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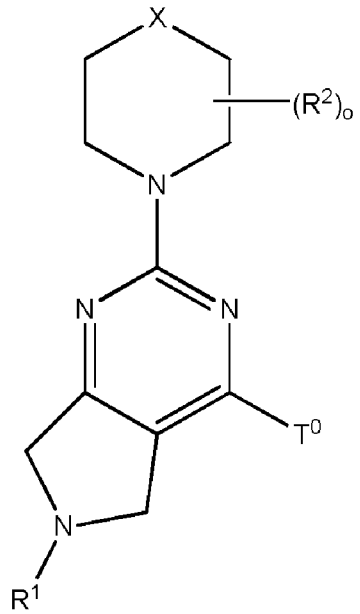
(54) **Title**: DIHYDROPYRROLO PYRIMIDINE DERIVATIVES AS MTOR INHIBITORS



(I)

(57) **Abstract**: The invention relates to compounds of formula (I), wherein X, R^1, R^2, T^0, o have the meaning as cited in the description and the claims. Said compounds are useful as inhibitors of mTOR for the treatment or prophylaxis of mTOR related diseases and disorders. The invention also relates to pharmaceutical compositions including said compounds, the preparation of such compounds as well as the use as medicaments.

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DIHYDROPYRROLO PYRIMIDINE DERIVATIVES AS MTOR INHIBITORS

The present invention relates to a novel class of kinase inhibitors, including pharmaceutically acceptable salts, prodrugs and metabolites thereof, which are useful for modulating protein kinase activity for modulating cellular activities such as signal transduction, proliferation, and cytokine secretion. More specifically the invention provides compounds which inhibit, regulate and/or modulate kinase activity, in particular mTOR activity, and signal transduction pathways relating to cellular activities as mentioned above. Furthermore, the present invention relates to pharmaceutical compositions comprising said compounds, e.g. for the treatment of diseases such as immunological, inflammatory, autoimmune, allergic disorders, or proliferative diseases such as cancer and processes for preparing said compounds.

Kinases catalyze the phosphorylation of proteins, lipids, sugars, nucleosides and other cellular metabolites and play key roles in all aspects of eukaryotic cell physiology. Especially, protein kinases and lipid kinases participate in the signaling events which control the activation, growth, differentiation and survival of cells in response to extracellular mediators or stimuli such as growth factors, cytokines or chemokines. In general, protein kinases are classified in two groups, those that preferentially phosphorylate tyrosine residues and those that preferentially phosphorylate serine and/or threonine residues.

Inappropriately high protein kinase activity is involved in many diseases including cancer, metabolic diseases and autoimmune/inflammatory disorders. This can be caused either directly or indirectly by the failure of control mechanisms due to mutation, overexpression or inappropriate activation of the enzyme. In all of these instances, selective inhibition of the kinase is expected to have a beneficial effect.

mTOR ("mammalian target of rapamycin", also known as FRAP or RAFT1) has become a recent focus of drug discovery efforts (Tsang et al., 2007, Drug Discovery Today 12, 112-124). It was discovered that the mTOR protein is the drug target for the immunosuppressive effect of rapamycin, a drug that is used to prevent transplant rejection. Rapamycin works through a gain-of-function mechanism by binding to the intracellular protein "FK-506-binding protein of 12 kDA" (FKBP12) to generate a drug-receptor complex that then binds to

and inhibits mTOR. Thus, rapamycin induces the formation of the ternary complex consisting of rapamycin and the two proteins FKBP12 and mTOR.

The mTOR protein is a large kinase of 289 kDA which occurs in all eukaryotic organisms sequenced so far (Schmelzle and Hall, 2000, Cell 103, 253-262). The sequence of the carboxy-terminal "phosphatidylinositol 3-kinase (PI3K)-related kinase" (PIKK) domain is highly conserved between species and exhibits serine and threonine kinase activity but no detectable lipid kinase activity. The intact PIKK domain is required for all known functions of mTOR. The FKBP12-rapamycin-binding (FRB) domain is located close to the PIKK domain and forms a hydrophobic pocket that binds to the rapamycin bound to FKBP12. The FRB domain does not appear to inhibit the enzymatic activity of the kinase domain directly. One explanation is that FKBP12-rapamycin prevents the interaction of mTOR with its substrates due to steric hindrance. The N-terminus of mTOR consists of approximately 20 tandem repeats of 37 to 43 amino acids termed HEAT repeats. The HEAT repeats interact with protein binding partners such as Raptor.

mTOR can form at least two distinct proteins complexes, mTORC1 and mTORC2. In the mTORC1 protein complex mTOR interacts with the proteins Raptor and mLST8/GβL and regulates cell growth by phosphorylating effectors such as p70S6K and 4E-BP1 to promote mRNA translation and protein synthesis. The mTORC1 complex is responsible for sensing nutrient signals (for example the availability of amino acids) in conjunction with insulin signaling. The activity of mTOR in mTORC1 can be inhibited by rapamycin.

The second protein complex, mTORC2, consists of the proteins mTOR, Rictor, mLST8/GβL and Sin1 and is involved in the organization of actin. The mTORC2 was originally described as rapamycin insensitive. A recent publication demonstrated that rapamycin affects the function of mTORC2 after prolonged treatment through an indirect mechanism by interfering with the assembly of the mTORC2 protein complex (Sarbassov et al., 2006. Molecular Cell 22, 159-168).

The biological function of mTOR is that of a central regulator of various extracellular and intracellular signals, including growth factors, nutrients, energy and stress. Growth factor and hormone (e.g. insulin) induced mTOR activation is mediated by PI3 kinases, Akt, and the tuberous sclerosis protein complex (TSC). For example, mTOR acts as a central regulator of

cell proliferation, angiogenesis, and cell metabolism (Tsang et al., 2007, Drug Discovery Today 12, 112-124).In addition to its immunosuppresive effects rapamycin (Sirolimus) is a potent inhibitor of the proliferation of vascular smooth muscle cells and was approved by the FDA as an anti-restenosis drug used in coronary stents. In addition, it was observed that rapamycin displays anti-tumour activity in several in vitro and animal models (Faivre et al., 2006. Nat. Rev. Drug. Discov. 5(8):671-688).

Because of the therapeutic potential of rapamycin several pharmaceutical companies started to develop rapamycin analogs to improve the pharmacokinetic properties of the molecule (Tsang et al., 2007, Drug Discovery Today 12, 112-124). For example, CCI779 (temsirolimus) represents a more water-soluble ester derivative of rapamycin for intravenous and oral formulation. CCI779 has antitumor activity either alone or in combination with cytotoxic agents in cell lines. RAD001 (everolimus) is a hydroxyethyl ether derivative of rapamycin that is developed for oral administration. AP23573 (deferolimus) is developed for either oral or intravenous administration.

