H), 3.94 (dd, 1H), 3.99 - 4.12 (m, 1H), 4.36 - 4.50 (m, 1H), 6.83 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 360.22; HPLC tR = 2.13 min.

The preparation of 2-chloro-4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 88: 1-[4-[4-(1-Ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)thiourea

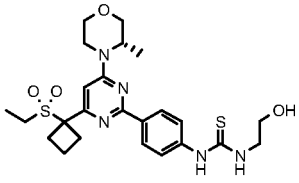
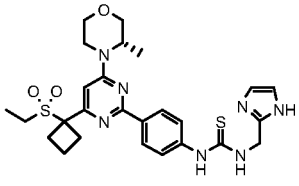


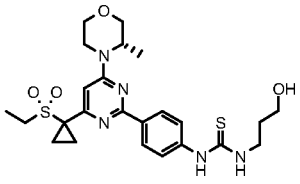
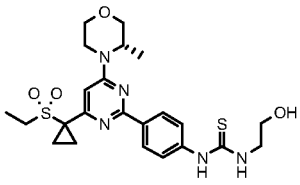
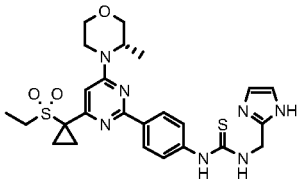
A solution of 1,1'-thiocarbonyldiimidazole (55.6 mg, 0.31 mmol) in DCM (2 mL) was added to a stirred solution of 4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (100 mg, 0.24 mmol) in THF (1 mL) and DCM (2 mL) at RT, over a period of 2 minutes under nitrogen. The resulting solution was stirred at RT for 2 hours. Triethylamine (0.033 mL, 0.24 mmol) and 3-amino-1-propanol (0.092 mL, 1.20 mmol) were added to the reaction mixture. The resulting solution was stirred at RT for 60 hours. The reaction mixture was evaporated to dryness and redissolved in acetonitrile (2 mL), filtered and purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to dryness to afford desired material as a beige solid. (100 mg)

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.24 (d, 3H), 1.72 (quintet, 2H), 1.86 - 1.97 (m, 1H), 2.03 - 2.12 (m, 1H), 2.77 - 2.88 (m, 2H), 2.91 - 3.00 (m, 4H), 3.18 - 3.26 (m, 1H), 3.45 - 3.59 (m, 5H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.19 - 4.29 (m, 1H), 4.49 - 4.63 (m, 2H), 6.75 (s, 1H), 7.57 (d, 2H), 7.86 - 7.94 (m, 1H), 8.28 (d, 2H), 9.65 - 9.74 (m, 1H)

LCMS Spectrum: m/z (ES+) (M+H)+= 534.8; HPLC tR= 2.16 min.

The compounds below were prepared in an analogous fashion from either 4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline or 4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
88a		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea	521	2.13
88b		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea	557	1.51

Example	Structure	NAME	LCMS MH+	Retention time (min)
88c		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)thiourea	5.21	2.33
88d		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea	507	2.30
88e		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea	543	2.36

Example 88a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.24 (d, 3H), 1.86 - 1.97 (m, 1H), 2.03 - 2.11 (m, 1H), 2.77 - 2.88 (m, 2H), 2.91 - 3.00 (m, 4H), 3.18 - 3.27 (m, 1H), 3.51 (td, 1H), 3.55 - 3.60 (m, 4H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.18 - 4.30 (m, 1H), 4.54 - 4.63 (m, 1H), 4.77 - 4.86 (m, 1H), 6.75 (s, 1H), 7.62 (d, 2H), 7.84 - 7.90 (m, 1H), 8.28 (d, 2H), 9.81 (s, 1H)

Example 88b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.24 (d, 3H), 1.86 - 1.97 (m, 1H), 2.02 - 2.12 (m, 1H), 2.78 - 2.88 (m, 2H), 2.91 - 3.00 (m, 4H), 3.18 - 3.26 (m, 1H), 3.51 (td, 1H), 3.66 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.19 - 4.30 (m, 1H), 4.53 - 4.63 (m, 1H), 4.71 (d, 2H), 6.75 (s, 1H), 6.99 (s, 2H), 7.69 (d, 2H), 8.18 - 8.25 (m, 1H), 8.30 (d, 2H), 9.98 - 10.09 (m, 1H), 11.84 - 12.09 (m, 1H)

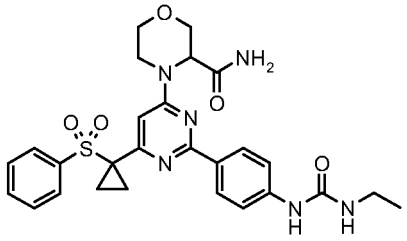
Example 88c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.24 (d, 3H), 1.33 (t, 3H), 1.54 - 1.59 (m, 2H), 1.61 - 1.66 (m, 2H), 1.72 (quintet, 2H), 3.22 (td, 1H), 3.40 - 3.59 (m, 7H), 3.64 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.16 - 4.28 (m, 1H), 4.52 - 4.64 (m, 2H), 6.83 (s, 1H), 7.58 (d, 2H), 7.90 - 7.97 (m, 1H), 8.25 (d, 2H), 9.74 (s, 1H)

Example 88d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.24 (d, 3H), 1.33 (t, 3H), 1.55 - 1.59 (m, 2H), 1.61 - 1.66 (m, 2H), 3.22 (td, 1H), 3.44 (q, 2H), 3.45 - 3.52 (m, 1H), 3.55 - 3.60 (m, 4H), 3.64 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.15 - 4.28 (m, 1H), 4.52 - 4.63 (m, 1H), 4.82 - 4.90 (m, 1H), 6.82 (s, 1H), 7.63 (d, 2H), 7.88 - 7.93 (m, 1H), 8.25 (d, 2H), 9.85 (s, 1H)

Example 88e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.24 (d, 3H), 1.33 (t, 3H), 1.54 - 1.59 (m, 2H), 1.61 - 1.66 (m, 2H), 3.22 (td, 1H), 3.45 (q, 2H), 3.45 - 3.52 (m, 1H), 3.64 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.15 - 4.28 (m, 1H), 4.53 - 4.63 (m, 1H), 4.69 - 4.74 (m, 2H), 6.83 (s, 1H), 6.86 - 7.15 (m, 2H), 7.70 (d, 2H), 8.22 - 8.29 (m, 1H), 8.27 (d, 2H), 10.05 (s, 1H), 11.95 (s, 1H)

The preparation of both 4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline and 4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline were described earlier.

Example 89: 4-[6-[1-(Benzenesulfonyl)cyclopropyl]-2-[4-(ethylcarbamoylamino)phenyl]pyrimidin-4-yl]morpholine-3-carboxamide



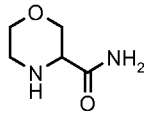
DIPEA (0.411 mL, 2.36 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.102 g, 0.20 mmol) and morpholine-3-carboxamide (as a mixture of the trifluoroacetic acid salts and the hydrochloride salt) (0.212 g, 1.63 mmol) in dioxane (5 mL) under nitrogen. The reaction was stirred at 70°C for several hours. The solvent was removed and then the gum was taken up in dioxane again. Ethyl isocyanate (0.032 mL, 0.41 mmol) was added and the reaction stirred at RT over the weekend. Further ethyl isocyanate (an excess) was added and the reaction stirred for several days. Methanol was added and the solvent was removed. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a yellow solid (0.027 g).

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.59-1.62 (1H, m), 1.65-1.68 (1H, m), 1.87-1.95 (2H, m), 3.09-3.17 (2H, m), 3.17-3.19 (1H, d), 3.41-3.54 (3H, m), 3.70-3.73 (1H, dd), 3.94-3.97 (1H, d), 4.30-4.33 (1H, d), 6.13-6.16 (1H, t), 6.72 (1H, s), 7.15 (1H, bs), 7.36-7.38 (2H, d), 7.52 (1H, bs), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.82 (4H, m), 8.62 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=551; HPLC tR=1.84min.

The preparation of [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate was described earlier

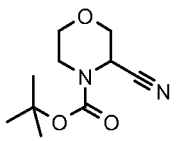
Morpholine-3-carboxamide



Hydrogen chloride (2.420 mL, 9.68 mmol) (4M solution in dioxane) was added to *tert*-butyl 3-cyanomorpholine-4-carboxylate (0.419 g, 1.98 mmol) in dioxane (15 mL) and the resulting solution stirred at RT over the weekend. The solvent was removed. The solid was taken up in dioxane and trifluoroacetic acid (1.2 eq) added. The reaction was allowed to stir at RT overnight. The solvent was removed, the crude material taken up in DCM and trifluoroacetic acid (0.734 mL, 9.88 mmol) added. The reaction was stirred overnight and then the solvent was removed to give the desired material (isolated as potentially a mixture of the trifluoroacetic acid salts and the hydrochloride salt). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.07-3.16 (1H, m), 3.58-3.70 (1H, m), 3.79-3.82 (1H, m), 3.87-3.93 (1H, m), 4.00-4.07 (1H, m), 4.11-4.22 (1H, m), 4.71-4.89 (1H, m), 7.76-8.16 (t) (TFA salt), 9.15-9.78 (bt) (HCl salt).

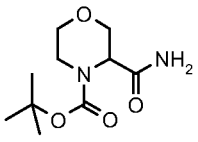
tert-Butyl 3-cyanomorpholine-4-carboxylate



tert-Butyl 3-carbamoylmorpholine-4-carboxylate (0.929 g, 4.03 mmol) was dissolved in dry DCM (10 mL) and triethylamine (1.181 mL, 8.47 mmol) was added. The solution was put under nitrogen and cooled to 0°C. Trifluoroacetic anhydride (0.627 mL, 4.44 mmol) was then added and the reaction was allowed to slowly warm up to RT, followed by stirring at RT for at least 3 hours. The solvent was removed and then ethyl acetate added. The organic layer was washed with brined, dried over $MgSO_4$, filtered and evaporated. he crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material as a light yellow crystalline solid (0.419 g).

NMR Spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (9H, s), 3.24 (1H, bt), 3.45-3.52 (1H, td), 3.60-3.64 (1H, dd), 3.80-3.83 (1H, d), 3.94-3.97 (1H, d), 4.04-4.07 (1H, d), 4.89 (1H, bs).

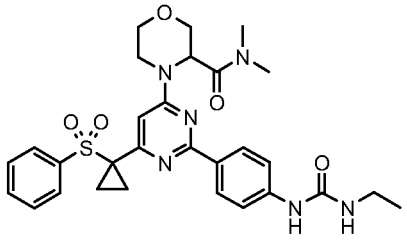
tert-butyl 3-carbamoylmorpholine-4-carboxylate



HATU (5.92 g, 15.57 mmol) was added to a solution of 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid (3 g, 12.97 mmol), DIPEA (3.40 mL, 19.46 mmol) and ammonium chloride (3.47 g, 64.87 mmol) in DMF (70 mL) and the resulting suspension stirred at RT for 12 hours under nitrogen. The reaction mixture was concentrated and diluted with ethyl acetate (150 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as an oil (4.0 g), which was used without further purification.

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.39 (9H, s), 3.15 (2H, m), 3.54 (2H, m), 3.63 (2H, m), 3.75 (1H, m), 4.17 (2H, m).

Example 90: 4-[6-[1-(Benzenesulfonyl)cyclopropyl]-2-[4-(ethylcarbamoylamino)phenyl]pyrimidin-4-yl]-*N*,*N*-dimethylmorpholine-3-carboxamide



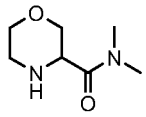
DIPEA (0.141 mL, 0.81 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.101 g, 0.20 mmol) and *N,N*-dimethylmorpholine-3-carboxamide (as the hydrochloride salt) (0.079 g, 0.41 mmol) in dioxane (5 mL) under nitrogen. The reaction was stirred at 70°C for several hours then allowed to cool and ethyl isocyanate (0.321 mL, 4.05 mmol) added. The reaction was stirred at RT overnight, additional ethyl isocyanate added and the reaction stirred at RT overnight. Methanol was added and the solvent was removed. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a cream solid (0.047 g).

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.58-1.62 (1H, m), 1.68-1.73 (1H, m), 1.86-1.97 (2H, m), 2.82 (3H, bs), 3.09-3.16 (2H, m), 3.19 (3H, bs), 3.53-3.60 (1H, m), 3.67-3.71 (1H, m), 3.79-3.84 (1H, dd), 4.00-4.02 (1H, d), 4.14-4.17 (1H, d), 5.44 (1H, bs), 6.15-6.18 (1H, t), 6.77 (1H, s), 7.37-7.39 (2H, d), 7.56-7.60 (2H, t), 7.70-7.74 (1H, t), 7.76-7.80 (4H, m), 8.61 (1H, s). (1 peak under water or solvent peak).

LCMS Spectrum: m/z (ES+)(M+H)+=579; HPLC tR=2.01min.

The preparation of [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate was described earlier

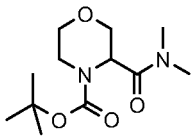
N,N-Dimethylmorpholine-3-carboxamide



Hydrogen chloride (3.57 mL, 14.28 mmol) (4M solution in dioxane) was added to *tert*-butyl 3-(dimethylcarbamoyl)morpholine-4-carboxylate (0.820 g, 3.17 mmol) in dioxane (25 mL) and the resulting solution stirred at RT overnight. The solvent was removed and the gum was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a solid which turned to a gum on standing (0.70 g).

NMR Spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (3H, s), 3.07 (3H, s), 3.13-3.16 (1H, dd), 3.20-3.23 (1H, dt), 3.42-3.48 (1H, m), 3.69-3.75 (1H, td), 3.92-3.96 (1H, dt), 4.15-4.19 (1H, dd), 4.57-4.61 (1H, dd), 9.47 (1H, bs).

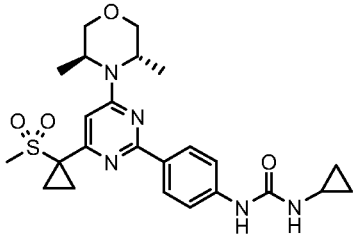
tert-Butyl 3-(dimethylcarbamoyl)morpholine-4-carboxylate



HATU (1.97 g, 5.19 mmol) was added to a solution of 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid (1 g, 4.32 mmol), DIPEA (1.133 ml, 6.49 mmol) and dimethylamine 2.0M in THF (10.81 mL, 21.62 mmol) in DMF and the resulting solution stirred at RT for 15 hours under nitrogen. The reaction mixture was concentrated and diluted with ethyl acetate (100 mL), and washed sequentially with water(25 mL), 5% aqueous citric acid solution (25 mL), and saturated brine (25 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product and dried under vacuum to the desired material as an oil (0.91 g), which was used without further purification.

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (9H, br s), 2.83 (3H, s), 2.98 (3H, s), 3.35 (1H, m), 3.48 (1H, m), 3.63 (1H, dd), 3.80 (1H, m), 3.90 - 4.04 (2H, m), 4.70 (1H, m).

Example 91: 3-Cyclopropyl-1-[4-[4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea

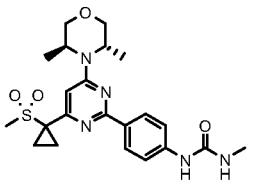
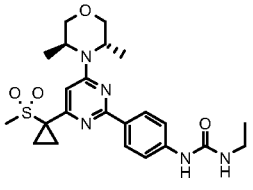
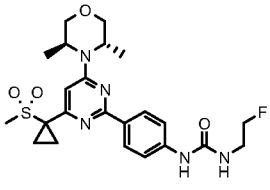
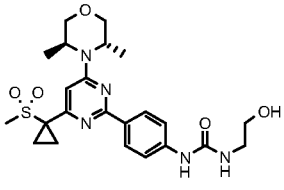


Cyclopropylamine (0.10 mmol) was added to phenyl *N*-[4-[4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (50 mg, 0.10 mmol) and triethylamine (0.027 mL, 0.19 mmol) in DMF (1 mL) at RT. The resulting solution was stirred at 50°C for 2 hours and the material purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (40mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.36 (6H, d), 1.53 - 1.61 (2H, m), 1.64 - 1.72 (2H, m), 2.54 - 2.59 (1H, m), 3.26 (3H, s), 3.72 (2H, dd), 4.16 (2H, dd), 4.25 - 4.31 (2H, m), 6.44 (1H, d), 6.72 (1H, s), 7.52 (2H, d), 8.21 (2H, d), 8.54 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=486; HPLC tR=2.13min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
91a		1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-methylurea	460	1.70
91b		1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-ethylurea	474	2.11
91c		1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	492	2.11
91d		1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	490	1.77

Example 91a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.36 (6H, d), 1.55 - 1.61 (2H, m), 1.64 - 1.70 (2H, m), 2.66 (3H, d), 3.26 (3H, s), 3.72 (2H, dd), 4.16 (2H, dd), 4.27 - 4.28 (2H, m), 6.07 - 6.08 (1H, m), 6.72 (1H, s), 7.51 (2H, d), 8.20 (2H, d), 8.74 (1H, s).

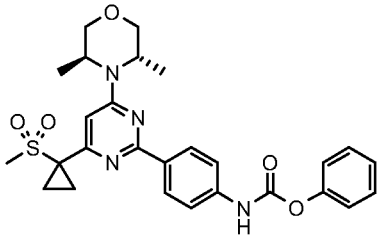
Example 91b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.36 (6H, d), 1.55 - 1.61 (2H, m), 1.64 - 1.73 (2H, m), 3.09 - 3.16 (2H, m), 3.26 (3H, s), 3.72 (2H, dd), 4.16 (2H, dd), 4.27 - 4.28 (2H, m), 6.17 (1H, t), 6.72 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.66 (1H, s).

Example 91c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.36 (6H, d), 1.55 - 1.59 (2H, m), 1.64 - 1.70 (2H, m), 3.26 (3H, s), 3.42 (2H, dq), 3.72 (2H, dd), 4.16 (2H, dd), 4.26 - 4.29 (2H, m), 4.42 (1H, t), 4.54 (1H, t), 6.44 (1H, t), 6.72 (1H, s), 7.51 (2H, d), 8.21 (2H, d), 8.81 (1H, s).

Example 91d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.36 (6H, d), 1.55 - 1.60 (2H, m), 1.65 - 1.72 (2H, m), 3.16 - 3.20 (2H, m), 3.26 (3H, s), 3.44 - 3.48 (2H, m), 3.72 (2H, dd), 4.16 (2H, dd), 4.24 - 4.31 (2H, m), 4.73 (1H, t), 6.26 (1H, t), 6.72 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.81 (1H, s).

The preparation of phenyl *N*-[4-[4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate

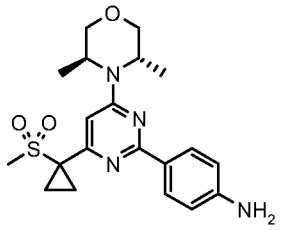


Sodium bicarbonate (104 mg, 1.24 mmol) was added to 4-[4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (250 mg, 0.62 mmol) in 1,4-dioxane (3 mL) and phenyl chloroformate (0.078 mL, 0.62 mmol) was added dropwise to the resulting suspension. The reaction stirred at RT for 2 hours then evaporated to dryness, redissolved in DCM (20 mL), and washed with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford a solid which was triturated with diethyl ether to give the desired material as a cream solid (250 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.37 (6H, d), 1.56 - 1.62 (2H, m), 1.65 - 1.71 (2H, m), 3.27 (3H, s), 3.73 (2H, dd), 4.17 (2H, dd), 4.29 - 4.31 (2H, m), 6.77 (1H, s), 7.24 - 7.30 (3H, m), 7.45 (2H, t), 7.65 (2H, d), 8.30 (2H, d), 10.45 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=523; HPLC tR=2.74min.