In general, the rapamycin derivatives act through the same molecular mechanism, the induction of the ternary rapamycin-FKBP12-mTOR complex. It is conceivable that the function of mTOR could be equally or even more effectively inhibited by inhibitors of the kinase function. For example, this could be achieved by identifying compounds that interact with the ATP-binding pocket of the mTOR kinase domain. For example Torin1 is a potent and selective ATP-competitive mTOR inhibitor that directly binds to both mTOR complexes and impairs cell growth and proliferation more efficiently than rapamycin (Thoreen et al., 2009. J. Biol. Chem. 284(12):8023-32; Feldman et al., 2009. PLOSBiology 7(2):e38).

Diseases and disorders associated with mTOR are further described, e.g. in WO-A 2008/116129, WO-A 2008/115974, WO-A 2008/023159, WO-A 2009/007748, WO-A 2009/007749, WO-A 2009/007750, WO-A 2009/007751, WO-A 2011/011716.

Several mTOR inhibitors have been reported in the literature which may be useful in the medical field, for example as anticancer agents (Faivre et al., 2006. Nat. Rev. Drug. Discov. 5(8):671-688). In WO-A 2008/116129 imidazolopyrimidine analogs are described as mixed mTOR and PI3K kinase inhibitors. Pyrazolopyrimidine analogs are described as mixed mTOR and PI3K kinase inhibitors in WO-A 2008/115974. Further pyrimidine derivatives as

mTOR kinase and/or PI3K enzyme active compounds are disclosed in WO-A 2008/023159, WO-A 2009/007748, WO-A 2009/007749, WO-A 2009/007750, WO-A 2009/007751, WO-A 2010/014939.

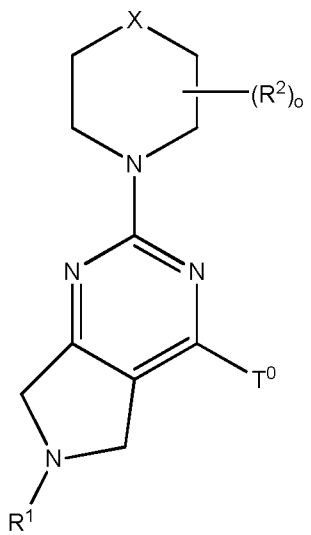
mTOR and mixed mTOR and PI3K kinase inhibitors are further described in WO-A 2010/103094, WO-A 2009/045174, WO-A 2010/005558, WO-A 2010/056320, WO-A 2010120996, WO-A 2010/120987, WO-A 2010/120998, WO-A 2010/120991 and WO-A 2010/120994.

mTOR inhibitors are also described in WO-A 2011/107585.

It is expected that a selective mTOR inhibitor that inhibits mTOR with greater potency than other kinases may have advantageous therapeutic properties because inhibition of other kinases may cause unwanted side effects (Richard et al., 2011. Current Opinion Drug Discovery and Development 13(4):428-440). Especially selectivity versus members of the phosphatidylinositol 3 kinase (PI3K) family (for example PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ) and PI3K related kinases (for example DMA-PK, ATM and ATR) may be important.

Even though mTOR inhibitors are known in the art there is a need for providing additional mTOR inhibitors having at least partially more effective pharmaceutically relevant properties, like activity, selectivity, and ADMET properties.

Accordingly, the present invention provides compounds of formula (I)



(I)

or a pharmaceutically acceptable salt, prodrug or metabolite (preferably pharmaceutically acceptable salt) thereof, wherein

X is O; or S;

R^1 is H; $C(O)R^3$; $C(O)OR^3$; $C(O)N(R^3R^{3a})$; $S(O)_2N(R^3R^{3a})$; $S(O)N(R^3R^{3a})$; $S(O)_2R^3$; $S(O)R^3$; T^1; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^4, which are the same or different;

R^3, R^{3a} are independently selected from the group consisting of H; T^1; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^4, which are the same or different;

R^4 is halogen; CN; $C(O)OR^5$; OR^5; $C(O)R^5$; $C(O)N(R^5R^{5a})$; $S(O)_2N(R^5R^{5a})$; $S(O)N(R^5R^{5a})$; $S(O)_2R^5$; $S(O)R^5$; $N(R^5)S(O)_2N(R^{5a}R^{5b})$; $N(R^5)S(O)N(R^{5a}R^{5b})$; SR^5; $N(R^5R^{5a})$; NO_2; $OC(O)R^5$; $N(R^5)C(O)R^{5a}$; $N(R^5)S(O)_2R^{5a}$; $N(R^5)S(O)R^{5a}$; $N(R^5)C(O)N(R^{5a}R^{5b})$; $N(R^5)C(O)OR^{5a}$; $OC(O)N(R^5R^{5a})$; or T^1;

R^5, R^{5a}, R^{5b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

T^1 is C_{3-7} cycloalkyl; 4 to 7 membered heterocyclyl; 8 to 11 membered heterobicyclyl; phenyl; naphthyl; indenyl; or indanyl, wherein T^1 is optionally substituted with one or more R^6, which are the same or different;

R^6 is halogen; CN; $C(O)OR^7$; OR^7; oxo (=O), where the ring is at least partially saturated; $C(O)R^7$; $C(O)N(R^7R^{7a})$; $S(O)_2N(R^7R^{7a})$; $S(O)N(R^7R^{7a})$; $S(O)_2R^7$; $S(O)R^7$; $N(R^7)S(O)_2N(R^{7a}R^{7b})$; $N(R^7)S(O)N(R^{7a}R^{7b})$; SR^7; $N(R^7R^{7a})$; NO_2; $OC(O)R^7$; $N(R^7)C(O)R^{7a}$; $N(R^7)S(O)_2R^{7a}$; $N(R^7)S(O)R^{7a}$; $N(R^7)C(O)N(R^{7a}R^{7b})$; $N(R^7)C(O)OR^{7a}$; $OC(O)N(R^7R^{7a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^8, which are the same or different;

R^7, R^{7a}, R^{7b} are independently selected from the group consisting of H; C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^8 is halogen; CN; $C(O)OR^9$; OR^9; $C(O)R^9$; $C(O)N(R^9R^{9a})$; $S(O)_2N(R^9R^{9a})$; $S(O)N(R^9R^{9a})$; $S(O)_2R^9$; $S(O)R^9$; $N(R^9)S(O)_2N(R^{9a}R^{9b})$; $N(R^9)S(O)N(R^{9a}R^{9b})$; SR^9; $N(R^9R^{9a})$; NO_2; $OC(O)R^9$; $N(R^9)C(O)R^{9a}$; $N(R^9)S(O)_2R^{9a}$; $N(R^9)S(O)R^{9a}$; $N(R^9)C(O)N(R^{9a}R^{9b})$; $N(R^9)C(O)OR^{9a}$; or $OC(O)N(R^9R^{9a})$;

R^9, R^{9a}, R^{9b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

o is 1; 2; 3; or 4;

Each R^2 is independently selected from the group consisting of H; halogen; CN; $C(O)OR^{10}$; OR^{10a}; oxo (=O); $C(O)R^{10}$; $C(O)N(R^{10}R^{10a})$; $S(O)_2N(R^{10}R^{10a})$; $S(O)N(R^{10}R^{10a})$; $S(O)_2R^{10}$; $S(O)R^{10}$; $N(R^{10})S(O)_2N(R^{10a}R^{10b})$; $N(R^{10})S(O)N(R^{10a}R^{10b})$; SR^{10}; $N(R^{10}R^{10a})$; NO_2; $OC(O)R^{10}$; $N(R^{10})C(O)R^{10a}$; $N(R^{10})S(O)_2R^{10a}$; $N(R^{10})S(O)R^{10a}$; $N(R^{10})C(O)N(R^{10a}R^{10b})$; $N(R^{10})C(O)OR^{10a}$; $OC(O)N(R^{10}R^{10a})$; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{11}, which are the same or different;

Optionally two R^2 are joined to form together with the ring to which they are attached an 8 to 11 membered heterobicycle.

R^{10}, R^{10a}, R^{10b} are independently selected from the group consisting of H; C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{11} is halogen; CN; $C(O)OR^{12}$; OR^{12}; $C(O)R^{12}$; $C(O)N(R^{12}R^{12a})$; $S(O)_2N(R^{12}R^{12a})$; $S(O)N(R^{12}R^{12a})$; $S(O)_2R^{12}$; $S(O)R^{12}$; $N(R^{12})S(O)_2N(R^{12a}R^{12b})$; $N(R^{12})S(O)N(R^{12a}R^{12b})$; SR^{12}; $N(R^{12}R^{12a})$; NO_2; $OC(O)R^{12}$; $N(R^{12})C(O)R^{12a}$; $N(R^{12})S(O)_2R^{12a}$; $N(R^{12})S(O)R^{12a}$; $N(R^{12})C(O)N(R^{12a}R^{12b})$; $N(R^{12})C(O)OR^{12a}$; or $OC(O)N(R^{12}R^{12a})$;

R^{12}, R^{12a}, R^{12b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

T^0 is phenyl; or 5 to 6 membered aromatic heterocycle, wherein T^0 is substituted with $N(R^{13a})C(O)N(R^{13b}R^{13})$ or $N(R^{13a})C(O)OR^{13}$ and optionally further substituted with one or more R^{14}, which are the same or different;

R^{14} is halogen; CN; $C(O)OR^{15}$; OR^{15}; $C(O)R^{15}$; $C(O)N(R^{15}R^{15a})$; $S(O)_2N(R^{15}R^{15a})$; $S(O)N(R^{15}R^{15a})$; $S(O)_2R^{15}$; $S(O)R^{15}$; $N(R^{15})S(O)_2N(R^{15a}R^{15b})$; $N(R^{15})S(O)N(R^{15a}R^{15b})$; SR^{15}; $N(R^{15}R^{15a})$; NO_2; $OC(O)R^{15}$; $N(R^{15})C(O)R^{15a}$; $N(R^{15})S(O)_2R^{15a}$; $N(R^{15})S(O)R^{15a}$; $N(R^{15})C(O)N(R^{15a}R^{15b})$; $N(R^{15})C(O)OR^{15a}$; $OC(O)N(R^{15}R^{15a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{13a}, R^{13b}, R^{15}, R^{15a}, R^{15b} are independently selected from the group consisting of H; C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{13} is H; T^2; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{16}, which are the same or different;

R^{16} is halogen; CN; $C(O)OR^{17}$; OR^{17}; $C(O)R^{17}$; $C(O)N(R^{17}R^{17a})$; $S(O)_2N(R^{17}R^{17a})$; $S(O)N(R^{17}R^{17a})$; $S(O)_2R^{17}$; $S(O)R^{17}$; $N(R^{17})S(O)_2N(R^{17a}R^{17b})$; $N(R^{17})S(O)N(R^{17a}R^{17b})$; SR^{17}; $N(R^{17}R^{17a})$; NO_2; $OC(O)R^{17}$; $N(R^{17})C(O)R^{17a}$; $N(R^{17})S(O)_2R^{17a}$; $N(R^{17})S(O)R^{17a}$; $N(R^{17})C(O)N(R^{17a}R^{17b})$; $N(R^{17})C(O)OR^{17a}$; $OC(O)N(R^{17}R^{17a})$; or T^2;

R^{17}, R^{17a}, R^{17b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

Optionally R^{13}, R^{13b} are joined to form together with the nitrogen atom to which they are attached an at least the nitrogen atom as ring heteroatom containing 4 to 7 membered heterocyclyl ring; or 8 to 11 membered heterobicyclyl ring, wherein the 4 to 7 membered heterocyclyl ring; and the 8 to 11 membered heterobicyclyl ring are optionally substituted with one or more R^{18}, which are the same or different;

T^2 is C_{3-7} cycloalkyl; 4 to 7 membered heterocyclyl; 8 to 11 membered heterobicyclyl; phenyl; naphthyl; indenyl; or indanyl, wherein T^2 is optionally substituted with one or more R^{18}, which are the same or different;

R^{18} is halogen; CN; $C(O)OR^{19}$; OR^{19}; oxo (=O), where the ring is at least partially saturated; $C(O)R^{19}$; $C(O)N(R^{19}R^{19a})$; $S(O)_2N(R^{19}R^{19a})$; $S(O)N(R^{19}R^{19a})$; $S(O)_2R^{19}$; $S(O)R^{19}$; $N(R^{19})S(O)_2N(R^{19a}R^{19b})$; $N(R^{19})S(O)N(R^{19a}R^{19b})$; SR^{19}; $N(R^{19}R^{19a})$; NO_2; $OC(O)R^{19}$; $N(R^{19})C(O)R^{19a}$; $N(R^{19})S(O)_2R^{19a}$; $N(R^{19})S(O)R^{19a}$; $N(R^{19})C(O)N(R^{19a}R^{19b})$; $N(R^{19})C(O)OR^{19a}$; $OC(O)N(R^{19}R^{19a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{20}, which are the same or different;

R^{19}, R^{19a}, R^{19b} are independently selected from the group consisting of H; C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{20} is halogen; CN; $C(O)OR^{21}$; OR^{21}; $C(O)R^{21}$; $C(O)N(R^{21}R^{21a})$; $S(O)_2N(R^{21}R^{21a})$; $S(O)N(R^{21}R^{21a})$; $S(O)_2R^{21}$; $S(O)R^{21}$; $N(R^{21})S(O)_2N(R^{21a}R^{21b})$; $N(R^{21})S(O)N(R^{21a}R^{21b})$; SR^{21}; $N(R^{21}R^{21a})$; NO_2; $OC(O)R^{21}$; $N(R^{21})C(O)R^{21a}$; $N(R^{21})S(O)_2R^{21a}$; $N(R^{21})S(O)R^{21a}$; $N(R^{21})C(O)N(R^{21a}R^{21b})$; $N(R^{21})C(O)OR^{21a}$; or $OC(O)N(R^{21}R^{21a})$;

R^{21}, R^{21a}, R^{21b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

In case a variable or substituent can be selected from a group of different variants and such variable or substituent occurs more than once the respective variants can be the same or different.