4-[4-[(3*S*,5*S*)-3,5-Dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline

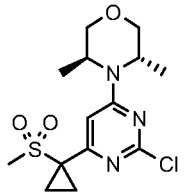


Bis(triphenylphosphine)palladium(II) chloride (35.5 mg, 0.05 mmol) was added to 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine (350 mg, 1.01 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (222 mg, 1.01 mmol) and 2M aqueous sodium carbonate solution (1.52 mL, 3.04 mmol), in ethanol (0.89 mL), DME (1.77 mL) and water (0.89 mL) and the reaction stirred at 90°C for 2 hours. The reaction mixture was diluted with ethyl acetate (20 mL), and washed sequentially with water (20 mL), and saturated brine(20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 2 to 10% methanol in DCM, to give the desired material as a beige solid (250 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.34 (6H, d), 1.50 - 1.58 (2H, m), 1.62 - 1.70 (2H, m), 3.25 (3H, s), 3.70 (2H, dd), 4.14 (2H, dd), 4.22 - 4.25 (2H, m), 5.56 (1H, s), 6.61 (2H, d), 8.04 (2H, d).

LCMS Spectrum: m/z (ES+)(M+H)+=403; HPLC tR=2.05min.

2-Chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine



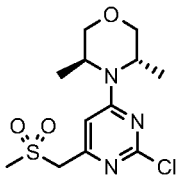
A solution of 50% w/v sodium hydroxide (6.12 mL, 154.44 mmol) was added portionwise to a stirred solution of 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (898 mg, 2.81 mmol), tetrabutylammonium bromide (91 mg, 0.28 mmol) and 1,2-dibromoethane (0.726 mL, 8.42 mmol) in toluene (50 mL) and the

resulting suspension stirred at 60°C for 6 hours. The reaction mixture was diluted with water (50 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a solid (350 mg).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.43 (3H, d), 1.44 (3H, d), 1.50 (2H, m), 1.82 (2H, m), 3.02 (3H, s), 3.78 (2H, dd), 4.16 (2H, m), 4.24 (2H, dd), 6.77 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=346; HPLC tR=1.83min.

2-Chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine

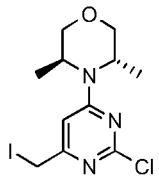


Sodium methanesulfinate (0.542 g, 5.31 mmol) was added portionwise to 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(iodomethyl)pyrimidine (1.86 g, 5.06 mmol) in acetonitrile (50 mL) and the resulting suspension stirred at 80°C for 6 hours. Further sodium methanesulfinate (0.5 equivalents) was added and the reaction was heated a further 8 hours. The solvent was removed and the solid was taken up in DMF. Further sodium methanesulfinate (1 equivalent) was added and the mixture allowed to stir until the reaction was complete. The solvent was removed and ethyl acetate added. The mixture was washed with 10% sodium thiosulfate, brine and water and the organics dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 25% ethyl acetate in DCM, to give the desired material as a yellow gum (0.898 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.44-1.45 (6H, d), 3.02 (3H, s), 3.77-3.80 (2H, dd), 4.14-4.16 (2H, m), 4.17-4.18 (2H, d), 4.23-4.27 (2H, dd), 6.46 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=320; HPLC tR=1.59 min.

2-Chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(iodomethyl)pyrimidine

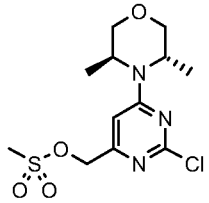


[2-Chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-4-yl]methyl methanesulfonate (5.21 g, 15.51 mmol) and lithium iodide (1.190 mL, 31.03 mmol) were added to dioxane (250 mL) and heated at 60°C for 1 hour and then at RT overnight. The mixture was evaporated to dryness and partitioned between saturated ammonium chloride solution (100 mL) and DCM (75 mL). The layers were separated and the aqueous layer further extracted with DCM (2 x 75 mL) then the combined organics washed sequentially with 10% sodium thiosulfate solution (100 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product as a brown oil (5.59 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.32 (6H, d), 3.69 (2H, dd), 4.08 (2H, m), 4.14 (2H, dd), 4.34 (2H, s), 6.84 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=368; HPLC tR=2.26min.

[2-Chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-4-yl]methyl methanesulfonate

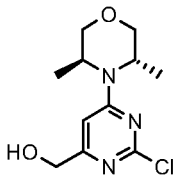


Methanesulfonyl chloride (1.802 mL, 23.28 mmol) was added dropwise to [2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-4-yl]methanol (4.00 g, 15.52 mmol) and DIPEA (4.03 mL, 23.28 mmol) in DCM (100 mL) at 0°C over a period of 2 minutes and the resulting solution allowed to gradually warm up to RT over a period of 2 hours. The reaction mixture was diluted with DCM (50 mL), and washed with water. The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as a yellow gum (5.56 g). This was used without further purification.

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.42-1.44 (6H, d), 3.14 (3H, s), 3.76-3.80 (2H, dd), 4.13-4.18 (2H, m), 4.22-4.26 (2H, dd), 5.11 (2H, d), 6.48 (1H, s).

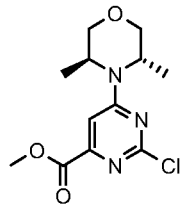
LCMS Spectrum: m/z (ES+)(M+H)+=336; HPLC tR=1.88min.

[2-Chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-4-yl]methanol



Lithium borohydride, 2M in THF (6.54 mL, 13.09 mmol) was added dropwise to methyl 2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine-4-carboxylate (4.40 g, 15.40 mmol) in THF (75 mL) at 0°C over a period of 30 minutes under nitrogen. The resulting solution was stirred at 0°C for 30 minutes then allowed to warm to RT. Water (250 mL) was added and the organics removed *in vacuo*. The aqueous residues were extracted with ethyl acetate then the combined organics were washed with brine. The organic layer was dried over $MgSO_4$ then evaporated to dryness to afford the desired material as a white solid (4.0 g).
NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.41-1.42 (6H, d), 2.69-2.71 (1H, t), 3.75-3.78 (2H, dd), 4.12-4.18 (2H, m), 4.21-4.25 (2H, dd), 4.59-4.60 (2H, d), 6.39 (1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=258; HPLC tR=1.38min.

Methyl 2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine-4-carboxylate

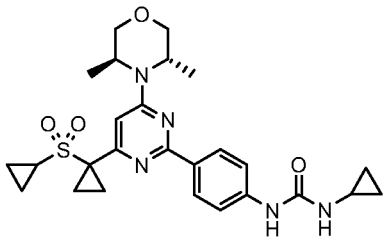


Methyl 2,4-dichloropyrimidine-6-carboxylate (4.45 g, 21.50 mmol) was dissolved in dry DCM (100mL) and DIPEA (9.67 mL, 55.89 mmol) was added. (3*S*,5*S*)-3,5-Dimethylmorpholine (as the hydrochloride salt) (3.42 g, 22.57 mmol)in DCM (20 mL) was added to this solution dropwise over several minutes and the reaction allowed to stir at RT for 5 days then at 50°C for several days. The crude reaction mixture was washed with water, dried over $MgSO_4$ and filtered. The crude product was purified by flash silica chromatography, elution gradient 0 to 25% ethyl acetate in DCM, to give the desired material as a cream solid (4.4 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.44-1.46 (6H, d), 3.78-3.81 (2H, dd), 3.98 (3H, s), 4.16-4.22 (2H, m), 4.24-4.28 (2H, dd), 7.10 (1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=286; HPLC tR=1.72min.

The preparation of (3*S*,5*S*)-3,5-dimethylmorpholine was described earlier.

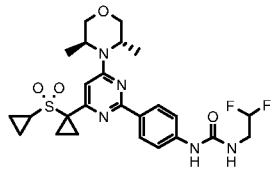
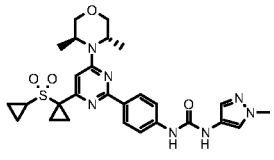
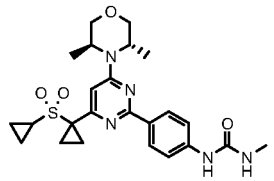
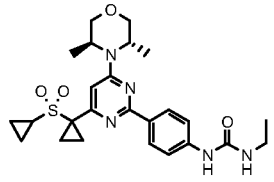
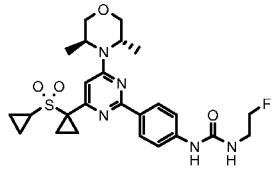
Example 92: 3-Cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

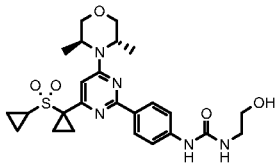


Cyclopropanamine (12.49 mg, 0.22 mmol) was added to phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.22 mmol) and triethylamine (0.091 mL, 0.66 mmol) in DMF (1 mL) at RT. The resulting solution was stirred at 50°C for 2 hours. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (82 mg).
NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 0.87 - 1.04 (4H, m), 1.36 (6H, d), 1.57 - 1.70 (4H, m), 2.54 - 2.58 (1H, m), 2.91 - 2.97 (1H, m), 3.71 (2H, dd), 4.16 (2H, dd), 4.25 - 4.27 (2H, m), 6.43 (1H, s), 6.81 (1H, s), 7.51 (2H, d), 8.22 (2H, d), 8.52 (1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=512; HPLC tR=2.25min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)

Example	Structure	NAME	LCMS MH+	Retention time (min)
92a		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	537	2.39
92b		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	552	1.83
92c		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	486	2.06
92d		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea	500	1.91
92e		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	518	1.94

Example	Structure	NAME	LCMS MH+	Retention time (min)
92f		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	516	1.88

Example 92a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87 - 1.06 (4H, m), 1.36 (6H, d), 1.55 - 1.70 (4H, m), 2.91 - 2.97 (1H, m), 3.50 - 3.60 (2H, m), 3.72 (2H, dd), 4.16 (2H, dd), 4.25 - 4.28 (2H, m), 6.07 (1H, t), 6.54 (1H, t), 6.82 (1H, s), 7.52 (2H, d), 8.24 (2H, d), 8.91 (1H, s).

Example 92b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 - 1.07 (4H, m), 1.36 (6H, d), 1.56 - 1.71 (4H, m), 2.91 - 2.98 (1H, m), 3.72 (2H, dd), 3.79 (3H, s), 4.16 (2H, dd), 4.26 - 4.29 (2H, m), 6.82 (1H, s), 7.39 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.25 (2H, d), 8.39 (1H, s), 8.83 (1H, s).

Example 92c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 - 1.04 (4H, m), 1.36 (6H, d), 1.57 - 1.68 (4H, m), 2.66 (3H, d), 2.91 - 2.97 (1H, m), 3.71 (2H, ddd), 4.16 (2H, dd), 4.25 - 4.27 (2H, m), 6.06 - 6.07 (1H, m), 7.50 (2H, d), 7.55 - 7.58 (1H, m), 8.21 (2H, d), 8.73 (1H, s).

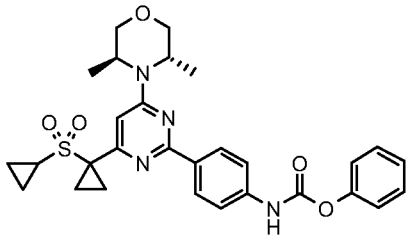
Example 92d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87 - 1.04 (4H, m), 1.07 (3H, t), 1.36 (6H, d), 1.55 - 1.70 (4H, m), 2.91 - 2.97 (1H, m), 3.09 - 3.16 (2H, m), 3.71 (2H, dd), 4.16 (2H, dd), 4.24 - 4.27 (2H, m), 6.16 (1H, t), 6.81 (1H, s), 7.49 (2H, d), 8.21 (2H, d), 8.65 (1H, s).

Example 92e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87 - 1.06 (4H, m), 1.36 (6H, d), 1.55 - 1.70 (4H, m), 2.91 - 2.97 (1H, m), 3.39 (1H, q), 3.46 (1H, q), 3.72 (2H, dd), 4.16 (2H, dd), 4.22 - 4.29 (2H, m), 4.42 (1H, t), 4.54 (1H, t), 6.44 (1H, t), 6.81 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.80 (1H, s).

Example 92f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87 - 1.04 (4H, m), 1.36 (6H, d), 1.55 - 1.69 (4H, m), 2.90 - 2.97 (1H, m), 3.16 - 3.20 (2H, m), 3.44 - 3.48 (2H, m), 3.71 (2H, dd), 4.16 (2H, dd), 4.24 - 4.29 (2H, m), 4.73 (1H, t), 6.26 (1H, t), 6.81 (1H, s), 7.49 (2H, d), 8.22 (2H, d), 8.79 (1H, s).

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

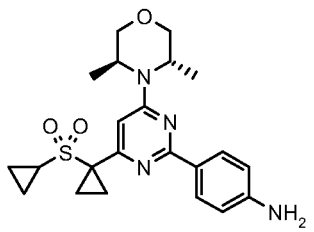
Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Sodium bicarbonate (286 mg, 3.41 mmol) was added to 4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]aniline (730 mg, 1.70 mmol), in 1,4-dioxane (8.3 mL) and phenyl chloroformate (0.214 mL, 1.70 mmol) added dropwise to the resulting suspension. The mixture was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (20 mL), and washed with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford a solid which was triturated with diethyl ether to give the desired material as a cream solid (800 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.88 - 1.05 (4H, m), 1.37 (6H, d), 1.59 - 1.70 (4H, m), 2.92 - 2.99 (1H, m), 3.73 (2H, dd), 4.17 (2H, dd), 4.28 - 4.30 (2H, m), 6.86 (1H, s), 7.24 - 7.30 (3H, m), 7.45 (2H, t), 7.64 (2H, d), 8.30 (2H, d), 10.45 (1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=549; HPLC tR=2.66min.

4-[4-(1-Cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]aniline



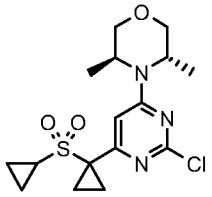
Bis(triphenylphosphine)palladium(II) chloride (60.4 mg, 0.09 mmol) was added to 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine

(640 mg, 1.72 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (490 mg, 2.24 mmol) and 2M sodium carbonate solution (2.6 mL, 5.16 mmol) in water (1.5 mL), ethanol (1.5 mL), and DME (3 mL) and the resulting solution was stirred at 95°C for 2 hours. The reaction mixture was diluted with ethyl acetate (20 mL), and washed sequentially with water (10 mL) and saturated brine(10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give the desired material as a beige solid (740 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.89 - 1.03 (4H, m), 1.34 (6H, d), 1.54 - 1.67 (4H, m), 2.89 - 2.96 (1H, m), 3.70 (2H, dd), 4.14 (2H, dd), 4.20 - 4.24 (2H, m), 6.61 (2H, d), 6.73 (1H, s), 8.05 (2H, d)

LCMS Spectrum: m/z (ES+)(M+H)+=429; HPLC tR=2.18min.

2-Chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine

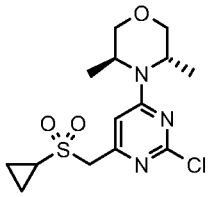


A solution of 50% w/v sodium hydroxide (7.06 mL, 176.52 mmol) was added portionwise to a stirred solution of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine (1.11 g, 3.21 mmol), tetrabutylammonium bromide (0.103 g, 0.32 mmol) and 1,2-dibromoethane (0.830 mL, 9.63 mmol) in toluene (50 mL) and the resulting suspension stirred at 60°C for 6 hours. The reaction mixture was diluted with water (50 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a solid (0.64 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.86 - 0.99 (2H, m), 1.01 (2H, m), 1.31 (3H, d), 1.33 (3H, d), 1.51 (2H, m), 1.63 (2H, m), 2.86 (1H, m), 3.70 (2H, dd), 4.13 (2H, m), 4.16 (2H, m), 6.90 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=372; HPLC tR=1.97min.

2-Chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine



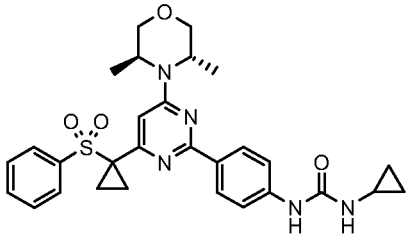
Sodium cyclopropanesulfinate (0.648 g, 5.06 mmol) was added portionwise to 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(iodomethyl)pyrimidine (1.86 g, 5.06 mmol) in acetonitrile (50 mL) and the resulting suspension stirred at 80°C for 6 hours. Further sodium cyclopropanesulfinate (259mg, 2.02mmol) was added in one portion and the suspension was stirred at 80°C for a further 2 hours. The reaction mixture was concentrated and diluted with DCM (200 mL), and washed sequentially with water (50 mL), 10% sodium thiosulfate solution (50 mL), and saturated brine(50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0to 20% ethyl acetate in DCM, to give the desired material as a yellow solid (1.11 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.97 (2H, m), 1.03 (2H, m), 1.32 (3H, d), 1.34 (3H, d), 2.79 (1H, m), 3.70 (2H, dd), 4.09 (2H, m), 4.15 (2H, dd), 4.49 (2H, d), 6.82 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=346; HPLC tR=1.77 min.

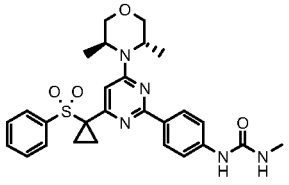
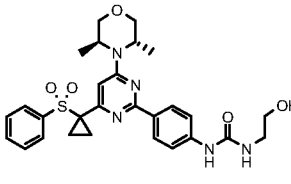
The preparation of 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(iodomethyl)pyrimidine was described earlier.

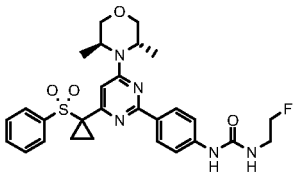
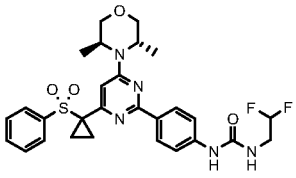
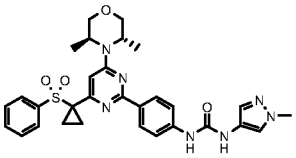
Example 93: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea



Cyclopropylamine (19.0 mg, 0.34 mmol) was added to phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) and triethylamine (52 mg, 0.51 mmol) in dioxane (10mL) at RT. The resulting solution was stirred at 50°C overnight. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (64 mg).
NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.43 - 0.39 (2H, m), 0.67 - 0.62 (2H, m), 1.28 (6H, d), 1.69 - 1.62 (2H, m), 1.93 - 1.89 (2H, m), 2.59 - 2.50 (m, 1H), 3.70 - 3.67 (2H, m), 4.18 - 4.10 (4H, m), 6.41 (1H, s), 6.60 (1H, s), 7.41 (2H, d), 7.59 (2H, t), 7.70 (1H, t), 7.79 (2H, d), 7.88 (2H, d), 8.49 (1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=548; HPLC tR=2.49min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
93a		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	522	2.32
93b		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	552	2.13

Example	Structure	NAME	LCMS MH+	Retention time (min)
93c		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	554	2.47
93d		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	572	2.60
93e		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	588	2.34

1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea (**Example 72**) can also be prepared in this fashion.