Within the meaning of the present invention the terms are used as follows:

"Alkyl" means a straight-chain or branched carbon chain. Each hydrogen of an alkyl carbon may be replaced by a substituent.

"C_{1-4} alkyl" means an alkyl chain having 1 - 4 carbon atoms, e.g. if present at the end of a molecule: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl tert-butyl, or e.g.

$-CH_2-$, $-CH_2-CH_2-$, $-CH(CH_3)-$, $-C(CH_2)-$, $-CH_2-CH_2-CH_2-$, $-CH(C_2H_5)-$, $-C(CH_3)_2-$, when two moieties of a molecule are linked by the alkyl group. Each hydrogen of a C_{1-4} alkyl carbon may be replaced by a substituent as indicated herein.

"C_{1-6} alkyl" means an alkyl chain having 1 - 6 carbon atoms, e.g. if present at the end of a molecule: C_{1-4} alkyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl; tert-butyl, n-pentyl, n-hexyl, or e.g. $-CH_2-$, $-CH_2-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-CH(C_2H_5)-$, $-C(CH_3)_2-$, when two moieties of a molecule are linked by the alkyl group. Each hydrogen of a C_{1-6} alkyl carbon may be replaced by a substituent as indicated herein.

"C_{3-7} cycloalkyl" or "C_{3-7} cycloalkyl ring" means a cyclic alkyl chain having 3 - 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl. Each hydrogen of a cycloalkyl carbon may be replaced by a substituent as indicated herein.

"Halogen" means fluoro, chloro, bromo or iodo. It is generally preferred that halogen is fluoro or chloro.

"4 to 7 membered heterocyclyl" or "4 to 7 membered heterocycle" means a ring with 4, 5, 6 or 7 ring atoms that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 4 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including $-S(O)-$, $-S(O)_2-$), oxygen and nitrogen (including $=N(O)-$) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a 4 to 7 membered heterocycle are azetidine, oxetane, thietane, furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, diazepane, azepine or homopiperazine.

"8 to 11 membered heterobicyclyl" or "8 to 11 membered heterobicycle" means a heterocyclic system of two rings with 8 to 11 ring atoms, where at least one ring atom is shared by both rings and that may contain up to the maximum number of double bonds

(aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 6 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -$S(O)_2$-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a 8 to 11 membered heterobicycle are indole, indoline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzimidazole, benzimidazoline, quinoline, quinazoline, dihydroquinazoline, quinoline, dihydroquinoline, tetrahydroquinoline, decahydroquinoline, isoquinoline, decahydroisoquinoline, tetrahydroisoquinoline, dihydroisoquinoline, benzazepine, purine or pteridine. The term 8 to 11 membered heterobicycle also includes spiro structures of two rings like 1,4-dioxa-8-azaspiro[4.5]decane or bridged heterocycles like 8-aza-bicyclo[3.2.1]octane.

"5 to 6 membered aromatic heterocyclyl" or "5 to 6 membered aromatic heterocycle" means a heterocycle derived from cyclopentadienyl or benzene, where at least one carbon atom is replaced by a heteoatom selected from the group consisting of sulfur (including -S(O)-, -$S(O)_2$-), oxygen and nitrogen (including =N(O)-). Examples for such heterocycles are furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, thiadiazole, pyranium, pyridine, pyridazine, pyrimidine, triazole, tetrazole.

"4 to 7 membered saturated heterocyclyl" or "4 to 7 membered saturated heterocycle" means a ring with 4, 5, 6 or 7 ring atoms of a fully saturated ring, wherein at least one ring atom up to 4 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -$S(O)_2$-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a 4 to 7 membered saturated heterocycle are azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, tetrahydropyran, imidazolidine, piperidine, morpholine, triazolidine, or tetrazolidine.

Preferred compounds of formula (I) are those compounds in which one or more of the residues contained therein have the meanings given below, with all combinations of preferred substituent definitions being a subject of the present invention. With respect to all preferred compounds of the formula (I) the present invention also includes all tautomeric and

stereoisomeric forms and mixtures thereof in all ratios, and their pharmaceutically acceptable salts.

In preferred embodiments of the present invention, the substituents mentioned below independently have the following meaning. Hence, one or more of these substituents can have the preferred or more preferred meanings given below.

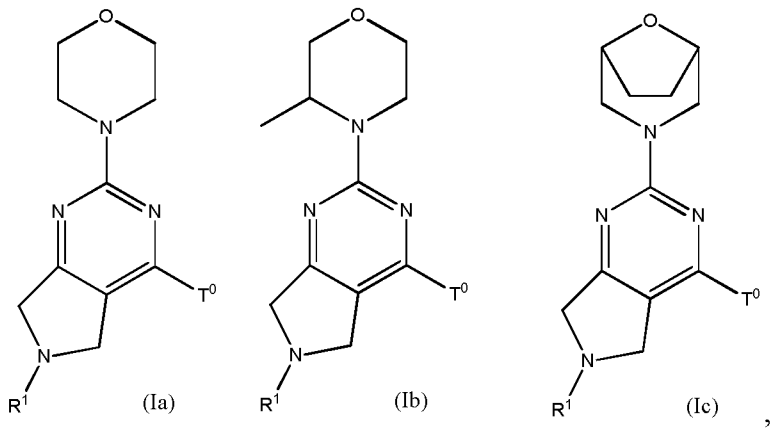
Preferably, X is O.

Preferably, R^1 is H; $C(O)R^3$; $S(O)_2R^3$; optionally substituted C_{1-6} alkyl (preferably unsubstituted C_{1-4} alkyl) ; $C(O)OR^3$; $C(O)NHR^3$; or optionally substituted T^1 (preferably unsubstituted C_{3-7} cycloalkyl). More preferably, R^1 is H; $C(O)R^3$; $S(O)_2R^3$; $C(O)OR^3$; $C(O)NHR^3$; isopropyl; isobutyl; cyclopropyl; or cyclohexyl. Even more preferably, R^1 is H.

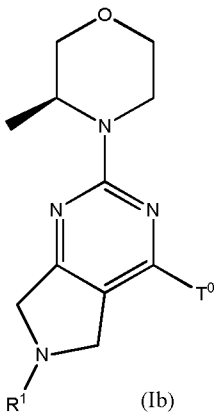
Preferably, R^3 is H; optionally substituted C_{1-6} alkyl (preferably C_{1-4} alkyl, unsubstituted or substituted with one OR^5, CN, $N(R^5R^{5a})$, wherein R^5, R^{5a} are independently selected from the group consisting of H and C_{1-4} alkyl); or optionally substituted T^1 (Preferably, unsubstituted C_{3-7} cycloalkyl or unsubstituted 3 to 7 membered saturated heterocycle). More preferably, R^3 is H; methyl; ethyl; CH_2OH; CH_2OCH_3; $CH_2CH_2OCH_3$; CH_2CN; CH_2NH_2; $CH_2CH_2NH_2$; $CH_2CH_2CH_2NH_2$; $CH_2N(CH_3)_2$; $CH_2CH_2N(CH_3)_2$; $CH_2CH_2CH_2N(CH_3)_2$; cyclopropyl; tetrahydrofuranyl; pyrrolidinyl; or CH_2-N-morpholinyl.

Preferably, o is 1 or 2. Preferably, R^2 is H; or methyl. Also preferably, two R^2 are joined to form together with the morpholine ring to which they are attached an 8-oxa-3-azabicyclo[3.2.1]octan-3-yl residue. Preferably, o is 1, R^2 is methyl and the ring carbon to which the methyl group is attached has (S)-configuration.

Preferably, o, X, and R^2 are selected to give formula (Ia), (Ib) or (Ic)



wherein R^1, T^0 have the (preferred, more preferred) meaning as mentionend herein. A further preferred formula (Ib) is



Preferably, T^0 is phenyl; pyridine; pyrimidine; pyridazine; or pyrazine (more preferably phenyl), wherein T^0 is substituted with $N(R^{13a})C(O)N(R^{13b}R^{13})$ and optionally further substituted with one or more R^{14}, which are the same or different.

Preferably, T^0 is only substituted with $N(R^{13a})C(O)N(R^{13b}R^{13})$.

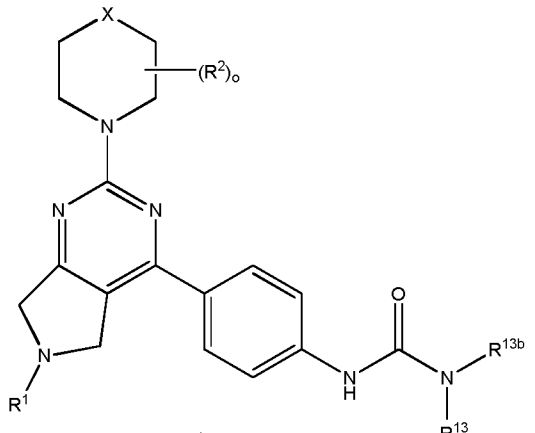
Preferably, R^{13a} is H.

Preferably, R^{13b} is H or R^{13b}, R^{13} are joined to form together with the nitrogen to which they are attached an optionally substituted (preferably unsubstituted or substituted with one methyl group) morpholine ring.

Preferably, R^{13} is H; optionally substituted C_{1-6} alkyl; optionally substituted C_{3-7} membered cycloalkyl; or optionally substituted pyridine. More preferably R^{13} is H; ethyl; CH_2CH_2OH; CH_2CH_2CN; $CH_2CH(OH)CH_3$; $CH_2CH(CH_3)CH_2OH$; unsubstituted cyclopropyl; or pyridyl, unsubstituted or substituted with one hydroxyl goup. also more preferably R^{13} is H; ethyl; CH_2CH_2CN; $CH_2CH(OH)CH_3$; $CH_2CH(CH_3)CH_2OH$; unsubstituted cyclopropyl; or pyridyl, unsubstituted or substituted with one hydroxyl goup.

Even more preferably, R^{13a}, R^{13b} are H and R^{13} is CH_2CH_2OH.

Preferably T^0 is selected to give formula (Id)



(Id)

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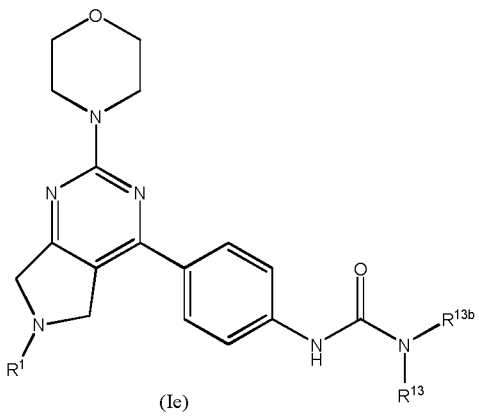
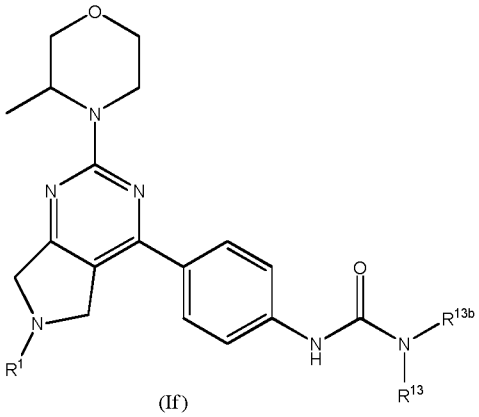
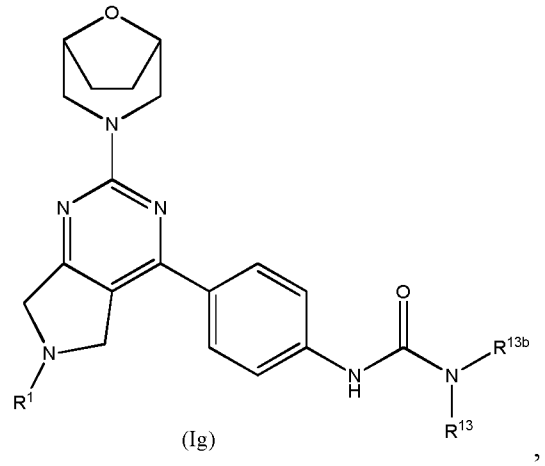
wherein X, R^1, R^2, o, R^{13}, R^{13b} have the (preferred, more preferred) meaning as mentionend herein. Even more preferred are compounds of formula (Ie), (If, (Ig)



(Ie)



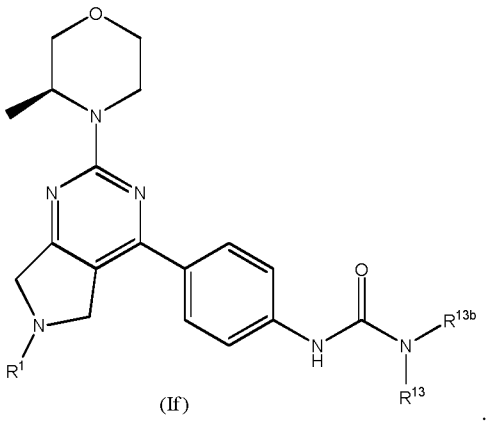
(If)



(Ig)

wherein R^1, R^{13}, R^{13b} have the (preferred, more preferred) meaning as mentionend herein.