Example 93a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.28 (6H, d), 1.69 - 1.62 (2H, m), 1.93 - 1.89 (2H, m), 2.68 - 2.65 (3H, m), 3.70 - 3.67 (2H, m), 4.16 - 4.10 (4H, m), 6.05 (1H, q), 6.59 (1H, s), 7.40 (2H, d), 7.59 (2H, t), 7.70 (1H, t), 7.79 (2H, d), 7.87 (2H, d), 8.69 (1H, s).

Example 93b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.28 (6H, d), 1.69 - 1.63 (2H, m), 1.93 - 1.89 (2H, m), 3.18 - 3.15 (2H, m), 3.46 (2H, q), 3.70 - 3.67 (2H, m), 4.18 - 4.10 (4H, m), 4.72 (1H, t), 6.24 (1H, t), 6.60 (1H, s), 7.39 (2H, d), 7.59 (2H, t), 7.70 (1H, t), 7.79 (2H, d), 7.88 (2H, d), 8.76 (1H, s).

Example 93c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.28 (6H, d), 1.69 - 1.64 (2H, m), 1.93 - 1.89 (2H, m), 3.41 (2H, dq), 3.70 - 3.68 (2H, m), 4.18 - 4.10 (4H, m), 4.47 (2H, dt), 6.42 (1H,

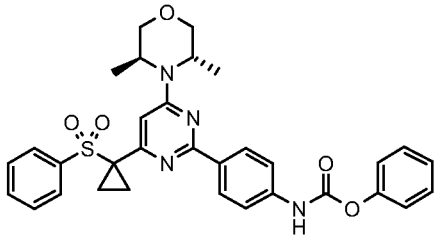
t), 6.60 (1H, s), 7.40 (2H, d), 7.59 (2H, t), 7.70 (1H, t), 7.79 (2H, d), 7.88 (2H, d), 8.76 (1H, s).

Example 93d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.28 (6H, d), 1.69 - 1.61 (2H, m), 1.93 - 1.90 (2H, m), 3.59 - 3.49 (2H, m), 3.70 - 3.68 (2H, m), 4.18 - 4.10 (4H, m), 6.07 (1H, tt), 6.52 (1H, t), 6.60 (1H, s), 7.41 (2H, d), 7.59 (2H, t), 7.70 (1H, t), 7.79 (2H, d), 7.89 (2H, d), 8.87 (1H, s).

Example 93e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.28 (6H, d), 1.72 - 1.62 (2H, m), 1.94 - 1.90 (2H, m), 3.70 - 3.68 (2H, m), 3.79 (3H, s), 4.18 - 4.10 (4H, m), 6.61 (1H, s), 7.38 (1H, s), 7.45 (2H, d), 7.59 (2H, t), 7.71 (1H, t), 7.76 (1H, s), 7.80 (2H, d), 7.91 (2H, d), 8.37 (1H, s), 8.79 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



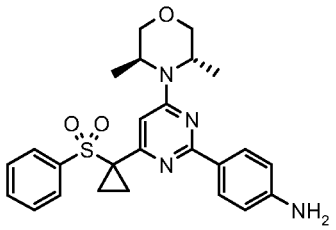
4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.6 g, 1.29 mmol) and sodium bicarbonate (1.085 g, 12.91 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.211 mL, 1.68 mmol) was added slowly and the reaction was stirred for 1 hour. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a yellow solid (0.73 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.29 (6H, d), 1.71 - 1.64 (2H, m), 1.94 - 1.89 (2H, m), 3.71 - 3.68 (2H, m), 4.18 - 4.11 (4H, m), 6.63 (1H, s), 7.30 - 7.23 (3H, m), 7.45

(2H, t), 7.54 (2H, d), 7.59 (2H, t), 7.70 (1H, t), 7.81 - 7.79 (2H, m), 7.97 (2H, d), 10.39 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=585; HPLC tR=3.02min.

4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]aniline

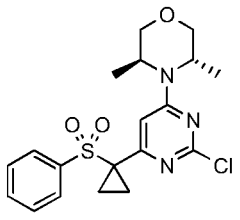


Bis(triphenylphosphine)palladium(II) chloride (0.053 g, 0.07 mmol) was added to 4-[1-(benzenesulfonyl)cyclopropyl]-2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine (0.611 g, 1.50 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.427 g, 1.95 mmol) and 2M sodium carbonate solution (2.247 mL, 4.49 mmol) in water (3 mL), ethanol (3 mL), and DME (6 mL) and the resulting solution stirred at 95°C overnight. The reaction mixture was diluted with ethyl acetate (75 mL), and washed sequentially with water (10 mL) and saturated brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in DCM, to give the desired material as a white foam (0.6 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.25 (6H, d), 1.69 - 1.60 (2H, m), 1.93 - 1.85 (2H, m), 3.68 - 3.64 (2H, m), 4.13 - 4.06 (4H, m), 5.50 (1H, s), 6.52 - 6.50 (4H, m), 7.58 (2H, t), 7.74 - 7.67 (3H, m), 7.80 - 7.78 (2H, m).

LCMS Spectrum: m/z (ES+)(M+H)+=465; HPLC tR=2.50min.

4-[1-(Benzenesulfonyl)cyclopropyl]-2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine

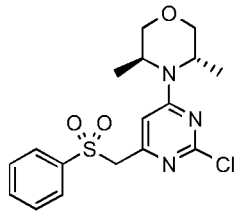


A solution of 50% w/v sodium hydroxide (4.99 mL, 124.73 mmol) was added portionwise to a stirred solution of 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine (866 mg, 2.27 mmol), tetrabutylammonium bromide (73.1 mg, 0.23 mmol) and 1,2-dibromoethane (0.586 mL, 6.80 mmol) in toluene (50 mL) and the resulting suspension stirred at 60°C for 6 hours. The reaction mixture was diluted with water (50 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a solid (611 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.20 (6H, m), 1.59 (2H, m), 1.86 (2H, m), 3.66 (2H, dd), 4.02 (2H, m), 4.10 (2H, dd), 6.62 (1H, s), 7.61 (2H, m), 7.74 (1H, m), 7.75 (2H, m).

LCMS Spectrum: m/z (ES+)(M+H)+=408; HPLC tR=2.26min.

4-(Benzenesulfonylmethyl)-2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine



Sodium benzenesulfinate (0.872 g, 5.31 mmol) was added portionwise to 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(iodomethyl)pyrimidine (1.86 g, 5.06 mmol) in acetonitrile (50 mL) and the resulting suspension stirred at 80°C for 6 hours. Further sodium benzenesulfinate (0.5 equivalents) was added and the reaction was heated for a further 8 hours. The solvent was removed and the solid was taken up in DMF. Further sodium benzenesulfinate (1 equivalent) was added and the reaction allowed to stir until complete (some sodium iodide was added to speed up the reaction). 10% Aqueous sodium thiosulfate solution was added and the acetonitrile removed, ethyl acetate was added and the layers separated. The organic layer was washed with brine and water, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 25% ethyl acetate in DCM, to give the desired material as a white solid (0.866 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.42-1.44(6H, d), 3.76-3.79(2H, dd), 4.10-4.16(2H, m), 4.22-4.26(2H, dd), 4.32(2H, s), 6.56(1H, s), 7.52-7.56(2H, t), 7.64-7.68(1H, t), 7.77-7.79(2H, d).

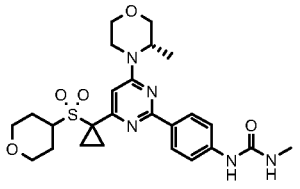
LCMS Spectrum: m/z (ES+)(M+H)+=382; HPLC tR=2.11min.

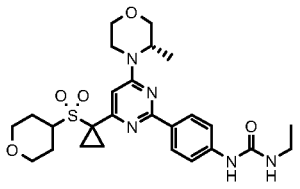
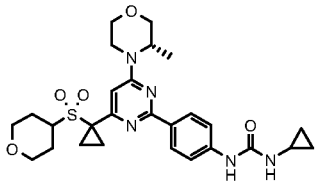
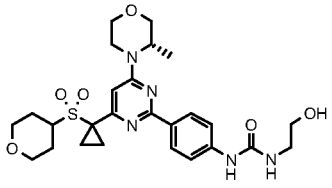
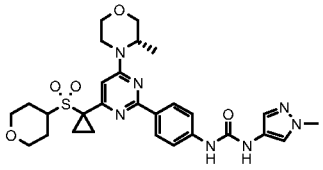
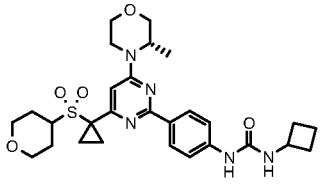
The preparation of 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(iodomethyl)pyrimidine was described earlier.

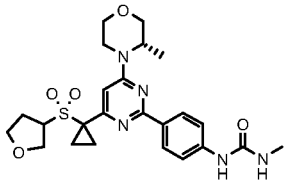
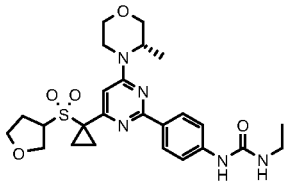
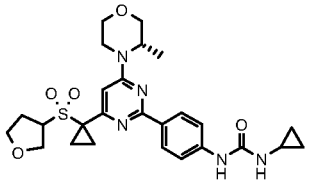
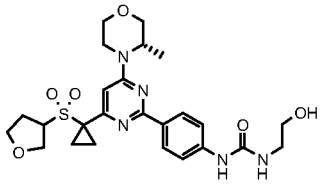
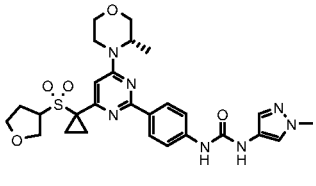
Example 94

The following samples were prepared by heating a mixture of the carbamate (1 equivalent), triethylamine (4 equivalents) and the amine (4 equivalents) in NMP (2 mL) at 70°C for 2 hours. The compounds were purified by preparative HPLC.

The following compounds were prepared in an analogous fashion from either phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
94a		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	516	1.98

Example	Structure	NAME	LCMS MH+	Retention time (min)
94b		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	530	2.14
94c		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	542	2.16
94d		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	546	1.80
94e		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	582	2.03
94f		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	556	2.44

Example	Structure	NAME	LCMS MH+	Retention time (min)
94g		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	502	1.98
94h		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	516	2.13
94i		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	528	2.15
94j		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	532	1.81
94k		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	568	2.03

Example 94a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.52 - 1.56 (2H, m), 1.58 - 1.61 (2H, m), 1.65 - 1.77 (2H, m), 2.10 - 2.19 (2H, m), 3.17 - 3.33 (3H, m), 3.48 (1H, td),

3.63 (1H, d), 3.75 - 3.87 (2H, m), 3.95 - 4.05 (3H, m), 4.17 - 4.27 (1H, m), 4.55 (1H, s), 6.00 - 6.15 (1H, m), 6.78 (1H, s), 7.52 (2H, d), 8.18 (2H, d), 8.75 (1H, s)

Example 94b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.24 (3H, d), 1.52 - 1.56 (2H, m), 1.57 - 1.62 (2H, m), 1.65 - 1.78 (2H, m), 2.09 - 2.19 (2H, m), 3.09 - 3.24 (3H, m), 3.26 - 3.35 (2H, m), 3.48 (1H, td), 3.63 (1H, d), 3.74 - 3.88 (2H, m), 3.94 - 4.04 (3H, m), 4.22 (1H, d), 4.55 (1H, s), 6.17 (1H, t), 6.78 (1H, s), 7.51 (2H, d), 8.18 (2H, d), 8.67 (1H, s)

Example 94c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.38 - 0.46 (2H, m), 0.62 - 0.69 (2H, m), 1.24 (3H, d), 1.50 - 1.56 (2H, m), 1.56 - 1.62 (2H, m), 1.66 - 1.78 (2H, m), 2.09 - 2.19 (2H, m), 2.54 - 2.60 (1H, m), 3.21 (1H, td), 3.28 - 3.34 (2H, m), 3.48 (1H, td), 3.63 (1H, d), 3.76 (1H, d), 3.79 - 3.88 (1H, m), 3.94 - 4.04 (3H, m), 4.22 (1H, d), 4.55 (1H, s), 6.45 (1H, s), 6.78 (1H, s), 7.52 (2H, d), 8.19 (2H, d), 8.55 (1H, s)

Example 94d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.50 - 1.56 (2H, m), 1.56 - 1.62 (2H, m), 1.64 - 1.77 (2H, m), 2.09 - 2.20 (2H, m), 3.15 - 3.23 (2H, m), 3.25 - 3.35 (2H, m), 3.43 - 3.50 (2H, m), 3.61 - 3.66 (1H, m), 3.74 - 3.87 (2H, m), 3.94 - 4.04 (3H, m), 4.22 (1H, d), 4.55 (1H, s), 4.73 (1H, t), 6.27 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.82 (1H, s)

Example 94e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.51 - 1.57 (2H, m), 1.58 - 1.62 (2H, m), 1.67 - 1.78 (2H, m), 2.10 - 2.21 (2H, m), 3.18 - 3.34 (3H, m), 3.49 (1H, td), 3.64 (1H, d), 3.73 - 3.88 (5H, m), 3.95 - 4.05 (3H, m), 4.23 (1H, d), 4.55 (1H, s), 6.79 (1H, s), 7.39 (1H, s), 7.56 (2H, d), 7.77 (1H, s), 8.22 (2H, d), 8.40 (1H, s), 8.85 (1H, s)

Example 94f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.49 - 1.77 (8H, m), 1.81 - 1.91 (2H, m), 2.09 - 2.25 (4H, m), 3.21 (1H, td), 3.26 - 3.35 (2H, m), 3.48 (1H, td), 3.63 (1H, d), 3.71 - 3.89 (2H, m), 3.94 - 4.04 (3H, m), 4.08 - 4.25 (2H, m), 4.55 (1H, s), 6.47 (1H, d), 6.78 (1H, s), 7.49 (2H, d), 8.18 (2H, d), 8.57 (1H, s)

Example 94g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.52 - 1.58 (2H, m), 1.62 - 1.70 (2H, m), 2.17 - 2.30 (2H, m), 2.66 (3H, d), 3.14 - 3.28 (1H, m), 3.49 (1H, td), 3.61 - 3.72 (2H, m), 3.73 - 3.82 (2H, m), 3.93 - 4.04 (2H, m), 4.21 (1H, d), 4.27 - 4.39 (1H, m), 4.55 (1H, s), 6.07 (1H, t), 6.79 (1H, s), 7.51 (2H, d), 8.20 (2H, d), 8.74 (1H, s)

Example 94h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.23 (3H, d), 1.52 - 1.59 (2H, m), 1.63 - 1.69 (2H, m), 2.18 - 2.30 (2H, m), 3.09 - 3.17 (2H, m), 3.17 - 3.24 (1H, m), 3.49 (1H, td), 3.61 - 3.71 (2H, m), 3.73 - 3.83 (2H, m), 3.94 - 4.02 (3H, m), 4.21 (1H, d), 4.30 - 4.38 (1H, m), 4.54 (1H, s), 6.17 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.66 (1H, s)

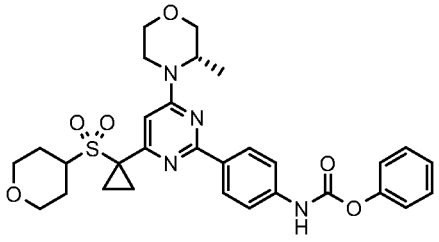
Example 94i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.68 (3H, m), 1.23 (4H, d), 1.52 - 1.60 (4H, m), 1.63 - 1.70 (3H, m), 2.16 - 2.30 (3H, m), 2.52 - 2.61 (18H, m), 3.21 (3H, td), 3.49 (1H, td), 3.59 - 3.72 (3H, m), 3.72 - 3.84 (3H, m), 3.93 - 4.03 (3H, m), 4.21 (1H, d), 4.28 - 4.40 (1H, m), 4.54 (1H, s), 6.44 (1H, s), 6.80 (1H, s), 7.52 (2H, d), 8.20 (2H, d), 8.54 (1H, s)

Example 94j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.51 - 1.60 (2H, m), 1.62 - 1.69 (2H, m), 2.18 - 2.30 (2H, m), 3.14 - 3.24 (4H, m), 3.43 - 3.50 (2H, m), 3.61 - 3.71 (1H, m), 3.74 - 3.81 (2H, m), 3.94 - 4.02 (3H, m), 4.21 (1H, d), 4.30 - 4.38 (1H, m), 4.54 (1H, s), 4.69 - 4.77 (1H, m), 6.26 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.81 (1H, s)

Example 94k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.50 - 1.60 (2H, m), 1.63 - 1.68 (2H, m), 2.20 - 2.30 (2H, m), 3.16 - 3.28 (1H, m), 3.44 - 3.57 (1H, m), 3.61 - 3.70 (1H, m), 3.74 - 3.84 (4H, m), 3.94 - 4.05 (3H, m), 4.22 (1H, d), 4.31 - 4.38 (1H, m), 4.55 (1H, s), 6.81 (1H, s), 7.39 (1H, s), 7.56 (2H, d), 7.76 (1H, s), 8.24 (2H, d), 8.39 (1H, s), 8.84 (1H, s)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate



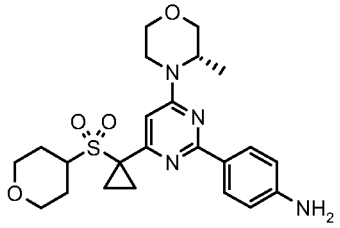
Phenyl chloroformate (0.436 mL, 3.47 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline (1.06 g, 2.31 mmol), sodium hydrogen carbonate (0.291 g, 3.47 mmol) in dioxane (40 mL) at 5°C under a nitrogen atmosphere. The resulting mixture was stirred at RT for 1.5 hours. The reaction mixture was diluted with ethyl acetate (150 mL), and washed sequentially with water (2 x 100 mL). The

organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product which was triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (1.14 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.52 - 1.58 (2H, m), 1.58 - 1.64 (2H, m), 1.65 - 1.77 (2H, m), 2.10 - 2.20 (2H, m), 3.17 - 3.54 (2H, m), 3.63 (2H, d), 3.74 - 3.87 (3H, m), 3.96 - 4.04 (3H, m), 4.24 (1H, d), 4.56 (1H, s), 6.83 (1H, s), 7.20 - 7.32 (3H, m), 7.42 - 7.50 (2H, m), 7.63 (2H, d), 8.28 (2H, d), 10.45 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 579; HPLC tR = 2.8 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline



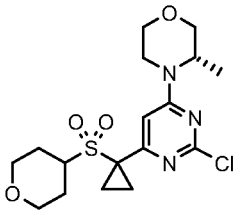
Bis(triphenylphosphine)palladium(II) chloride (0.187 g, 0.27 mmol) was added to 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidine (1.6 g, 3.98 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.308 g, 5.97 mmol) and 2M aqueous sodium carbonate solution (1 mL, 2.00 mmol) in a solvent mixture of DMF (5 mL), DME (12 mL), water (1 mL) and ethanol (1 mL) at RT . The resulting mixture was stirred at 90°C for 7 hours under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, and the crude product then further purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give a solid. The solid was further purified by trituration with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (1.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.48 - 1.53 (2H, m), 1.55 - 1.59 (2H, m), 1.66 - 1.76 (2H, m), 2.11 - 2.18 (2H, m), 3.18 (1H, dd), 3.30 - 3.34 (2H,

m), 3.47 (1H, td), 3.62 (1H, d), 3.75 (1H, d), 3.81 - 3.90 (1H, m), 3.93 - 4.05 (3H, m), 4.18 (1H, d), 4.51 (1H, s), 5.58 (2H, s), 6.62 (2H, d), 6.67 (1H, s), 8.02 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 459; HPLC tR = 2.11 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidine

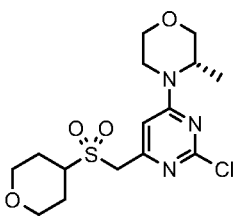


Aqueous sodium hydroxide solution (10 mL, 186.39 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxan-4-ylsulfonylmethyl)pyrimidine (1.5 g, 3.99 mmol), tetraethylammonium bromide (0.168 g, 0.80 mmol) and1,2-dibromoethane (2.75 mL, 31.93 mmol) in toluene (10 mL) at RT under a nitrogen atmosphere. After stirring at RT for 2 hours the reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired material as an oil which solidified on standing (1.64 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 - 1.25 (3H, m), 1.50 - 1.54 (2H, m), 1.55 - 1.59 (2H, m), 1.61 - 1.72 (2H, m), 1.97 - 2.07 (2H, m), 3.18 - 3.27 (1H, m), 3.26 - 3.36 (2H, m), 3.44 (1H, td), 3.58 (1H, d), 3.65 - 3.78 (2H, m), 3.90 - 4.01 (3H, m), 4.01 - 4.10 (1H, m), 4.39 (1H, s), 6.96 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 402; HPLC tR = 1.99 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxan-4-ylsulfonylmethyl)pyrimidine

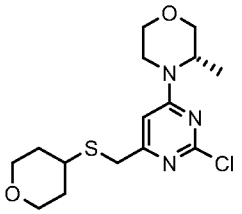


3-Chloroperoxybenzoic acid (381 mg, 2.21 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxan-4-ylsulfanylmethyl)pyrimidine (345 mg, 1.00 mmol)in DCM

(10 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at RT for 2 hours then diluted with DCM (100 mL), and washed sequentially with 10% aqueous sodium metabisulphite solution (200 mL), saturated aqueous sodium hydrogencarbonate (200 mL), dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (200 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 - 1.26 (3H, m), 1.60 - 1.76 (2H, m), 1.95 - 2.06 (2H, m), 3.19 - 3.29 (1H, m), 3.31 - 3.39 (2H, m), 3.40 - 3.65 (3H, m), 3.74 (1H, d), 3.90 - 4.04 (3H, m), 4.30 (1H, s), 4.48 (2H, s), 6.93 (1H, s)

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxan-4-ylsulfanylmethyl)pyrimidine



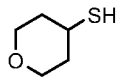
DIPEA (1.762 mL, 10.18 mmol) was added to oxane-4-thiol (1.203 g, 10.18 mmol), in acetonitrile (20 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at RT for 5mins then 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.4 g, 6.79 mmol) added. The resulting mixture was stirred at RT for 1 hour then diluted with ethyl acetate (75 mL), and washed sequentially with water (2 x 75 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give the desired material as a brown gum (2.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.39 - 1.51 (2H, m), 1.82 - 1.92 (2H, m), 2.92 - 3.02 (1H, m), 3.13 - 3.23 (1H, m), 3.26 - 3.37 (2H, m), 3.44 (1H, td), 3.54 - 3.66 (1H, m), 3.72 (1H, d), 3.78 - 3.88 (2H, m), 3.90 - 4.02 (2H, m), 4.31 (1H, s), 6.81 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 344; HPLC tR = 1.99 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Oxane-4-thiol

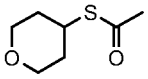


7M Ammonia in methanol (20 mL, 140.00 mmol) was added to *S*-(oxan-4-yl) ethanethioate (2.27 g, 14.17 mmol) at RT. The resulting solution was stirred at RT for 1 hour then the mixture concentrated *in vacuo* and used without further purifiaction.

NMR Spectrum: none

LCMS Spectrum: no mass ion; HPLC tR = 0.61 min.

S-(Oxan-4-yl) ethanethioate



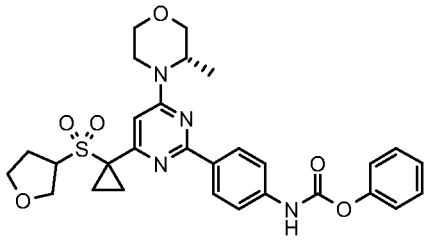
Potassium thioacetate (4.68 g, 40.98 mmol) was added to oxan-4-yl methanesulfonate (4.2 g, 23.30 mmol), in DMA (80 mL) at RT. The resulting mixture was stirred at 65°C for 18 hours. The reaction mixture was diluted with ethyl acetate (400 mL), and washed sequentially with water (2 x 150 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 30% ethyl acetate in isohexane, to give the desired material as a orange oil (2.27 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.47 - 1.65 (2H, m), 1.76 - 1.90 (2H, m), 2.35 (3H, s), 3.36 - 3.51 (2H, m), 3.53 - 3.69 (1H, m), 3.67 - 3.82 (2H, m).

LCMS Spectrum: no mass ion; HPLC tR = 1.45 min.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below.

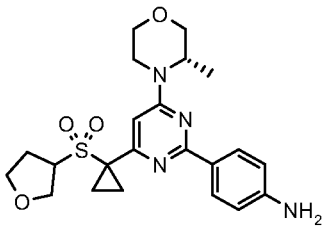
Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.297 mL, 2.36 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline (700 mg, 1.57 mmol), sodium hydrogen carbonate (198 mg, 2.36 mmol) in dioxane (30 mL) at 5°C under a nitrogen atmosphere. The resulting mixture was stirred at RT for 1.5 hours then diluted with ethyl acetate (150 mL), and washed sequentially with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (600 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.52 - 1.59 (2H, m), 1.64 - 1.71 (2H, m), 2.15 - 2.30 (2H, m), 3.22 (1H, td), 3.44 - 3.54 (1H, m), 3.61 - 3.70 (2H, m), 3.73 - 3.83 (2H, m), 3.94 - 4.03 (3H, m), 4.23 (1H, d), 4.30 - 4.38 (1H, m), 4.56 (1H, s), 6.84 (1H, s), 7.21 - 7.32 (3H, m), 7.41 - 7.50 (2H, m), 7.64 (2H, d), 8.30 (2H, d), 10.44 (1H, s)

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline



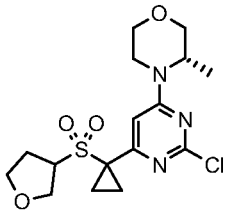
Bis(triphenylphosphine)palladium(II) chloride (0.233 g, 0.33 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidine (1.92 g, 4.95 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.627 g, 7.42 mmol) and sodium carbonate (1 mL, 2.00 mmol) in a solvent mixture of DMF (5 mL), DME (12 mL),

water (1 mL) and ethanol (1 mL) at RT. The resulting mixture was stirred at 90°C for 7 hours under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (2 x 100 mL).The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, to give a product that was further purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give a solid. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (0.821 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.49 - 1.54 (2H, m), 1.61 - 1.66 (2H, m), 2.16 - 2.26 (2H, m), 3.18 (1H, dd), 3.39 - 3.53 (1H, m), 3.59 - 3.71 (3H, m), 3.70 - 3.83 (2H, m), 3.90 - 4.01 (3H, m), 4.17 (1H, d), 4.33 (1H, q), 4.51 (1H, s), 5.57 (2H, s), 6.61 (2H, d), 6.69 (1H, s), 8.03 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 447; HPLC tR = 1.91 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidine

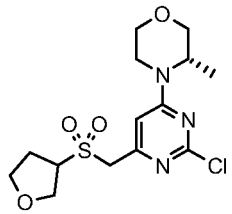


Aqueous sodium hydroxide solution (10 mL, 186.39 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxolan-3-ylsulfonylmethyl)pyrimidine (1.9 g, 5.25 mmol), tetraethylammonium bromide (0.221 g, 1.05 mmol), and1,2-dibromoethane (3.62 mL, 42.01 mmol) in toluene (30 mL) at RT under a nitrogen atmosphere. After being stirred at RT for 1.5 hours the reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (125 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 60% ethyl acetate in isohexane, to give the desired material as a colourless gum (1.92 g).

NMR Spectrum: none

LCMS Spectrum: m/z (ESI+)(M+H)+ = 388; HPLC tR = 1.91 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxolan-3-ylsulfonylmethyl)pyrimidine

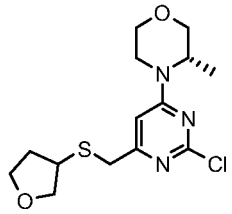


3-Chloroperoxybenzoic acid (4.26 g, 24.68 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxolan-3-ylsulfanylmethyl)pyrimidine (3.7 g, 11.22 mmol)in DCM (200 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at RT for 2 hours then diluted with DCM (100 mL), and washed sequentially with 10% aqueous sodium metabisulphite solution (200 mL) and a saturated aqueous solution of sodium hydrogencarbonate (200 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (3.03 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 - 1.26 (3H, m), 2.18 - 2.31 (2H, m), 3.20 - 3.31 (1H, m), 3.37 - 3.52 (1H, m), 3.60 (1H, d), 3.65 - 3.77 (2H, m), 3.80 - 3.89 (1H, m), 3.90 - 3.99 (3H, m), 4.03 - 4.16 (2H, m), 4.31 (1H, s), 4.49 (2H, s), 6.94 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 362; HPLC tR = 1.59 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxolan-3-ylsulfanylmethyl)pyrimidine



DIPEA (3.67 mL, 21.21 mmol) was added to oxolane-3-thiol (2.210 g, 21.21 mmol), in acetonitrile (100 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred for 5 minutes then 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (5 g, 14.14 mmol) added. The resulting mixture was stirred at RT for 1 hour then diluted with ethyl acetate (75 mL), and washed sequentially with water (2 x 75 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was

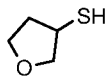
purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give the desired material as a brown gum (3.75 g).

NMR Spectrum: ^{1}H NMR (399.902MHz, DMSO-d_6) δ 1.17 - 1.24 (3H, m), 1.63 - 1.75 (2H, m), 2.17 - 2.30 (2H, m), 3.19 (1H, td), 3.40 - 3.50 (2H, m), 3.59 (1H, d), 3.63 - 3.80 (3H, m), 3.91 - 4.04 (4H, m), 4.33 (1H, s), 6.82 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 330; HPLC tR = 1.89 min.

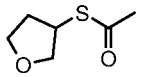
The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Oxolane-3-thiol



7M ammonia in methanol (20 mL, 140.00 mmol) was added to *S*-(Oxolan-3-yl) ethanethioate (20.47 g, 140.00 mmol) at RT. The resulting solution was stirred at RT for 1 hour then concentrated *in vacuo* to give the desired material which was used without further purification or characterisation.

S-(Oxolan-3-yl) ethanethioate

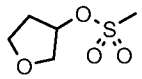


Potassium thioacetate (16.60 g, 145.31 mmol) was added to oxolan-3-yl methanesulfonate (13.8 g, 83.03 mmol), in DMA (150 mL) at RT. The resulting mixture was stirred at 65°C for 7 hours. The reaction mixture was diluted with ethyl acetate (400 mL), and washed sequentially with water (2 x 150 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in isohexane, to give the desired material as a brown oil (9.50 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.70 - 1.80 (1H, m), 2.25 - 2.40 (4H, m), 3.44 - 3.52 (1H, m), 3.67 - 3.81 (2H, m), 3.84 - 3.94 (1H, m), 3.97 - 4.08 (1H, m)

LCMS Spectrum: no mass ion; HPLC tR = 1.18 min.

Oxolan-3-yl methanesulfonate



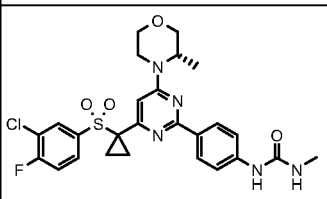
Methanesulfonyl chloride (11.86 mL, 153.23 mmol) was added dropwise to tetrahydrofuran-3-ol (9 g, 102.15 mmol) and triethylamine (21.36 mL, 153.23 mmol) in DCM (300 mL) at RT over a period of 30 minutes under a nitrogen atmosphere. The resulting mixture was stirred at RT for 1 hour then diluted with ethyl acetate (400 mL) and washed with water (250 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford the desired material, which was used without further purification.

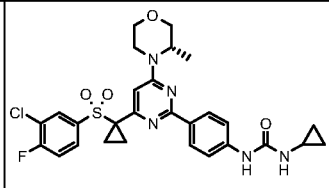
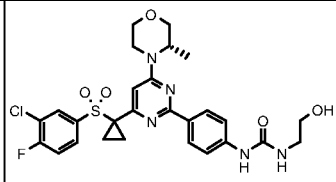
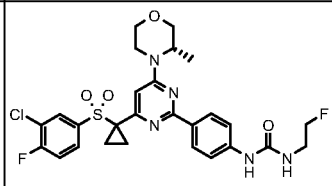
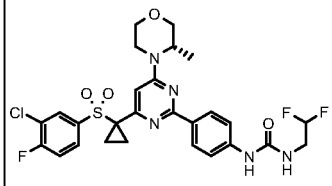
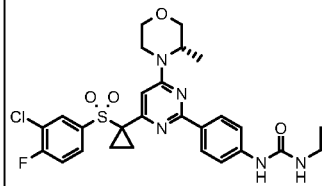
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.03 - 2.14 (1H, m), 2.17 - 2.29 (1H, m), 3.21 (3H, s), 3.69 - 3.92 (4H, m), 5.28 - 5.33 (1H, m)

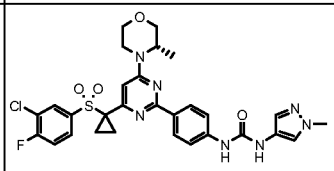
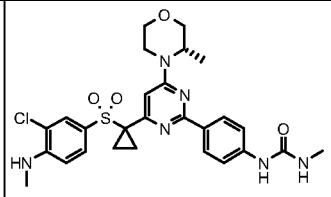
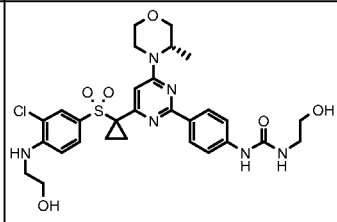
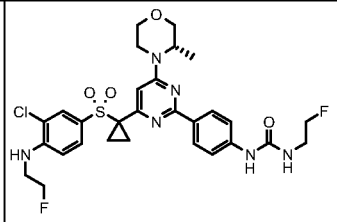
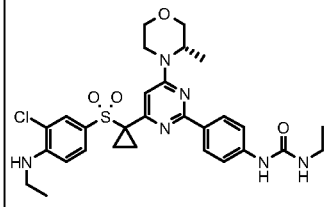
Example 95

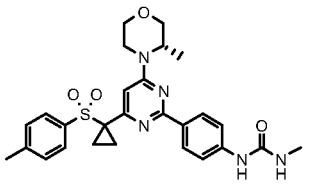
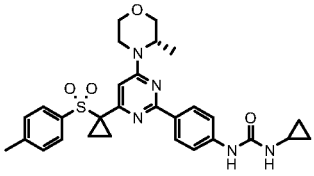
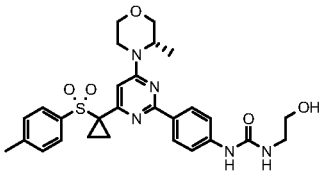
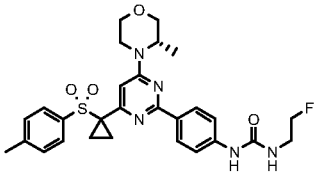
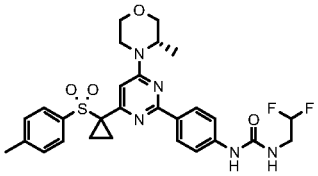
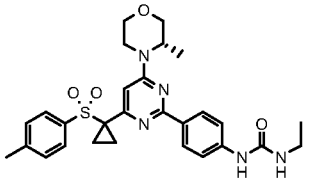
The following samples were prepared by heating a mixture of the carbamate (1 equivalent), triethylamine (4 equivalents) and the amine (1.2 equivalents) in NMP (2 mL) at 50°C for 2 hours. The compounds were purified by preparative HPLC.

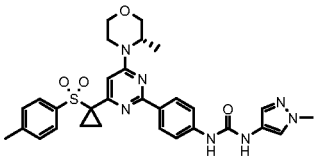
The following compounds were prepared in an analogous fashion from either phenyl *N*-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
95a		1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	560	2.29

Example	Structure	NAME	LCMS MH+	Retention time (min)
95b		1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	586	2.44
95c		1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	590	2.10
95d		1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	592	2.41
95e		1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	610	2.54
95f		3-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	574	2.45

Example	Structure	NAME	LCMS MH+	Retention time (min)
95g		1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	626	2.29
95h*		1-[4-[4-[1-(3-chloro-4-methylaminophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	571	2.11
95i*		1-[4-[4-[1-[3-chloro-4-(2-hydroxyethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	631	1.79
95j*		1-[4-[4-[1-[3-chloro-4-(2-fluoroethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	635	2.30
95k*		1-[4-[4-[1-(3-chloro-4-ethylaminophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea	599	2.41

Example	Structure	NAME	LCMS MH+	Retention time (min)
95l		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	522	2.14
95m		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	548	2.29
95n		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	552	1.98
95o		3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	554	2.28
95p		3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	572	2.40
95q		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	536	2.28

Example	Structure	NAME	LCMS MH+	Retention time (min)
95r		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	588	2.16

* 4 equivalents of amine used.