A preferred formula (If) is



(If)

Compounds of formula (I) in which some or all of the above-mentioned groups have the preferred meanings are also an object of the present invention.

Further preferred compounds of the present invention are selected from the group consisting of

(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-ethyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-ethyl-3-(4-(6-formyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

1-ethyl-3-(4-(2-morpholino-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
1-cyclopropyl-3-(4-(2-morpholino-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
1-(4-(2-morpholino-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
ethyl 4-(4-(3-ethylureido)phenyl)-2-morpholino-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate;
(S)-ethyl 4-(4-(3-ethylureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate;
(S)-ethyl 4-(4-(3-cyclopropylureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate;
(S)-ethyl (4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)carbamate;
(S)-1-cyclopropyl-3-(4-(6-methyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-(4-(6-acetyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;
(S)-1-cyclopropyl-3-(4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-cyclopropyl-3-(4-(6-cyclopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-3-methyl-N-(4-(2-((S)-3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)morpholine-4-carboxamide;
(S)-4-(4-(3-cyclopropylureido)phenyl)-N-ethyl-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxamide;
1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;
(S)-1-(2-hydroxyethyl)-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-cyclopropyl-3-(4-(6-(2-(dimethylamino)acetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-cyclopropyl-3-(4-(6-(3-(dimethylamino)propanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-cyclopropyl-3-(4-(6-(2-hydroxyacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-(4-(6-(2-cyanoacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;

(S)-1-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(pyridin-4-yl)urea;

(S)-1-(6-hydroxypyridin-2-yl)-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(R)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-cyclopropyl-3-(4-(6-(2-methoxyacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-(4-(6-(2-aminoacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;

(S)-1-(4-(6-(3-aminopropanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;

(S)-1-(4-(6-(4-aminobutanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;

(S)-1-cyclopropyl-3-(4-(6-(3-methoxypropanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-cyclopropyl-3-(4-(6-(4-(dimethylamino)butanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

1-cyclopropyl-3-(4-(2-((S)-3-methylmorpholino)-6-(tetrahydrofuran-2-carbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-(2-hydroxyethyl)-3-(4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-cyclopropyl-3-(4-(6-(cyclopropylsulfonyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-(2-hydroxyethyl)-3-(4-(2-(3-methylmorpholino)-6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-N-ethyl-4-(4-(3-(2-hydroxyethyl)ureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxamide;

(S)-1-(4-(6-cyclohexyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea;

(S)-1-(4-(6-acetyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea;
1-cyclopropyl-3-(4-(2-((S)-3-methylmorpholino)-6-(tetrahydrofuran-3-carbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
1-cyclopropyl-3-(4-(2-((S)-3-methylmorpholino)-6-(pyrrolidine-2-carbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-4-(4-(3-cyclopropylureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxamide;
1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea;
1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-ethylurea;
1-(2-hydroxypropyl)-3-(4-(6-isopropyl-2-((S)-3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-ethyl-3-(4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6-(2-morpholinoacetyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6-isobutyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea;
1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6-isopropyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-ethylurea;
1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;
1-(1-hydroxypropan-2-yl)-3-(4-(6-isopropyl-2-((S)-3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-(2-cyanoethyl)-3-(4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea; and
pharmaceutically acceptable salts, prodrugs or metabolites thereof.

Prodrugs of the compounds of the present invention are also within the scope of the present invention.

"Prodrug" means a derivative that is converted into a compound according to the present invention by a reaction with an enzyme, gastric acid or the like under a physiological condition in the living body, e.g. by oxidation, reduction, hydrolysis or the like, each of which is carried out enzymatically. Examples of a prodrug are compounds, wherein the amino group in a compound of the present invention is acylated, alkylated or phosphorylated to form, e.g., eicosanoylamino, alanylamino, pivaloyloxymethylamino or wherein the hydroxyl group is acylated, alkylated, phosphorylated or converted into the borate, e.g. acetyloxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaryloxy, alanyloxy or wherein the carboxyl group is esterified or amidated. These compounds can be produced from compounds of the present invention according to well-known methods.

Metabolites of compounds of formula (I) are also within the scope of the present invention.

The term "metabolites" refers to all molecules derived from any of the compounds according to the present invention in a cell or organism, preferably mammal.

Preferably the term relates to molecules which differ from any molecule which is present in any such cell or organism under physiological conditions

The structure of the metabolites of the compounds according to the present invention will be obvious to any person skilled in the art, using the various appropriate methods.

Where tautomerism, like e.g. keto-enol tautomerism, of compounds of general formula (I) may occur, the individual forms, like e.g. the keto and enol form, are comprised separately and together as mixtures in any ratio. The same applies for stereoisomers, like e.g. enantiomers, cis/trans isomers, conformers and the like.

Especially, compounds of formula (I), wherein the morpholino or thiomorpholino ring is substituted with one R^2 in 3-position are encompassed by the present invention as isomers or enantiomers or mixtures thereof concerning the respective chiral carbon center.

If desired, isomers can be separated by methods well known in the art, e.g. by liquid chromatography. The same applies for enantiomers by using e.g. chiral stationary phases. Additionally, enantiomers may be isolated by converting them into diastereomers, i.e.

coupling with an enantiomerically pure auxiliary compound, subsequent separation of the resulting diastereomers and cleavage of the auxiliary residue. Alternatively, any enantiomer of a compound of formula (I) may be obtained from stereoselective synthesis using optically pure starting materials.

The compounds of formula (I) may exist in crystalline or amorphous form. Furthermore, some of the crystalline forms of the compounds of formula (I) may exist as polymorphs, which are included within the scope of the present invention. Polymorphic forms of compounds of formula (I) may be characterized and differentiated using a number of conventional analytical techniques, including, but not limited to, X-ray powder diffraction (XRPD) patterns, infrared (IR) spectra, Raman spectra, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and solid state nuclear magnetic resonance (ssNMR).

In case the compounds according to formula (I) contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the formula (I) which contain acidic groups can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula (I) which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula (I) simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts according to the formula (I) can be obtained by customary methods which are known to the person skilled in the art like, for

example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the formula (I) which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

Throughout the invention, the term "pharmaceutically acceptable" means that the corresponding compound, carrier or molecule is suitable for administration to humans. Preferably, this term means approved by a regulatory agency such as the EMEA (Europe) and/or the FDA (US) and/or any other national regulatory agency for use in animals, preferably in humans.

The present invention furthermore includes all solvates of the compounds according to the invention.