Example 95a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 - 1.64 (2H, m), 1.90 - 1.98 (2H, m), 2.68 (3H, s), 3.12 - 3.23 (1H, m), 3.46 (1H, dd), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.15 (1H, d), 4.48 (1H, s), 6.04 (1H, s), 6.67 (1H, s), 7.39 (2H, d), 7.58 - 7.68 (1H, m), 7.73 - 7.83 (3H, m), 7.99 (1H, d), 8.74 (1H, s)

Example 95b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.37 - 0.44 (2H, m), 0.60 - 0.69 (2H, m), 1.20 (3H, d), 1.60 - 1.64 (2H, m), 1.89 - 1.98 (2H, m), 2.56 - 2.60 (1H, m), 3.11 - 3.23 (1H, m), 3.42 - 3.52 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.95 (1H, d), 4.15 (1H, d), 4.49 (1H, s), 6.39 (1H, s), 6.67 (1H, s), 7.40 (2H, d), 7.57 - 7.68 (1H, m), 7.73 - 7.85 (3H, m), 7.92 - 8.03 (1H, m), 8.54 (1H, s)

Example 95c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 - 1.64 (2H, m), 1.91 - 1.96 (2H, m), 3.14 - 3.22 (2H, m), 3.40 - 3.50 (3H, m), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.16 (1H, d), 4.48 (1H, s), 4.72 (1H, t), 6.23 (1H, s), 6.67 (1H, s), 7.38 (2H, d), 7.63 (1H, t), 7.75 - 7.84 (3H, m), 7.98 (1H, d), 8.80 (1H, s)

Example 95d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 - 1.65 (2H, m), 1.88 - 1.97 (2H, m), 3.36 - 3.51 (4H, m), 3.62 (1H, d), 3.75 (1H, d), 3.95 (1H, d), 4.12 - 4.23 (1H, m), 4.41 (1H, t), 4.45 - 4.51 (1H, m), 4.53 (1H, t), 6.40 (1H, s), 6.68 (1H, s), 7.39 (2H, d), 7.60 - 7.69 (1H, m), 7.72 - 7.86 (3H, m), 7.99 (1H, d), 8.81 (1H, s)

Example 95e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 - 1.65 (2H, m), 1.89 - 1.97 (2H, m), 3.12 - 3.22 (1H, m), 3.41 - 3.64 (3H, m), 3.75 (1H, d), 3.96 (1H, d), 4.15 (1H, d), 4.49 (1H, s), 5.87 - 6.22 (1H, m), 6.49 (1H, t), 6.68 (1H, s), 7.40 (2H, d), 7.63 (1H, t), 7.77 - 7.86 (3H, m), 7.97 - 8.00 (1H, m), 8.92 (1H, s)

Example 95f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.20 (3H, d), 1.59 - 1.65 (2H, m), 1.90 - 1.98 (2H, m), 3.09 - 3.21 (3H, m), 3.42 - 3.52 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.09 - 4.21 (1H, m), 4.44 - 4.53 (1H, m), 6.12 (1H, t), 6.67 (1H, s), 7.39 (2H, d), 7.63 (1H, t), 7.75 - 7.85 (3H, m), 7.99 (1H, d), 8.66 (1H, s)

Example 95g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 - 1.66 (2H, m), 1.91 - 1.99 (2H, m), 3.11 - 3.21 (1H, m), 3.47 (1H, td), 3.62 (1H, d), 3.70 - 3.83 (4H, m), 3.96 (1H, d), 4.17 (1H, d), 4.49 (1H, s), 6.69 (1H, s), 7.38 (1H, s), 7.44 (2H, d), 7.64 (1H, t), 7.75 - 7.85 (3H, m), 7.99 (1H, d), 8.34 (1H, s), 8.84 (1H, s)

Example 95h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.53 - 1.59 (2H, m), 1.77 - 1.83 (2H, m), 2.63 - 2.67 (3H, m), 2.82 (3H, d), 3.10 - 3.19 (1H, m), 3.46 (1H, dd), 3.61 (1H, d), 3.75 (1H, d), 3.95 (1H, d), 4.09 (1H, d), 4.39 (1H, s), 6.00 - 6.08 (1H, m), 6.47 (1H, t), 6.59 (1H, s), 6.70 (1H, d), 7.41 (2H, d), 7.48 - 7.57 (2H, m), 7.94 (2H, d), 8.70 (1H, s)

Example 95i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.53 - 1.60 (2H, m), 1.77 - 1.83 (2H, m), 3.14 - 3.19 (2H, m), 3.25 - 3.32 (2H, m), 3.39 - 3.50 (3H, m), 3.55 - 3.65 (3H, m), 3.75 (1H, d), 3.96 (1H, d), 4.10 (1H, d), 4.38 (1H, s), 4.73 (1H, t), 4.82 (1H, t), 6.15 (1H, t), 6.24 (1H, t), 6.59 (1H, s), 6.84 (1H, d), 7.40 (2H, d), 7.48 (2H, d), 7.54 (1H, d), 7.95 (2H, d), 8.76 (1H, s)

Example 95j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.52 - 1.60 (2H, m), 1.78 - 1.83 (2H, m), 3.09 - 3.19 (1H, m), 3.35 - 3.49 (4H, m), 3.52 - 3.58 (1H, m), 3.57 - 3.65 (2H, m), 3.74 (1H, d), 3.95 (1H, d), 4.07 (1H, d), 4.37 - 4.44 (2H, m), 4.49 - 4.55 (1H, m), 4.63 (1H, t), 6.38 - 6.50 (2H, m), 6.58 (1H, s), 6.89 (1H, d), 7.40 (2H, d), 7.48 (2H, d), 7.53 (1H, s), 7.96 (2H, d), 8.76 (1H, s)

Example 95k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.13 - 1.21 (6H, m), 1.49 - 1.58 (2H, m), 1.78 - 1.82 (2H, m), 3.08 - 3.18 (2H, m), 3.22 - 3.33 (7H, m), 3.46 (1H, dd), 3.61 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.09 (1H, d), 4.39 (1H, s), 6.13 (1H, t), 6.28 (1H, t), 6.59 (1H, s), 6.77 (1H, d), 7.39 (2H, d), 7.46 (2H, d), 7.52 (1H, s), 7.96 (2H, d), 8.61 (1H, s)

Example 95l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.56 - 1.64 (2H, m), 1.82 - 1.89 (2H, m), 2.40 (3H, s), 2.68 (3H, s), 3.08 - 3.17 (1H, m), 3.45 (1H, td), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.10 (1H, d), 4.38 (1H, s), 6.04 (1H, t), 6.61 (1H, s), 7.33 - 7.44 (4H, m), 7.66 (2H, d), 7.82 (2H, d), 8.70 (1H, s)

Example 95m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.42 - 0.50 (2H, m), 0.66 - 0.75 (2H, m), 1.23 (3H, d), 1.60 - 1.69 (2H, m), 1.87 - 1.98 (2H, m), 2.46 (3H, s), 2.62 - 2.70 (1H, m),

3.19 (1H, td), 3.46 - 3.57 (1H, m), 3.66 (1H, d), 3.80 (1H, d), 4.01 (1H, d), 4.16 (1H, d), 4.43 (1H, s), 6.46 (1H, s), 6.67 (1H, s), 7.39 - 7.49 (4H, m), 7.71 (2H, d), 7.88 (2H, d), 8.56 (1H, s)

Example 95n: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.57 - 1.65 (2H, m), 1.83 - 1.90 (2H, m), 2.42 (3H, s), 3.13 - 3.20 (3H, m), 3.40 - 3.50 (3H, m), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.09 (1H, d), 4.37 (1H, s), 4.72 (1H, t), 6.22 (1H, t), 6.61 (1H, s), 7.35 - 7.43 (4H, m), 7.66 (2H, d), 7.82 (2H, d), 8.77 (1H, s)

Example 95o: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.56 - 1.65 (2H, m), 1.81 - 1.90 (2H, m), 2.40 (3H, s), 3.07 - 3.22 (1H, m), 3.36 - 3.50 (3H, m), 3.60 (1H, d), 3.74 (1H, d), 3.96 (1H, d), 4.12 (1H, d), 4.33 - 4.45 (2H, m), 4.53 (1H, t), 6.41 (1H, t), 6.61 (1H, s), 7.34 - 7.43 (4H, m), 7.66 (2H, d), 7.83 (2H, d), 8.77 (1H, s)

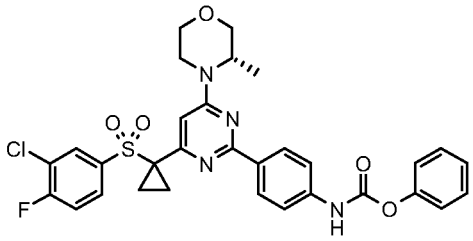
Example 95p: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.56 - 1.65 (2H, m), 1.82 - 1.91 (2H, m), 2.40 (3H, s), 3.10 - 3.18 (1H, m), 3.41 - 3.65 (4H, m), 3.74 (1H, d), 3.96 (1H, d), 4.09 (1H, d), 4.37 (1H, s), 5.91 - 6.23 (1H, m), 6.50 (1H, t), 6.62 (1H, s), 7.35 - 7.44 (4H, m), 7.66 (2H, d), 7.84 (2H, d), 8.89 (1H, s)

Example 95q: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.17 (3H, d), 1.52 - 1.66 (2H, m), 1.85 - 1.90 (2H, m), 2.40 (3H, s), 3.07 - 3.20 (3H, m), 3.45 (1H, td), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.12 (1H, d), 4.37 (1H, s), 6.13 (1H, t), 6.61 (1H, s), 7.35 - 7.44 (4H, m), 7.66 (2H, d), 7.82 (2H, d), 8.62 (1H, s)

Example 95r: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.57 - 1.66 (2H, m), 1.84 - 1.90 (2H, m), 2.41 (3H, s), 3.08 - 3.18 (1H, m), 3.46 (1H, td), 3.61 (1H, d), 3.72 - 3.83 (4H, m), 3.96 (1H, d), 4.10 (1H, d), 4.37 (1H, s), 6.62 (1H, s), 7.35 - 7.49 (5H, m), 7.66 (2H, d), 7.76 (1H, s), 7.86 (2H, d), 8.35 (1H, s), 8.80 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

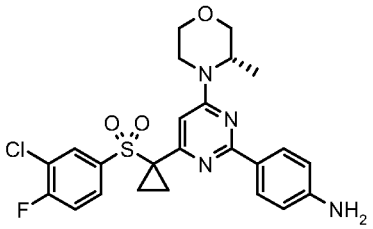


Sodium hydrogen carbonate (0.501 g, 5.96 mmol) was added to 4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (2 g, 3.98 mmol) in dioxane (30 mL) at 5°C under nitrogen. Phenyl chloroformate (0.749 mL, 5.96 mmol) was then added and the resulting mixture stirred at RT for 2 hours. The reaction mixture was diluted with DCM (50 mL) and washed with water (75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (1.45 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.59 - 1.66 (2H, m), 1.91 - 1.96 (2H, m), 3.12 - 3.24 (1H, m), 3.40 - 3.52 (1H, m), 3.62 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.18 (1H, d), 4.50 (1H, s), 6.74 (1H, s), 7.23 - 7.32 (3H, m), 7.41 - 7.49 (2H, m), 7.54 (2H, d), 7.58 - 7.68 (1H, m), 7.79 - 7.83 (1H, m), 7.88 (2H, d), 7.96 - 8.02 (1H, m), 10.40 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 622; HPLC tR = 3.21 min.

4-[4-[1-(3-Chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



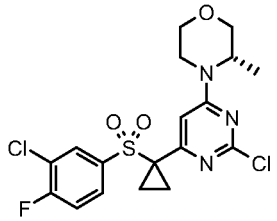
Bis(triphenylphosphine)palladium(II) chloride (0.242 g, 0.35 mmol) was added to 2-chloro-4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (2.3 g, 5.15 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

(1.411 g, 6.44 mmol) and 2M aqueous sodium carbonate solution (3 mL, 6.00 mmol) in a solvent mixture of DMF (5 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT. The resulting mixture was stirred at 90°C, under an inert atmosphere for 5 hours then left at RT for 16 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 80% ethyl acetate in isohexane, to give the desired material as a yellow gum (2.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.57 - 1.61 (2H, m), 1.87 - 1.96 (2H, m), 3.14 (1H, td), 3.41 - 3.50 (1H, m), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.13 (1H, d), 4.44 (1H, s), 5.52 (1H, d), 6.49 (2H, d), 6.57 (1H, s), 7.57 - 7.68 (3H, m), 7.75 - 7.85 (1H, m), 7.99 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 503; HPLC tR = 2.66 min.

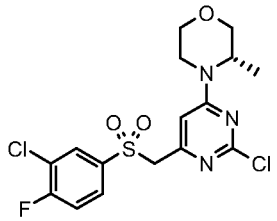
2-Chloro-4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Aqueous sodium hydroxide solution (20 mL, 142.76 mmol) was added to 2-chloro-4-[(3-chloro-4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.5 g, 5.95 mmol), 1,2-dibromoethane (2.56 mL, 29.74 mmol) and tetrabutylammonium bromide (0.192 g, 0.59 mmol) in toluene (100 mL) at RT under a nitrogen atmosphere and the mixture stirred for 3 hours. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 100% ethyl acetate in isohexane, to give the desired material as a colourless gum (2.3 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.98 (1H, d), 1.18 (3H, d), 1.54 - 1.61 (2H, m), 1.84 - 1.91 (2H, m), 3.15 (1H, td), 3.36 - 3.45 (1H, m), 3.55 (1H, d), 3.70 (1H, d), 3.90 (1H, d), 4.08 (1H, s), 4.31 (1H, s), 6.74 (1H, s), 7.62 - 7.71 (1H, m), 7.76 - 7.83 (1H, m)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 446; HPLC tR = 2.56 min.

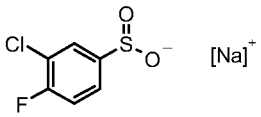
2-Chloro-4-[(3-chloro-4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine



Sodium 3-chloro-4-fluorobenzenesulfinate (3.52 g, 16.26 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (5 g, 14.14 mmol) in acetonitrile (150 mL) at RT under a nitrogen atmosphere. The resulting mixture was stirred at 80°C for 3 hours. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with water (100 mL), The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 70% ethyl acetate in isohexane, to give a colourless oil which solidified on standing. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (4.0 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 3.18 (1H, dd), 3.28 (1H, d), 3.43 (1H, td), 3.58 (1H, d), 3.72 (1H, d), 3.94 (1H, d), 4.21 (1H, s), 4.73 (2H, s), 6.78 (1H, s), 7.66 - 7.74 (1H, m), 7.78 - 7.87 (1H, m), 8.02 (1H, d)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 420; HPLC tR = 2.38 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Sodium 3-chloro-4-fluorobenzenesulfinate

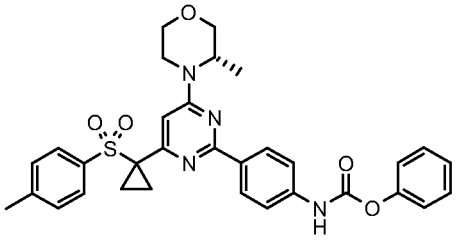


A solution of sodium sulfite (8.25 g, 65.49 mmol) in water (75 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (11.0 g, 130.97 mmol) was added to the stirred solution and the resulting solution stirred at 50°C for 1 hour. 3-Chloro-4-fluorobenzene-1-sulfonyl chloride (15 g, 65.49 mmol) was added portionwise to the solution and was stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (300 mL). The suspension was allowed to stir at RT for 20 minutes then filtered and the filtrate evaporated to afford the desired material as a white solid, which was air dried overnight under vacuum and used without further purification (16.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.34 (1H, t), 7.40 - 7.46 (1H, m), 7.58 (1H, d)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate



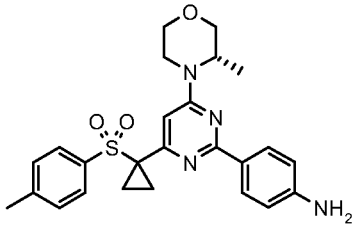
Sodium hydrogen carbonate (0.570 g, 6.78 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]aniline (2.1 g, 4.52 mmol) in dioxane (6 mL) at 5°C under a nitrogen atmosphere. Phenyl chloroformate (0.852 mL, 6.78 mmol) was then added and the resulting mixture stirred at RT for 2 hours. The reaction mixture was diluted with DCM (50 mL) and washed with water (75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (1.52 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.58 - 1.64 (2H, m), 1.85 - 1.91 (2H, m), 2.40 (3H, s), 3.09 - 3.23 (1H, m), 3.41 - 3.51 (1H, m), 3.60 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.12 (1H, d), 4.39 (1H, s), 6.65 (1H, s), 7.21 - 7.31 (3H, m), 7.36 - 7.41

(2H, m), 7.42 - 7.48 (2H, m), 7.50 - 7.56 (2H, m), 7.63 - 7.71 (2H, m), 7.89 (2H, d), 10.38 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 535; HPLC tR = 3.1 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]aniline

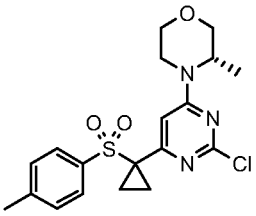


Bis(triphenylphosphine)palladium(II) chloride (0.225 g, 0.32 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidine (1.95 g, 4.78 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.362 g, 6.21 mmol) and 2M aqueous sodium carbonate solution (3 mL, 6.00 mmol) in a solvent mixture of DMF (5 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT. The resulting mixture was stirred at 90°C for 5 hours under an inert atmosphere, then left at RT for 16 hours. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 80% ethyl acetate in isohexane, to give crude material which was further purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give the desired material as a white solid (2.1 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.54 - 1.63 (2H, m), 1.81 - 1.89 (2H, m), 1.99 (3H, s), 3.11 (1H, td), 3.37 - 3.49 (1H, m), 3.59 (1H, d), 3.73 (1H, d), 3.94 (1H, d), 4.06 (1H, s), 4.32 (1H, s), 5.50 (1H, s), 6.50 (3H, d), 7.38 (2H, d), 7.62 - 7.72 (4H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 465; HPLC tR = 2.48 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidine

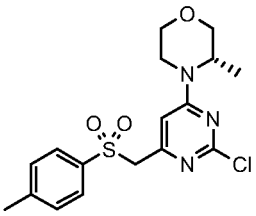


Aqueous sodium hydroxide solution (20 mL, 125.69 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine (2 g, 5.24 mmol), 1,2-dibromoethane (2.257 mL, 26.19 mmol) and tetrabutylammonium bromide (0.169 g, 0.52 mmol) in DCM (100 mL) at RT under a nitrogen atmosphere then stirred for 3 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 60% ethyl acetate in isohexane, to give the desired material as a colourless gum (1.9 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.52 - 1.56 (2H, m), 1.79 - 1.84 (2H, m), 1.99 (3H, s), 3.12 (1H, td), 3.35 - 3.47 (1H, m), 3.54 (1H, d), 3.71 (1H, d), 3.84 - 3.95 (2H, m), 4.17 (1H, s), 6.63 (1H, s), 7.41 (2H, d), 7.63 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 408; HPLC tR = 2.35 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine

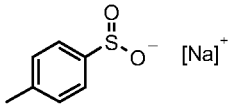


Sodium 4-methylbenzenesulfinate (2.9 g, 16.28 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (5 g, 14.14 mmol), in acetonitrile (150 mL) at RT under a nitrogen atmosphere. The resulting mixture was stirred at 80°C for 3 hours. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with water (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in isohexane, to give the desired material as a beige solid (3.10 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 2.41 (3H, s), 3.14 (1H, td), 3.38 - 3.46 (1H, m), 3.56 (1H, d), 3.71 (1H, d), 3.80 - 3.96 (2H, m), 4.13 (1H, s), 4.60 (2H, s), 6.60 (1H, s), 7.43 (2H, d), 7.66 (2H, d)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 382; HPLC tR = 2.16 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Sodium 4-methylbenzenesulfinate

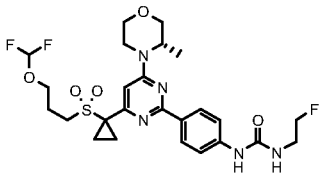
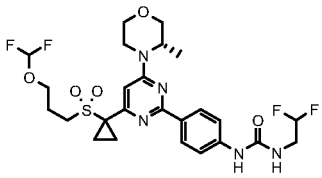
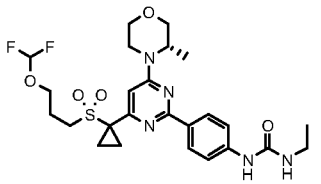
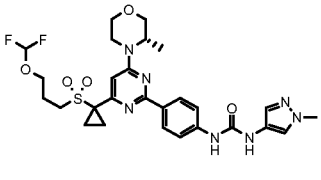


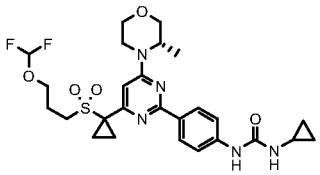
A solution of sodium sulfite (9.92 g, 78.68 mmol) in water (75 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (13.22 g, 157.36 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 1 hour. 4-Methylbenzene-1-sulfonyl chloride (15 g, 78.68 mmol) was added portionwise to the solution and was stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (400 mL). The suspension was allowed to stir at RT for 20 minutes then filtered and the filtrate evaporated to afford the desired material as a white solid, which was air dried overnight under vacuum and used without further purification (17.3 g).

Example 96

The following samples were prepared by heating a mixture of the carbamate (1 equivalent), triethylamine (4 equivalents) and the amine (4 equivalents) in NMP (2 mL) at RT for between 2 –16 hours. The compounds were purified by preparative HPLC.

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (contaminated with phenyl *N*-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]propyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate) and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
96a		1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	572	2.28
96b.		3-(2,2-difluoroethyl)-1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	590	2.32
96c		1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea	554	2.21
96d		1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	606	2.09

Example	Structure	NAME	LCMS MH+	Retention time (min)
96e		3-cyclopropyl-1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	none	

Example 96a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.59 (2H, m), 1.62 - 1.69 (2H, m), 2.09 - 2.18 (2H, m), 3.17 - 3.25 (1H, m), 3.35 - 3.42 (1H, m), 3.43 - 3.52 (2H, m), 3.56 - 3.66 (3H, m), 3.78 (1H, d), 3.94 - 4.02 (3H, m), 4.21 (1H, d), 4.42 (1H, t), 4.52 - 4.60 (2H, m), 6.43 (1H, t), 6.47 - 6.89 (1H, m), 6.77 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.81 (1H, s)

Example 96b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.53 - 1.60 (2H, m), 1.62 - 1.69 (2H, m), 2.08 - 2.17 (2H, m), 3.16 - 3.25 (1H, m), 3.43 - 3.66 (6H, m), 3.76 (1H, d), 3.94 - 4.00 (3H, m), 4.22 (1H, d), 4.56 (1H, s), 5.91 - 6.23 (1H, m), 6.43 - 6.88 (1H, m), 6.52 (1H, t), 6.77 (1H, s), 7.50 (2H, d), 8.21 (2H, d), 8.93 (1H, s)

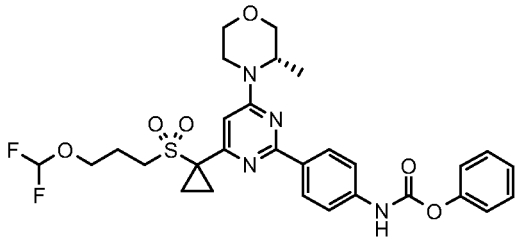
Example 96c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, t), 1.23 (3H, d), 1.54 - 1.60 (2H, m), 1.63 - 1.69 (2H, m), 2.09 - 2.18 (2H, m), 3.07 - 3.25 (3H, m), 3.48 (1H, td), 3.55 - 3.66 (3H, m), 3.76 (1H, d), 3.93 - 4.01 (3H, m), 4.21 (1H, d), 4.56 (1H, s), 6.15 (1H, t), 6.42 - 6.88 (1H, m), 6.76 (1H, s), 7.49 (2H, d), 8.18 (2H, d), 8.66 (1H, s)

Example 96d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.60 (2H, m), 1.63 - 1.69 (2H, m), 2.09 - 2.18 (2H, m), 3.18 - 3.26 (1H, m), 3.44 - 3.53 (1H, m), 3.55 - 3.67 (3H, m), 3.72 - 3.80 (4H, m), 3.93 - 4.03 (3H, m), 4.22 (1H, d), 4.57 (1H, s), 6.43 - 6.86 (1H, m), 6.78 (1H, s), 7.38 (1H, s), 7.54 (2H, d), 7.77 (1H, s), 8.22 (2H, d), 8.37 (1H, s), 8.85 (1H, s)

Example 96e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.38-0.40 (2H,m), 0.61-0.64 (2H,m), 1.20-1.22 (3H,d), 1.51-1.53 (2H,m), 1.61-1.64 (2H,m), 2.18-2.24 (2H,m), 2.52-2.58 (1H,m), 3.18-3.20 (1H,dd), 3.55-3.68 (3H,m), 3.72-3.78 (1H,m), 3.90-3.95 (3H,m), 4.20 (1H,s), 4.55 (1H,s), 6.40 (1H,s), 6.60 (1H,s), 7.45 (2H,d), 8.18 (2H,d), 8.54 (1H,s)

The preparation of phenyl *N*-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

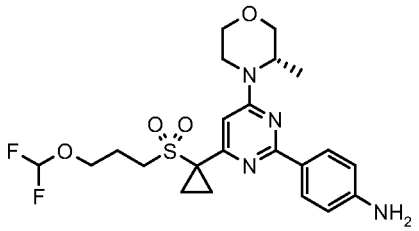


Sodium hydrogen carbonate (65.3 mg, 0.78 mmol) was added to 4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (contaminated with 4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]propyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline) (250 mg, 0.52 mmol) in dioxane (6 mL) at 5ºC under a nitrogen atmosphere. Phenyl chloroformate (0.098 mL, 0.78 mmol) was added and the resulting mixture stirred at RT for 2 hours. The reaction mixture was diluted with DCM (50 mL), the organics dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude material was triturated with a mixture of diethyl ether and isohexane to give the desired material (contaminated with phenyl *N*-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]propyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate) as a cream solid (200 mg). The material was used without further purification.

NMR Spectrum: none

LCMS Spectrum: m/z (ESI+)(M+H)+ = 604; HPLC tR = 2.97 min.

4-[4-[1-[3-(Difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



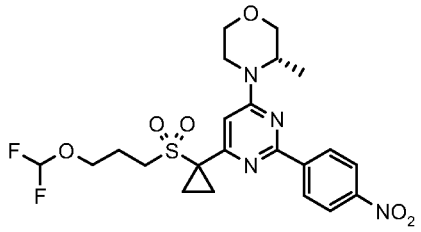
5% Palladium on charcoal (400 mg, 3.6 mmol) was added to 4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]-2-(4-nitrophenyl)pyrimidine (2 g, 3.90 mmol) in ethyl acetate (200 mL) and methanol (30 mL) at RT. The flask was evacuated and the atmosphere replaced with first nitrogen and then hydrogen and the mixture left to stir under hydrogen at RT for 36 hours. The crude product was purified by flash silica chromatography, elution gradient 30 to 90% ethyl acetate in isohexane, to give a white solid (1.7 g) which appears to be the desired material (~30%) contaminated with 4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]propyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (~60%). The material was used without further purification.

NMR Spectrum: none

LCMS Spectrum: m/z (ESI+)(M+H)+ = 483; HPLC tR = 1.76 min.

LCMS Spectrum: (4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]propyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline) m/z (ESI+)(M+H)+ = 485; HPLC tR = 2.0 min.

4-[1-[3-(Difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]-2-(4-nitrophenyl)pyrimidine

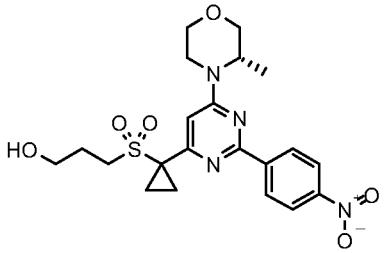


A solution of 2,2-difluoro-2-(fluorosulfonyl)acetic acid (4.56 mL, 44.11 mmol) in acetonitrile (25 mL) was added dropwise over 1.5 hours to a stirred solution of 3-[1-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-(4-nitrophenyl)pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol (3.4g, 7.35 mmol) and copper(I) iodide (280 mg, 1.47 mmol) in acetonitrile (100 mL) at 55°C under a nitrogen atmosphere. The mixture was stirred at 55°C for a further 1 hour then diluted with ethyl acetate (300 mL) and washed with water (100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (2.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.26 (3H, d), 1.59 - 1.64 (2H, m), 1.67 - 1.72 (2H, m), 2.11 - 2.17 (2H, m), 3.22 - 3.28 (1H, m), 3.46 - 3.59 (3H, m), 3.65 (1H, d), 3.78 (1H, d), 3.93 - 4.01 (3H, m), 4.25 (1H, s), 4.61 (1H, s), 6.96 (1H, s), 8.33 (2H, d), 8.55 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 513; HPLC tR = 2.87 min.

3-[1-[6-[(3*S*)-3-Methylmorpholin-4-yl]-2-(4-nitrophenyl)pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol



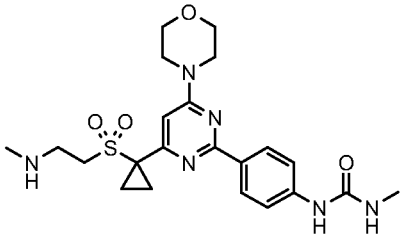
Bis(triphenylphosphine)palladium(II) chloride (0.636 g, 0.91 mmol) was added to 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropoxy-tri(propan-2-yl)silane (7.2 g, 13.53 mmol), 2M aqueous sodium carbonate solution (15 mL, 30.00 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nitrobenzene (6.74 g, 27.06 mmol) in DME (100 mL) and water (5 mL) at RT. The mixture was stirred at 90°C for 16 hours under a nitrogen atmosphere then allowed to cool. The reaction mixture was diluted with ethyl acetate (400 mL), and washed sequentially with water (100 mL) then additional water (200 mL).The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was dissolved in DCM then tetrabutylammonium fluoride (67.6 mL, 67.64 mmol) added and left to stir for 1 hour. A saturated aqueous solution of ammonium chloride was added, the organics separated and dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 10 to 100% ethyl acetate in isohexane, to give crude material which was further purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give the desired material as a brown solid (3.60 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.26 (3H, d), 1.56 - 1.63 (2H, m), 1.66 - 1.70 (2H, m), 1.91 - 1.98 (2H, m), 3.22 - 3.29 (3H, m), 3.47 - 3.57 (3H, m), 3.65 (1H, d), 3.78 (1H, d), 3.99 (1H, dd), 4.25 (1H, d), 4.60 (1H, s), 4.72 (1H, t), 6.96 (1H, s), 8.33 (2H, d), 8.58 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 463; HPLC tR = 2.37 min.

The preparation of 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropoxy-tri(propan-2-yl)silane was described earlier.

Example 97: 3-Methyl-1-[4-[4-[1-(2-methylaminoethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea



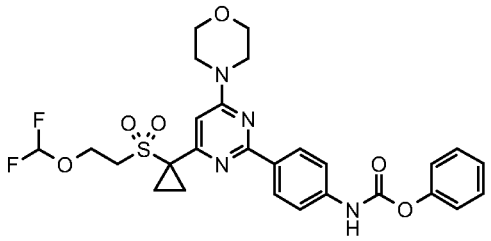
Methylamine (2 M in THF, 4 equivalents) was added to phenyl *N*-[4-[4-[1-[2-(difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate in NMP and resulting solution stirred at RT for 30 minutes then purified by preparative HPLC to give the desired material (0.012 g)

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.52 - 1.57 (2H, m), 1.62 - 1.66 (2H, m), 2.67 (3H, d), 2.92 - 3.01 (2H, m), 3.31 (3H, s), 3.55 - 3.64 (2H, m), 3.72 (8H, s), 6.06 (1H, t), 6.81 (1H, s), 7.50 (2H, d), 8.21 (2H, d), 8.75 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 475; HPLC tR = 1.65 min.

The preparation of phenyl *N*-[4-[4-[1-[2-(difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[2-(difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate

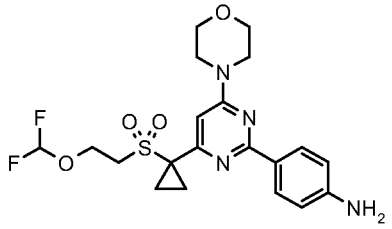


Sodium hydrogen carbonate (1.5 equivalents) was added to 4-[4-[1-[2-(difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline (1 equivalent) in dioxane at 5°C under nitrogen. Phenyl chloroformate (1.5 equivalents) was then added. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with DCM, the organics dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of ethyl acetate and isohexane to give the desired material as a cream solid.

NMR Spectrum: none

LCMS Spectrum: m/z (ESI+) (M+H)+ = 575; HPLC tR = 2.8 min.

4-[4-[1-[2-(Difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline

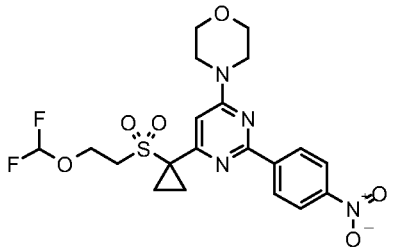


Palladium, 5% On Charcoal (6.59 mg, 0.06 mmol) was added to 4-[1-[2-(difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-yl-2-(4-nitrophenyl)pyrimidine (150 mg, 0.31 mmol), in ethyl acetate (20 mL) and methanol (3 mL) at RT and left to stir under an atmosphere of hydrogen for 24 hours. The mixture was filtered through celite® and the filtrate purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give the desired material as a yellow gum (90 mg).

NMR Spectrum: none

LCMS Spectrum: m/z (ESI+) (M+H)+ = 455; HPLC tR = 2.2 min.

4-[1-[2-(Difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-yl-2-(4-nitrophenyl)pyrimidine

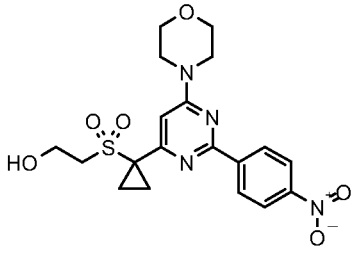


A solution of 2,2-difluoro-2-(fluorosulfonyl)acetic acid (0.856 mL, 8.29 mmol) in acetonitrile (4 mL) was added dropwise over 1 hour to a stirred solution of 2-[1-[6-morpholin-4-yl-2-(4-nitrophenyl)pyrimidin-4-yl]cyclopropyl]sulfonylethanol (480 mg, 1.10 mmol) and copper(I) iodide (742 mgl, 0.22 mmol) in acetonitrile (15 mL) at 55°C under a nitrogen atmosphere. The mixture was stirred at 55°C for 90 minutes, allowed to cool and diluted with ethyl acetate (300 mL) and washed with water (100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (195 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.59 - 1.68 (2H, m), 1.70 - 1.78 (2H, m), 3.70 - 3.81 (8H, m), 3.88 - 3.96 (2H, m), 4.28 - 4.35 (2H, m), 7.01 (1H, s), 8.33 (2H, d), 8.56 (2H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 485; HPLC tR = 2.73 min.

2-[1-[6-Mrpholin-4-yl-2-(4-nitrophenyl)pyrimidin-4-yl]cyclopropyl]sulfonylethanol



Bis(triphenylphosphine)palladium(II) chloride (84 mg, 0.12 mmol) was added to 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane (900 mg, 1.79 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nitrobenzene (889 mg, 3.57 mmol) and 2M aqueous solution of sodium carbonate (3 mL, 6.00 mmol) in a solvent mixture of DME (25 mL) and water (1 mL). The mixture was stirred at 90°C for 18 hours

under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was dissolved in DCM then 1M solution of tetrabutylammonium fluoride (8.93 mL, 8.93 mmol) added and left to stir 1 hour. A saturated aqueous solution of ammonium chloride was added, the layers separated and the organics dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give a material which was further purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, and finally triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (670 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.53 - 1.62 (2H, m), 1.65 - 1.73 (2H, m), 3.56 - 3.67 (2H, m), 3.66 - 3.82 (8H, m), 3.80 - 3.97 (2H, m), 5.01 (1H, t), 7.01 (1H, s), 8.34 (2H, d), 8.57 (2H, d)

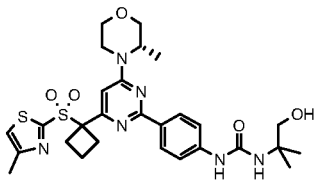
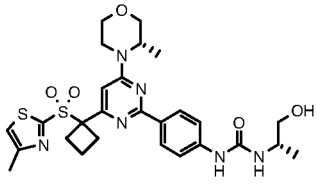
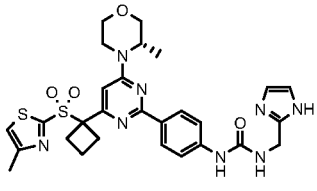
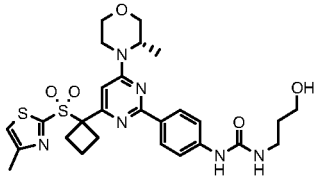
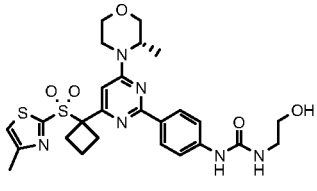
LCMS Spectrum: m/z (ESI+) (M+H)+ = 435; HPLC tR = 2.18 min.

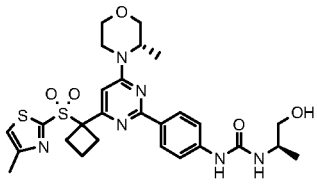
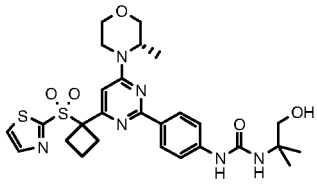
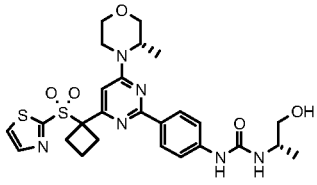
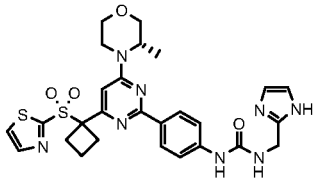
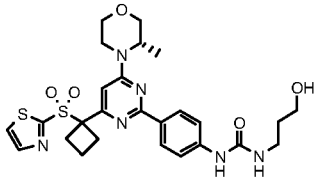
The preparation of 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane was described earlier.

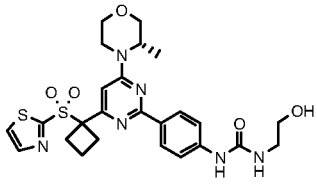
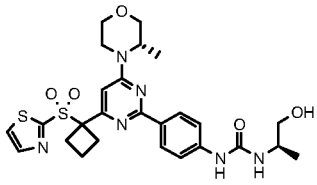
Example 98

The following samples were prepared by heating a mixture of the carbamate (1 equivalent), triethylamine (4 equivalents) and the amine (4 equivalents) in NMP (2 mL) at 50°C for 2 hours. The compounds were purified by preparative HPLC.