If desired, the effects of the claimed compounds on mTOR activity may e.g. be tested using transiently expressed epitope-tagged mTOR in a mammalian cell line such as HEK293 that is immunoprecipitated with a monoclonal antibody directed against the epitope tag (Knight et al. 2004, Bioorganic and Medicinal Chemistry 12, 4749-4759). Another assay employs mTOR protein enriched from cells or tissue lysates using conventional protein purification methods. In this assay a GST-fusion protein of the P70 S6 kinase is used as a substrate. The phosphorylation of P70 S6 is detected using a primary phospho-specific antibody (directed against phophorylated threonine 389) and an enzyme linked secondary anti-body in an ELISA assay (US-A 2004/0191836).

According to the present invention, the expression "mTOR" or "mTOR kinase" means the mTOR protein (Tsang et al., 2007, Drug Discovery Today 12, 112-124). The gene encoding mTOR is located on human chromosome map locus 1p36.2 and it is widely expressed in human tissues.

As shown in the examples, compounds of the invention were tested for their selectivity for mTOR over other kinases. As shown, all tested compounds bind mTOR more selectively than the kinases PI3Kd or DNA-PK (see table 2 below). Consequently, the compounds of the

present invention are considered to be useful for the prevention or treatment of diseases and disorders associated with mTOR, e.g. immunological, inflammatory, autoimmune, or allergic disorders, or proliferative diseases, transplant rejection, Graft-versus-Host-Disease, cardiovascular diseases, metabolic diseases or neurodegenerative diseases.

Therefore, the present invention provides pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as active ingredient together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

"Pharmaceutical composition" means one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred carriers when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid carriers for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate,

sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the therapeutic, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

A pharmaceutical composition of the present invention may comprise one or more additional compounds as active ingredients like one or more compounds of formula (I) not being the first compound in the composition or mTOR inhibitors. Further bioactive compounds for may be steroids, leukotriene antagonists, cyclosporine or rapamycin.

The compounds of the present invention or pharmaceutically acceptable salt(s) thereof and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, this may occur separately or sequentially in any order. When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

It is further included within the present invention that the compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formula (I) is administered in combination with another drug or pharmaceutically active agent and/or that the pharmaceutical composition of the invention further comprises such a drug or pharmaceutically active agent.

In this context, the term “drug or pharmaceutically active agent” includes a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician.

“Combined” or “in combination” or “combination” should be understood as a functional coadministration, wherein some or all compounds may be administered separately, in different formulations, different modes of administration (for example subcutaneous, intravenous or oral) and different times of administration. The individual compounds of such

combinations may be administered either sequentially in separate pharmaceutical compositions as well as simultaneously in combined pharmaceutical compositions.

For example, in rheumatoid arthritis therapy, combination with other chemotherapeutic or antibody agents is envisaged. Suitable examples of pharmaceutically active agents which may be employed in combination with the compounds of the present invention and their salts for rheumatoid arthritis therapy include: immunosuppresants such as amtolmetin guacil, mizoribine and rimexolone; anti-TNFα agents such as etanercept, infliximab, Adalimumab, Anakinra, Abatacept, Rituximab; tyrosine kinase inhibitors such as leflunomide; kallikrein antagonists such as subreum; interleukin 11 agonists such as oprelvekin; interferon beta 1 agonists; hyaluronic acid agonists such as NRD-101 (Aventis); interleukin 1 receptor antagonists such as anakinra; CD8 antagonists such as amiprilose hydrochloride; beta amyloid precursor protein antagonists such as reumacon; matrix metalloprotease inhibitors such as cipemastat and other disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulphasalazine, cyclosporin A, hydroxychoroquine, auranofin, aurothioglucose, gold sodium thiomalate and penicillamine.

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 proliferative diseases such as 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-yloxy-quinazoline (AZD0530) and N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-l-yl]-2-methylpyrimidin- 4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825), 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-erbBl 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, ZD 1839), Λ/-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-Λ/-(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-fiuoroanilino)-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-l-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SUl 1248 (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 Application WO 99/02166;

(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 BRCAl 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.

Further combination treatments are described in WO-A 2009/008992, incorporated herein by reference.

Accordingly, the individual compounds of such combinations may be administered either sequentially in separate pharmaceutical compositions as well as simultaneously in combined pharmaceutical compositions.

The pharmaceutical compositions of the present invention include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the

conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of formula (I) can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.*, oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or non-aqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally, for example, as liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir

may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of formula (I) may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of formula (I) are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

A therapeutically effective amount of a compound of the present invention will normally depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration. However, an effective amount of a compound of formula (I) for

the treatment of an inflammatory disease, for example rheumatoid arthritis (RA), will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70 kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a pharmaceutically acceptable salt, prodrug or metabolite thereof, may be determined as a proportion of the effective amount of the compound of formula (I) per se. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician.

Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

Another aspect of the present invention is a compound of the present invention or a pharmaceutically acceptable salt thereof for use as a medicament.

Another aspect of the present invention is a compound of the present invention or a pharmaceutically acceptable salt thereof for use in a method of treating or preventing a disease or disorder associated with mTOR.

In the context of the present invention, a disease or disorder associated with mTOR is defined as a disease or disorder where mTOR is involved.

In a preferred embodiment, the diseases or disorder associated with mTOR is an immunological, inflammatory, autoimmune, or allergic disorder or disease or a transplant rejection or a Graft-versus host disease.

Consequently, another aspect of the present invention is a compound or a pharmaceutically acceptable salt thereof of the present invention for use in a method of treating or preventing an immunological, inflammatory, autoimmune, or allergic disorder or disease or a transplant rejection or a Graft-versus host disease.

According to the present invention, an autoimmune disease is a disease which is at least partially provoked by an immune reaction of the body against own components, e.g. proteins, lipids or DNA.

In a preferred embodiment, the autoimmune disease is selected from the group consisting of rheumatoid arthritis (RA), inflammatory bowel disease (IBD; Crohns's disease and ulcerative colitis), psoriasis, systemic lupus erythematosus (SLE), and multiple sclerosis (MS).

Rheumatoid arthritis (RA) is a chronic progressive, debilitating inflammatory disease that affects approximately 1% of the world's population. RA is a symmetric polyarticular arthritis that primarily affects the small joints of the hands and feet. In addition to inflammation in the synovium, the joint lining, the aggressive front of tissue called pannus invades and destroys local articular structures (Firestein 2003, Nature 423:356-361).

Inflammatory bowel disease (IBD) is characterized by a chronic relapsing intestinal inflammation. IBD is subdivided into Crohn's disease and ulcerative colitis phenotypes. Crohn disease involves most frequently the terminal ileum and colon, is transmural and discontinuous. In contrast, in ulcerative colitis, the inflammation is continuous and limited to rectal and colonic mucosal layers. In approximately 10% of cases confined to the rectum and colon, definitive classification of Crohn disease or ulcerative colitis cannot be made and are designated 'indeterminate colitis.' Both diseases include extraintestinal inflammation of the skin, eyes, or joints. Neutrophil-induced injuries may be prevented by the use of neutrophils migration inhibitors (Asakura et al., 2007. World J. Gastroenterol. 13(15):2145-9).