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
98a		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea	601	2.49
98b		3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea	587	2.25
98c		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea	609	2.22
98d		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea	587	2.18
98e		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea	573	2.14

Example	Structure	NAME	LCMS MH+	Retention time (min)
98f		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea	587	2.24
98g		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea	587	2.41
98h		3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea	573	2.20
98i		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea	595	2.17
98j		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea	573	2.13

Example	Structure	NAME	LCMS MH+	Retention time (min)
98k		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea	559	2.09
98l		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea	573	2.18

Example 98a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.24 (6H, s), 1.83 - 2.01 (1H, m), 2.12 - 2.20 (1H, m), 2.37 (3H, s), 2.83 - 2.92 (2H, m), 3.10 - 3.22 (4H, m), 3.36 - 3.41 (1H, m), 3.49 (1H, td), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.13 (1H, d), 4.48 (1H, s), 4.95 (1H, t), 5.99 (1H, s), 6.54 (1H, s), 7.36 (2H, d), 7.68 (1H, s), 7.86 (2H, d), 8.71 (1H, s)

Example 98b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.21 (3H, d), 1.88 - 1.99 (1H, m), 2.12 - 2.21 (1H, m), 2.82 - 2.92 (2H, m), 3.10 - 3.23 (2H, m), 3.31 (3H, s), 3.32 - 3.42 (3H, m), 3.44 - 3.54 (1H, m), 3.61 - 3.78 (3H, m), 3.97 (1H, d), 4.09 - 4.17 (1H, m), 4.49 (1H, s), 4.78 (1H, t), 6.08 (1H, d), 6.54 (1H, s), 7.39 (2H, d), 7.68 (1H, s), 7.87 (2H, d), 8.68 (1H, s)

Example 98c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.89 - 1.99 (1H, m), 2.11 - 2.20 (1H, m), 2.37 (3H, s), 2.85 - 2.95 (2H, m), 3.10 - 3.22 (3H, m), 3.43 - 3.54 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.14 (1H, d), 4.33 (2H, s), 4.50 (1H, s), 6.53 - 6.63 (2H, m), 6.93 - 7.05 (1H, m), 7.43 (2H, d), 7.68 (1H, s), 7.85 - 7.93 (2H, m), 8.90 (1H, s)

Example 98d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.56 - 1.63 (2H, m), 1.86 - 1.97 (2H, m), 2.12 - 2.22 (2H, m), 2.77 - 2.92 (2H, m), 3.13 - 3.22 (3H, m), 3.25 - 3.34 (2H, m), 3.43 - 3.52 (3H, m), 3.64 (1H, d), 3.72 - 3.80 (1H, m), 3.97 (1H, d), 4.13 (1H, d), 4.44 - 4.53 (2H, m), 6.18 (1H, t), 6.54 (1H, s), 7.41 (2H, d), 7.68 (1H, s), 7.87 (2H, d), 8.68 (1H, s)

Example 98e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.87 - 1.97 (1H, m), 2.15 - 2.21 (1H, m), 2.37 (3H, s), 2.79 - 2.94 (2H, m), 3.12 - 3.21 (3H, m), 3.27 - 3.34 (2H, m), 3.42 - 3.52 (3H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.13 (1H, d), 4.49 (1H, s), 4.72 (1H, t), 6.24 (1H, t), 6.54 (1H, s), 7.40 (2H, d), 7.68 (1H, s), 7.87 (2H, d), 8.78 (1H, s)

Example 98f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.21 (3H, d), 1.87 - 1.99 (1H, m), 2.12 - 2.23 (1H, m), 2.37 (3H, s), 2.83 - 2.92 (2H, m), 3.12 - 3.23 (4H, m), 3.34 - 3.41 (1H, m), 3.45 - 3.52 (1H, m), 3.64 (1H, d), 3.75 (1H, d), 3.97 (1H, d), 4.13 (1H, d), 4.50 (1H, s), 4.78 (1H, t), 6.05 - 6.10 (1H, m), 6.54 (1H, s), 7.40 (2H, d), 7.68 (1H, s), 7.87 (2H, d), 8.68 (1H, s)

Example 98g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.25 (6H, s), 1.90 - 1.99 (1H, m), 2.14 - 2.21 (1H, m), 2.84 - 2.93 (2H, m), 3.17 - 3.25 (2H, m), 3.29 - 3.33 (1H, m), 3.45 - 3.52 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.13 (1H, d), 4.48 (1H, s), 4.95 (1H, t), 5.99 (1H, s), 6.53 (1H, s), 7.35 (2H, d), 7.83 (2H, d), 8.15 (1H, s), 8.70 (1H, s)

Example 98h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.20 (3H, d), 1.91 - 2.00 (1H, m), 2.13 - 2.22 (1H, m), 2.85 - 2.95 (2H, m), 3.14 - 3.21 (2H, m), 3.30 - 3.42 (4H, m), 3.44 - 3.52 (1H, m), 3.64 - 3.78 (2H, m), 3.96 (1H, d), 4.13 (1H, d), 4.49 (1H, s), 4.78 (1H, t), 6.06 - 6.13 (1H, m), 6.53 (1H, s), 7.38 (2H, d), 7.85 (2H, d), 8.14 (1H, s), 8.67 (1H, s)

Example 98i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.93 - 2.00 (1H, m), 2.13 - 2.20 (1H, m), 2.83 - 2.93 (2H, m), 3.14 - 3.24 (3H, m), 3.43 - 3.53 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.96 (1H, d), 4.15 (1H, d), 4.32 (2H, s), 4.48 (1H, s), 6.54 (1H, s), 6.63 (1H, t), 6.93 (1H, s), 7.42 (2H, d), 7.87 (2H, d), 8.14 (1H, s), 8.90 (1H, s)

Example 98j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.56 - 1.63 (2H, m), 1.88 - 2.01 (1H, m), 2.09 - 2.22 (1H, m), 2.84 - 2.94 (2H, m), 3.12 - 3.24 (5H, m), 3.43 - 3.54 (3H, m), 3.65 (1H, d), 3.76 (1H, d), 3.95 (1H, d), 4.06 - 4.20 (1H, m), 4.46 - 4.51 (1H, m), 6.19 (1H, t), 6.53 (1H, s), 7.39 (2H, d), 7.85 (2H, d), 8.15 (1H, s), 8.67 (1H, s)

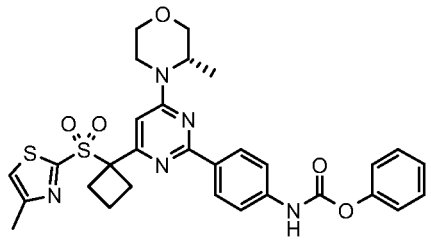
Example 98k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.90 - 2.00 (1H, m), 2.12 - 2.22 (1H, m), 2.84 - 2.94 (2H, m), 3.14 - 3.22 (3H, m), 3.25 - 3.34 (2H, m), 3.39 - 3.52 (3H, m), 3.63 (1H, d), 3.76 (1H, d), 3.96 (1H, d), 4.13 (1H, d), 4.48 (1H, s), 4.72 (1H, t), 6.24 (1H, t), 6.53 (1H, s), 7.39 (2H, d), 7.85 (2H, d), 8.15 (1H, s), 8.76 (1H, s)

Example 98l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.20 (3H, d), 1.89 - 1.98 (1H, m), 2.12 - 2.23 (1H, m), 2.80 - 2.93 (2H, m), 3.14 - 3.24 (3H, m), 3.30 - 3.40 (2H, m),

3.45 - 3.53 (1H, m), 3.60 - 3.77 (3H, m), 3.96 (1H, d), 4.13 (1H, d), 4.49 (1H, s), 4.78 (1H, t), 6.08 (1H, d), 6.53 (1H, s), 7.38 (2H, d), 7.85 (2H, d), 8.15 (1H, s), 8.67 (1H, s)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]carbamate

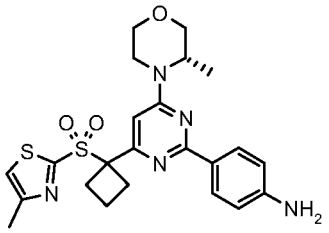


Sodium hydrogen carbonate (0.311 g, 3.71 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]aniline (1.2 g, 2.47 mmol) in dioxane (30 mL) at 5°C under nitrogen. Phenyl chloroformate (0.466 mL, 3.71 mmol) was then added and the resulting mixture stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (75 mL) and the organic layer dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (1.2 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.88 - 2.00 (1H, m), 2.10 - 2.21 (1H, m), 2.36 (3H, s), 2.83 - 2.95 (2H, m), 3.10 - 3.24 (3H, m), 3.44 - 3.53 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.15 (1H, d), 4.52 (1H, s), 6.59 (1H, s), 7.21 - 7.32 (3H, m), 7.39 - 7.47 (2H, m), 7.55 (2H, d), 7.68 (1H, s), 7.97 (2H, d), 10.39 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 606; HPLC tR = 3.12 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]aniline

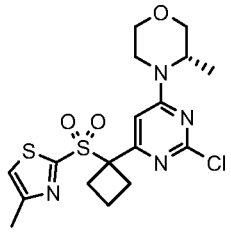


Bis(triphenylphosphine)palladium(II) chloride (0.115 g, 0.16 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidine (1.4 g, 3.26 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.073 g, 4.90 mmol) and 2M aqueous odium carbonate solution (5 mL, 10.00 mmol) in a solvent mixture of DMF (6 mL), DME (12 mL), ethanol (3 mL) and water (3.5 mL) and the resulting mixture stirred at 95°Cfor 5 hours under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (250 mL), and washed with water (2 x 150 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 60% ethyl acetate in isohexane, to give the desired material as a beige solid (1.17 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.92 (1H, m), 1.99 (1H, s), 2.10 - 2.18 (1H, m), 2.39 (3H, s), 2.80 - 2.91 (2H, m), 3.09 - 3.24 (2H, m), 3.47 (1H, td), 3.62 (1H, d), 3.75 (1H, d), 3.95 (1H, d), 4.09 (1H, d), 4.45 (1H, s), 5.50 (2H, s), 6.43 (1H, s), 6.54 (2H, d), 7.61 - 7.80 (3H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 486; HPLC tR = 2.51 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidine



Tetrabutylammonium bromide (0.912 g, 2.83 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (11 g, 28.29

mmol), 1,3-dibromopropane (17.23 mL, 169.71 mmol) and sodium hydroxide solution (50% w/w) (30 mL) in toluene (200 mL) and the resulting mixture stirred at 35°C for 2.5 hours under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, to give the desired material as a yellow gum (1.7 g).

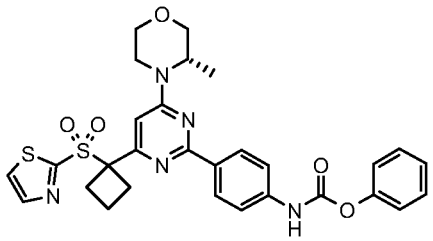
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.88 (1H, s), 1.18 (3H, d), 1.85 - 1.97 (1H, m), 2.04 - 2.18 (1H, m), 2.70 - 2.85 (2H, m), 3.00 - 3.21 (3H, m), 3.29 (3H, s), 3.37 - 3.49 (1H, m), 3.57 (1H, d), 3.71 (1H, d), 3.86 - 4.01 (2H, m), 4.34 (1H, s), 6.59 (1H, s) 7.91(1H,s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 429; HPLC tR = 2.36 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]carbamate



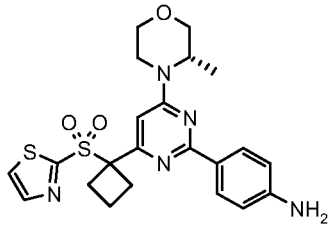
Sodium hydrogen carbonate (0.267 g, 3.18 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]aniline (1 g, 2.12 mmol) in dioxane (30 mL) at 5°C under nitrogen .Phenyl chloroformate (0.4 mL, 3.18 mmol) was then added. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude gum

was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (0.80 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.89 - 2.01 (1H, m), 2.12 - 2.22 (1H, m), 2.84 - 2.97 (2H, m), 3.11 - 3.26 (3H, m), 3.44 - 3.54 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.15 (1H, d), 4.50 (1H, s), 6.57 (1H, s), 7.15 - 7.35 (3H, m), 7.38 - 7.48 (2H, m), 7.49 - 7.60 (2H, m), 8.15 (2H, s), 10.39 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 592; HPLC tR = 3.06 min.

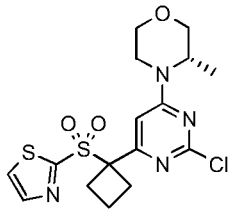
4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]aniline



Bis(triphenylphosphine)palladium(II) chloride (0.093 g, 0.13 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidine (1.1 g, 2.65 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.871 g, 3.98 mmol) and 2M aqueous sodium carbonate solution (5 mL, 10.00 mmol) in a solvent mixture of DMF (6 mL), DME (12 mL), ethanol (3 mL) and water (3.5 mL) and the resulting mixture stirred at 95°Cfor 5 hours under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (250 mL), and washed with water (2 x 150 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 70% ethyl acetate in isohexane, to give the desired material as a yellow solid (0.99 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.88 - 1.96 (1H, m), 2.11 - 2.21 (1H, m), 2.82 - 2.91 (2H, m), 3.05 - 3.23 (3H, m), 3.47 (1H, td), 3.62 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.10 (1H, s), 4.44 (1H, s), 5.50 (2H, s), 6.42 (1H, s), 6.51 (2H, d), 7.70 (2H, d), 8.15 (2H, s)

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidine



Tetrabutylammonium bromide (0.559 g, 1.73 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfonylmethyl)pyrimidine (6.5 g, 17.34 mmol), 1,3-dibromopropane (10.56 mL, 104.04 mmol) and sodium hydroxide (50% w/w) (10 mL) in toluene (20 mL) and the resulting mixture stirred at 70°C for 30 minutes. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 60% ethyl acetate in isohexane, to give the desired material as a yellow gum (1.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.86 - 1.97 (1H, m), 2.07 - 2.18 (1H, m), 2.72 - 2.84 (2H, m), 3.04 - 3.19 (3H, m), 3.42 (1H, td), 3.57 (1H, d), 3.70 (1H, d), 3.89 - 3.99 (2H, m), 4.33 (1H, s), 6.60 (1H, s), 8.19 (1H, d), 8.30 (1H, d)

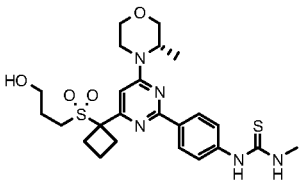
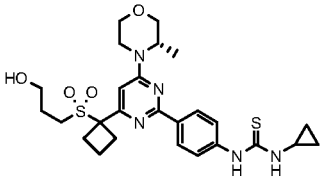
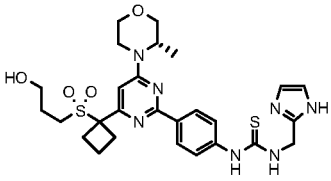
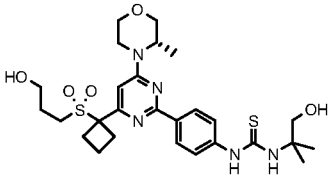
The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfonylmethyl)pyrimidine was described earlier.

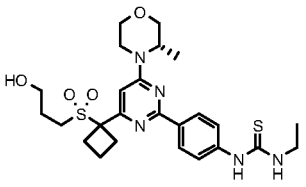
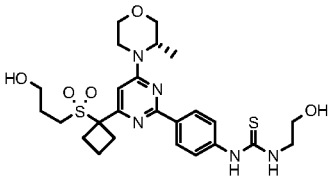
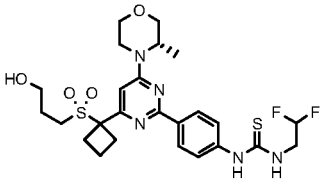
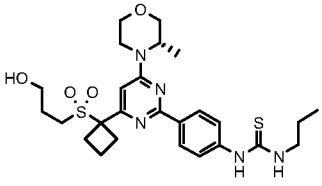
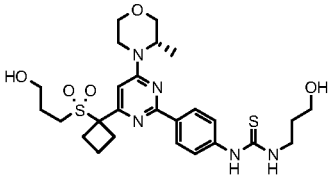
Example 99

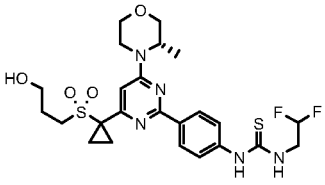
The following samples were prepared by heating a mixture of the aniline (1 equivalent) and 1,1 thiocarbonyldiimidazole (1.2 equivalents) in a mixture of DCM:THF (2:1) at RT for 30 minutes then adding the amine (5 equivalents) and stirring at 50°C for 2 hours. The compounds were purified by preparative HPLC.

The following compounds were prepared in an analogous fashion from either 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclobutyl]sulfonylpropan-1-

ol or 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
99a		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea	520	1.92
99b		3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	546	2.07
99c		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea	586	1.83
99d		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	578	2.02

Example	Structure	NAME	LCMS MH+	Retention time (min)
99e		1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	534	2.07
99f		3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	550	1.75
99g		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	570	2.21
99h		3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylthiourea	548	2.38
99i		3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	564	1.91

Example	Structure	NAME	LCMS MH+	Retention time (min)
99j		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	556	2.06

Example 99a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.73 - 1.81 (2H, m), 1.88 - 1.97 (1H, m), 2.03 - 2.10 (1H, m), 2.76 - 2.87 (2H, m), 2.89 - 3.05 (7H, m), 3.19 - 3.26 (1H, m), 3.36 - 3.41 (2H, m), 3.46 - 3.55 (1H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.23 (1H, d), 4.52 - 4.61 (2H, m), 6.76 (1H, s), 7.55 (2H, d), 7.85 (1H, s), 8.28 (2H, d), 9.73 (1H, s)

Example 99b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.56 - 0.64 (2H, m), 0.73 - 0.80 (2H, m), 1.25 (3H, d), 1.72 - 1.81 (2H, m), 1.88 - 1.96 (1H, m), 2.03 - 2.10 (1H, m), 2.80 - 3.04 (6H, m), 3.17 - 3.26 (1H, m), 3.34 - 3.41 (2H, m), 3.45 - 3.57 (1H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.23 (1H, d), 4.49 - 4.64 (2H, m), 6.76 (1H, s), 7.59 - 7.66 (2H, m), 7.96 (1H, s), 8.28 (2H, d), 9.51 (1H, s)

Example 99c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.73 - 1.82 (2H, m), 1.89 - 1.97 (1H, m), 2.04 - 2.11 (1H, m), 2.78 - 2.88 (2H, m), 2.92 - 2.99 (2H, m), 2.98 - 3.05 (2H, m), 3.20 - 3.26 (1H, m), 3.34 - 3.42 (2H, m), 3.46 - 3.57 (1H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.04 - 4.10 (1H, m), 4.25 (1H, d), 4.54 - 4.63 (2H, m), 4.71 (2H, s), 6.76 (1H, s), 6.99 (2H, s), 7.69 (2H, d), 8.21 (1H, s), 8.29 (2H, d), 10.03 (1H, s)

Example 99d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.45 (6H, s), 1.73 - 1.80 (2H, m), 1.87 - 1.95 (1H, m), 2.03 - 2.10 (1H, m), 2.79 - 2.87 (2H, m), 2.92 - 2.98 (2H, m), 2.97 - 3.05 (2H, m), 3.20 - 3.24 (1H, m), 3.35 - 3.42 (2H, m), 3.48 - 3.57 (3H, m), 3.66 (1H, d), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.03 - 4.09 (1H, m), 4.25 (1H, d), 4.52 - 4.62 (2H, m), 6.75 (1H, s), 7.61 (2H, d), 8.27 (2H, d), 9.92 (1H, s)

Example 99e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, t), 1.24 (3H, d), 1.72 - 1.82 (2H, m), 1.88 - 1.98 (1H, m), 2.01 - 2.11 (1H, m), 2.76 - 2.87 (2H, m), 2.89 - 2.98 (2H, m), 2.98 - 3.06 (2H, m), 3.21 - 3.27 (1H, m), 3.35 - 3.42 (2H, m), 3.46 - 3.56 (3H, m), 3.66 (1H,

d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.52 - 4.62 (2H, m), 6.75 (1H, s), 7.57 (2H, d), 7.89 (1H, s), 8.28 (2H, d), 9.63 (1H, s)

Example 99f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.73 - 1.81 (2H, m), 1.86 - 1.97 (1H, m), 2.02 - 2.12 (1H, m), 2.79 - 2.87 (2H, m), 2.92 - 2.99 (2H, m), 2.97 - 3.05 (2H, m), 3.20 - 3.28 (1H, m), 3.35 - 3.43 (2H, m), 3.47 - 3.60 (3H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.25 (1H, d), 4.50 - 4.63 (2H, m), 4.81 (1H, s), 6.75 (1H, s), 7.63 (2H, d), 7.88 (1H, s), 8.28 (2H, d), 9.81 (1H, s)

Example 99g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 10.01 (1H, s), 8.31 (2H, d), 8.12 (1H, s), 7.59 (2H, d), 6.77 (1H, s), 6.39 - 6.03 (1H, m), 4.64 - 4.54 (2H, m), 4.25 (1H, d), 4.05 - 3.94 (3H, m), 3.77 (1H, d), 3.66 (1H, d), 3.56 - 3.46 (1H, m), 3.42 - 3.36 (2H, m), 3.27 - 3.19 (1H, m), 3.05 - 2.98 (2H, m), 2.98 - 2.91 (2H, m), 2.89 - 2.79 (2H, m), 2.12 - 1.98 (1H, m), 1.97 - 1.87 (1H, m), 1.81 - 1.73 (2H, m), 1.25 (3H, d)

Example 99h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 10.01 (1H, s), 8.31 (2H, d), 8.12 (1H, s), 7.59 (2H, d), 6.77 (1H, s), 6.39 - 6.03 (1H, m), 4.64 - 4.54 (2H, m), 4.25 (1H, d), 4.05 - 3.94 (3H, m), 3.77 (1H, d), 3.66 (1H, d), 3.56 - 3.46 (1H, m), 3.42 - 3.36 (2H, m), 3.27 - 3.19 (1H, m), 3.05 - 2.98 (2H, m), 2.98 - 2.91 (2H, m), 2.89 - 2.79 (2H, m), 2.12 - 1.98 (1H, m), 1.97 - 1.87 (1H, m), 1.81 - 1.73 (2H, m), 1.25 (3H, d)

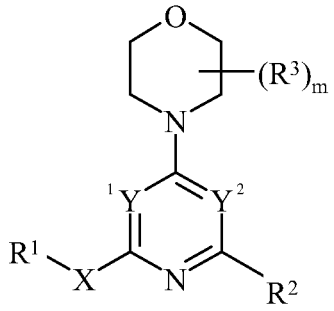
Example 99i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.69 - 1.80 (4H, m), 1.88 - 1.98 (1H, m), 2.03 - 2.09 (1H, m), 2.78 - 2.89 (2H, m), 2.90 - 2.97 (2H, m), 2.98 - 3.05 (2H, m), 3.17 - 3.25 (1H, m), 3.35 - 3.42 (2H, m), 3.46 - 3.59 (5H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.25 (1H, d), 4.52 - 4.61 (2H, m), 6.75 (1H, s), 7.58 (2H, d), 7.90 (1H, s), 8.28 (2H, d), 9.69 (1H, s)

Example 99j: Spectrum not recorded.

The preparations of 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclobutyl]sulfonylpropan-1-ol and 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol were described earlier.

CLAIMS

1. A compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}Y and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, and $-S(O)_2NR^4CR^6R^7-$;

R^1 is a group selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $-NR^9SO_2R^{10}$;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ and $-NR^{13}SO_2R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or R^1 and R^4 together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is

optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, **R^{14}**, **R^{15}** and **R^{16}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or **R^{18}** and **R^{19}** together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-}

$_{6}$alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

2. A compound, or a pharmaceutically acceptable salt thereof, according to claim 1, wherein

m is 0, 1 or 2;

^{1}Y and **Y^{2}** are independently N or CR^{8} provided that one of ^{1}Y and Y^{2} is N and the other is CR^{8};

X is a linker group selected from $-NR^{4}CR^{6}R^{7}-$, $-OCR^{6}R^{7}-$, $-SCR^{6}R^{7}-$, $-S(O)CR^{6}R^{7}-$, $-S(O)_{2}CR^{6}R^{7}-$, $-C(O)NR^{4}CR^{6}R^{7}-$, $-NR^{4}C(O)CR^{6}R^{7}-$, $-NR^{4}C(O)NR^{5}CR^{6}R^{7}-$ and $-S(O)_{2}NR^{4}CR^{6}R^{7}$;

R^{1} is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^{9}, $-OR^{9}$, $-COR^{9}$, $-CONR^{9}R^{10}$, $-NR^{9}R^{10}$ and $-NR^{9}COR^{10}$;

or **X-R^{1}** is $-CR^{6}R^{7}OH$;

R^{2} is a group selected from carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_{2}R^{11}$, $-COR^{11}$, $-CO_{2}R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_{2}R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each R^{3}, when present, is selected from cyano, R^{13}, and $-CONR^{13}R^{14}$;

R^{4} and **R^{5}** are independently hydrogen or C_{1-6}alkyl;

or, when **X** is $-NR^{4}CR^{6}R^{7}-$, $-NR^{4}C(O)CR^{6}R^{7}-$ or $-NR^{4}C(O)NR^{5}CR^{6}R^{7}-$, **$R^{1}$** and **$R^{4}$** together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{13} and R^{14} are independently hydrogen or a C_{1-3}alkyl which is optionally substituted by one or more substituent groups selected from halo, cyano, hydroxy and C_{1-3}alkoxy; and

R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

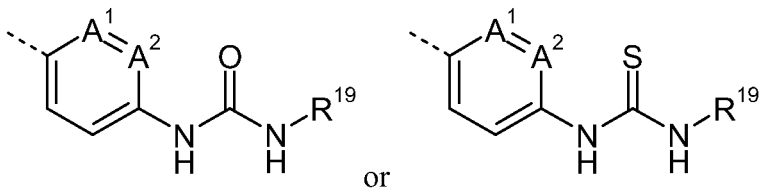
or **R**[18] and **R**[19] together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

3. A compound, or a pharmaceutically acceptable salt thereof, according to claim 1 or 2 wherein ^{1}Y is CH and Y^{2} is N.

4 A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 wherein **X** is a -$S(O)_2CR^6R^7$- linker group

5. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 4 wherein R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, imidazolyl, pyrrolidinyl, thiadiazolyl, thiazolyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -$NHCOCH_3$, -$CONH_2$ and -$CONHCH_3$.

6. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5 wherein R^2 is

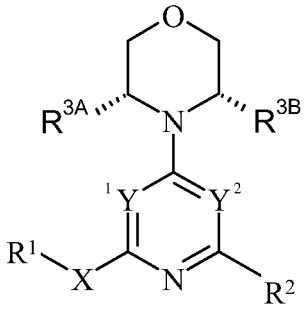


wherein A^1 and A^2 are selected from CH or N provided that at least one of A^1 or A^2 is CH

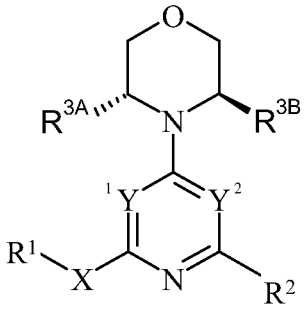
7. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6 wherein R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, imidazoylmethyl, isoxazolyl, pyrazolyl, pyrazolylmethyl, pyridinyl and pyrimidinyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

8. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7 wherein **R^6** and **R^7** together with the carbon atom to which they are attached form a 3- to 5-membered carbocyclic ring

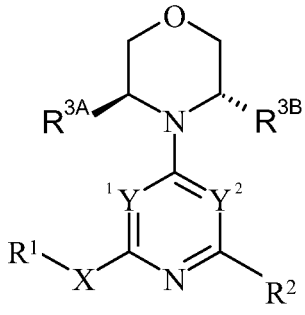
9. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

where

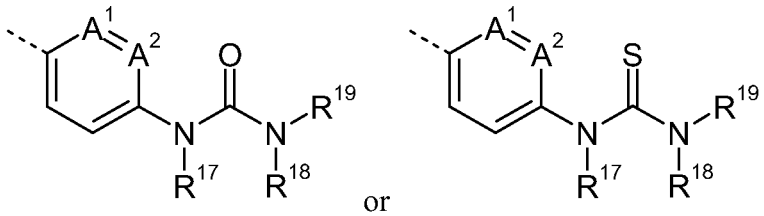
X is a $-S(O)_2CR^6R^7-$ linker group;

^1Y is CH and **Y^2** is N;

R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2CH_2NHMe$,

phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-fluoro-4-methylaminophenyl, 4-fluoro-2-methylphenyl, 5-fluoro-2-methylphenyl, 3-fluoro-4-(2-hydroxyethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-carbamoyl-2-chlorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-4-methylaminophenyl, 3-chloro-4-ethylaminophenyl, 3-chloro-4-(2-fluoroethylamino)phenyl, 3-chloro-4-(2-hydroxyethylamino)phenyl, 2-chloro-4-cyanophenyl, 4-cyanophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-(trifluoromethyl)phenyl, 2-methylphenyl, 4-methylphenyl, 4-(2-hydroxyethylamino)phenyl, 1H-imidazol-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 1-(difluoromethyl)pyrazol-4-yl, 1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl, 1,3-dimethylpyrazol-4-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, 5-fluoropyridin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2,4-dimethylthiazol-5-yl, 5-methyl-1,3,4-thiadiazol-2-yl, terahydrofuran-3-yl and terahydropyran-4-yl;

$\mathbf{R^2}$ is



or

wherein $\mathbf{A^1}$ and $\mathbf{A^2}$ are CH;

$\mathbf{R^{17}}$ is hydrogen;

$\mathbf{R^{18}}$ is hydrogen; and

$\mathbf{R^{19}}$ is is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, i-butyl, t-butyl, cyclopropyl, cyclobutyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, $-CH_2CO_2H$, 1-(methyl)cyclopropyl, $-CH_2$(1-hydroxycyclopropyl), 1-(hydroxymethyl)cyclopropyl, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 4-

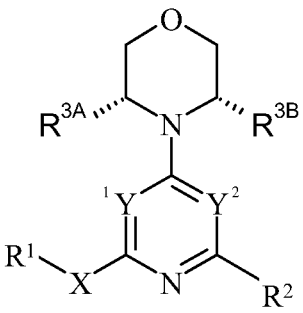
fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, -CH_2CH_2(pyrrolidin-1-yl),-CH_2(imidazol-2-yl), 1-methylimidazol-4-yl, oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 1,1-dioxothiolan-3-yl, 5-methylisoxazol-3-yl, -CH_2(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, -CH_2(1-methylpyrazol-4-yl), 5-methylpyrazin-2-yl, -CH_2(2H-1,2,4-triazol-3-yl), 6-methoxypryridin-3-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl and 1-methylpyrazol-3-yl;

R^6 and **R^7** together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

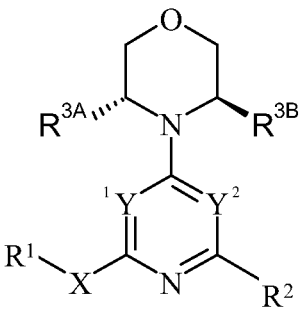
when **R^{3A}** is hydrogen, **R^{3B}** is hydrogen, methyl, ethyl, hydroxymethyl, dimethylcarbamoyl or carbamoyl; or

when **$R^{3'}$** is methyl, **R^3** is methyl.

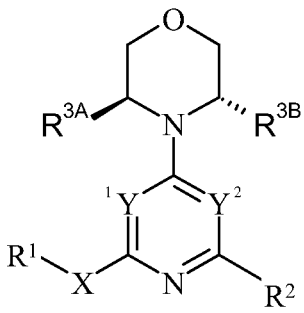
10. A compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

where

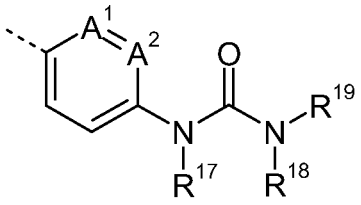
X is a -$S(O)_2CR^6R^7$- linker group;

^1Y is CH and **Y^2** is N;

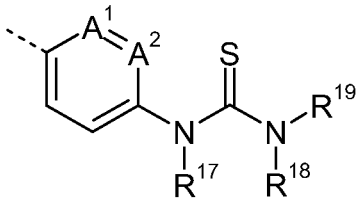
R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2C(OH)(CH_3)_2$, -$CH_2CH_2CH_2OCHF_2$, -$CH_2CH_2OCH_3$, -$CH_2CH_2NHC(O)CH_3$, -CH_2CH_2NHMe, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-fluoro-4-methylaminophenyl, 4-fluoro-2-methylphenyl, 5-fluoro-2-methylphenyl, 3-fluoro-4-(2-hydroxyethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-carbamoyl-2-chlorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3-chloro-4-fluorophenyl,

3-chloro-4-methylaminophenyl, 3-chloro-4-ethylaminophenyl, 3-chloro-4-(2-fluoroethylamino)phenyl, 3-chloro-4-(2-hydroxyethylamino)phenyl, 2-chloro-4-cyanophenyl, 4-cyanophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-methylphenyl, 4-methylphenyl, 1H-imidazol-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 1-(difluoromethyl)pyrazol-4-yl, 1,3-dimethylpyrazol-4-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2,4-dimethylthiazol-5-yl and 5-methyl-1,3,4-thiadiazol-2-yl;

$\mathbf{R^2}$ is



or



wherein $\mathbf{A^1}$ and $\mathbf{A^2}$ are CH;

$\mathbf{R^{17}}$ is hydrogen;

$\mathbf{R^{18}}$ is hydrogen; and

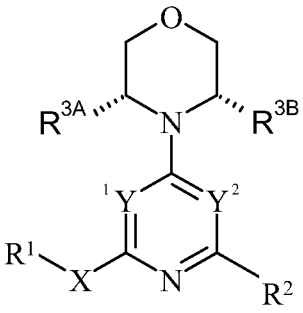
$\mathbf{R^{19}}$ is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, cyclopropyl, cyclobutyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CN$, $-CH_2$(1-hydroxycyclopropyl), 1-(hydroxymethyl)cyclopropyl, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, $-CH_2CH_2$(pyrrolidin-1-yl),$-CH_2$(imidazol-2-yl), 1-methylimidazol-4-yl, oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, 6-methoxypryridin-3-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl and 1-methylpyrazol-3-yl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

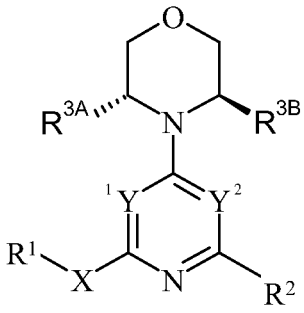
when $\mathbf{R^{3A}}$ is hydrogen, $\mathbf{R^{3B}}$ is hydrogen, methyl or ethyl; or

when $\mathbf{R^{3A}}$ is methyl, $\mathbf{R^{3B}}$ is methyl.

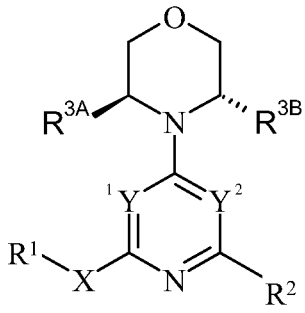
11. A compound according to claim 10, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

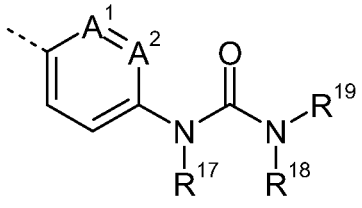
where

X is a $-S(O)_2CR^6R^7-$ linker group;

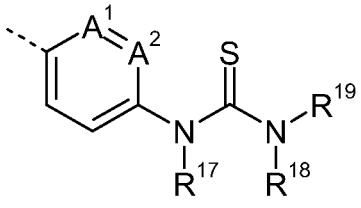
^{1}**Y** is CH and **Y^2** is N;

R^1 is a group selected from methyl, ethyl, cyclopropyl, $-CH_2CH_2CH_2OH$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 5-fluoropyridin-2-yl, pyridin-2-yl, thiazol-2-yl and 4-methylthiazol-2-yl;

R^2 is



or



wherein **A^1** and **A^2** are CH;

R^{17} is hydrogen;

R^{18} is hydrogen; and

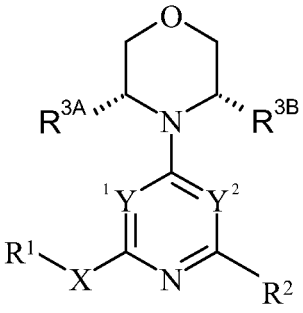
R^{19} is a group selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, $-CH_2$(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, thiazol-2-yl and 1,2,4-thiadiazol-5-yl;

R^6 and **R^7** together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

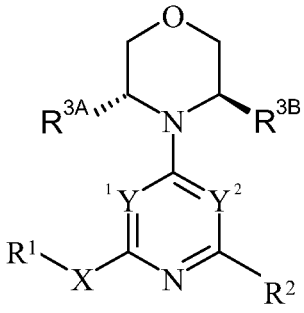
when **R^{3A}** is hydrogen, **R^{3B}** is hydrogen, methyl or ethyl; or

when $\mathbf{R^{3A}}$ is methyl, $\mathbf{R^{3B}}$ is methyl.

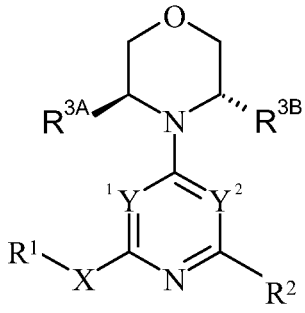
12. A compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (Ia), (Ib) or (Ic)



(IA)



(IB)



(IC)

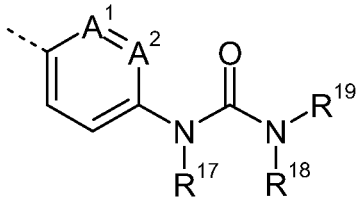
or a pharmaceutically acceptable salt thereof;

X is a $-S(O)_2CR^6R^7-$ linker group;

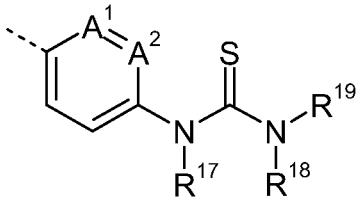
^{1}**Y** is CH and $\mathbf{Y^2}$ is N;

$\mathbf{R^1}$ is a group selected from methyl, ethyl, cyclopropyl, $-CH_2CH_2CH_2OH$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 5-fluoropyridin-2-yl, pyridin-2-yl, thiazol-2-yl and 4-methylthiazol-2-yl;

$\mathbf{R^2}$ is



or



wherein $\mathbf{A^1}$ and $\mathbf{A^2}$ are CH;

$\mathbf{R^{17}}$ is hydrogen;

$\mathbf{R^{18}}$ is hydrogen; and

$\mathbf{R^{19}}$ is a group selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, $-CH_2$(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, thiazol-2-yl and 1,2,4-thiadiazol-5-yl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

when R^{3A} is hydrogen, R^{3B} is methyl or ethyl; or
when R^{3A} is methyl, R^{3B} is methyl.

13. A compound according to any one of claims 1 to 12 where R^6 and R^7 together with the carbon atom to which they are attached form a cyclopropyl or cyclobutyl ring

14. A compound of formula (I) according to claim 1 selected from any one of the Examples, or a pharmaceutically acceptable salt thereof.

15. A compound of formula (I) according to claim 1 selected from any one of
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,

3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-cyclopropyl-1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea,
1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,
1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-ethylurea,
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea, and
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
or a pharmaceutically acceptable salt thereof.

16. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 15 for use as a medicament.

17. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 15 in the manufacture of a medicament for use in the treatment of proliferative disease.

18. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 15 for the production of an anti-proliferative effect in a warm-blooded animal such as man.

19. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 15 in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

20. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 15 in the manufacture of a medicament for use in the providing a mTOR kinase inhibitory effect in a warm-blooded animal such as man.

21. A method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 15.

22. A method for producing a mTOR kinase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 15.

23. A method for treating cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 15.

24. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

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