Psoriasis is a chronic inflammatory dermatosis that affects approximately 2% of the population. It is characterized by red, scaly skin patches that are usually found on the scalp, elbows, and knees, and may be associated with severe arthritis. The lesions are caused by abnormal keratinocyte proliferation and infiltration of inflammatory cells into the dermis and epidermis (Schön et al., 2005. New Engl. J. Med. 352:1899-1912).

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease generated by T cell-mediated B-cell activation, which results in glomerulonephritis and renal failure. Human SLE is characterized at early stages by the expansion of long-lasting autoreactive CD4+ memory cells (D'Cruz et al., 2007. Lancet 369(9561):587-596).

Multiple sclerosis (MS) is an inflammatory and demyelating neurological disease. It has bee considered as an autoimmune disorder mediated by CD4+ type 1 T helper cells, but recent studies indicated a role of other immune cells (Hemmer et al., 2002. Nat. Rev. Neuroscience 3, 291-301).

Graft-versus-host disease (GVDH) is a major complication in allogeneic bone marrow transplantation. GVDH is caused by donor T cells that recognize and react to recipient differences in the histocompatibility complex system, resulting in significant morbidity and mortality.

Transplant rejection (allograft transplant rejection) includes, without limitation, acute and chronic allograft rejection following for example transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea. It is known that T cells play a central role in the specific immune response of allograft rejection.

In a further preferred embodiment, the disease or disorder associated with mTOR is a proliferative disease, especially cancer.

Diseases and disorders associated especially with mTOR are proliferative disorders or diseases, especially cancer.

Therefore, another aspect of the present invention is a compound or a pharmaceutically acceptable salt thereof of the present invention for use in a method of treating or preventing a proliferative disease, especially cancer.

Cancer comprises a group of diseases characterized by uncontrolled growth and spread of abnormal cells. All types of cancers generally involve some abnormality in the control of cell growth, division and survival, resulting in the malignant growth of cells. Key factors contributing to said malignant growth of cells are independence from growth signals,

insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, and genome instability (Hanahan and Weinberg, 2000. The Hallmarks of Cancer. Cell 100, 57-70).

Typically, cancers are classified as hematological cancers (for example leukemias and lymphomas) and solid cancers such as sarcomas and carcinomas (for example cancers of the brain, breast, lung, colon, stomach, liver, pancreas, prostate, ovary).

Especially cancers in which the PI3K/Akt signal transduction pathway is activated, for example due to inactivation of the tumour suppressor PTEN or activating mutations in PIK3A, the gene encoding the catalytic phosphoinositide-3 kinase subunit p110α (p110alpha) are expected to respond to treatment with mTOR inhibitors (Garcia-Echeverria and Sellers, 2008, Oncogene 27, 5511-5526). Examples of cancers with a high incidence of PTEN mutations and/or activation of PI3K/Akt are endometrial carcinoma, glioblastoma, head and neck cancer, colon cancer, pancreatic cancer, gastric cancer, hepatocarcinoma, ovarian cancer, thyroid carcinoma, renal cell cancer, breast cancer, prostate cancer and gastrointestinal stromal tumours (GIST). The most promising results with mTOR inhibitors have been obtained in renal cell carcinoma (RCC), mantle cell lymphoma and endometrial cancers (Faivre et al., 2006. Nat. Rev. Drug. Discov. 5(8):671-688). In addition, mTOR inhibitors may be useful for the treatment of leukemias including ALL and CML), multiple myeloma and lymphomas.

In addition, cancers harbouring activating mTOR mutations, for example single amino acid changes that confer constitutive activation of mTOR such as S2215Y or R2505P, may be treated with mTOR inhibitors (Sato et al., 2010. Oncogene 29(18):2746-2752.

mTOR plays an important role in angiogenesis, the formation of new blood vessels to provide oxygen and nutrients to growing and dividing cells. In this context mTOR controls the production of the HIF1-α and HIF1-β proteins, which are subunits of hypoxia-inducible factor (HIF), a transcription factor that controls the expression of genes whose products play a role in angiogenesis, cell proliferation, motility and survival. Two important proteins induced by HIF are vascular endothelial growth factors (VEGFs) and angiopoietin-2. Recently it has been reported that a small molecule mTOR inhibitor can reduce tumour growth, tumour

angiogenesis an vascular permeability (Xue et al., 2008. Cancer Research 68(22): 9551-9557).

In addition to tumourigenesis, there is evidence that mTOR plays a role in harmatoma syndromes. Recent studies have shown that the tumour suppressor proteins such as TSC1, TSC2, PTEN and LKB1 tightly control mTOR signalling. Loss of these tumour suppressor proteins leads to a range of hamartoma conditions as a result of elevated mTOR signalling (Rosner et al., 2008. Mutation Research 659(3):284-292). Syndromes with an established molecular link to dysregulation of mTOR include Peutz-Jeghers syndrome (PJS), Cowden disease, Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome, Lhermitte-Duclos disease and Tuberous sclerosis (TSC). Patients with these syndromes characteristically develop benign hamartomatous tumours in multiple organs. Other tumour suppressor proteins having an influence on mTOR activity are VHL, NF1 and PKD whose loss can trigger von Hippel-Lindau disease, Neurofibromatosis type 1, and Polycystic kidney disease respectively.

Proliferative diseases or disorders comprise a group of diseases characterized by increased cell multiplication. One example is restenosis caused by the overgrowth of vascular smooth muscle (VSM) cells after coronary angioplasty with stents. To circumvent this issue, drug-eluting stents have been developed to inhibit the growth of VSM cells. Rapamycin-coated stents effectively reduce restenosis and have been approved by the FDA (Serruys et al., 2006. N. Engl. J. Med. 354(5):483-95).

In a further preferred embodiment, the disease or disorder associated with mTOR is a cardiovascular disease, a metabolic disease or a neurodegenerative disease.

Therefore, another aspect of the present invention is a compound or a pharmaceutically acceptable salt thereof of any of the present invention for use in a method of treating or preventing a cardiovascular disease, a metabolic disease or a neurodegenerative disease.

Recent studies have revealed a role of mTOR in cardiovascular diseases, for example elevated mTOR kinase activity has been associated with cardiac hypertrophy (heart enlargement), which is a major risk factor for heart failure. At the cellular level, cardiac hypertrophy is characterized by an increase in cell size and enhanced protein synthesis. Although there are various hypertrophic stimuli, such as neurohormones and peptide growth factors, and several

protein kinase cascades are involved in cardiac hypertrophy, it is likely that all forms of hypertrophic stimuli activate the general protein translational machinery in an mTOR dependent manner. Remarkably, inhibition of mTOR by rapamycin prevents cardiac hypertrophy in numerous transgenic mouse models. In addition, stress-induced cardiac hypertrophy is dependent on mTOR in mice. These results indicate that mTOR is crucial for the abnormal cardiac overgrowth, and that mTOR inhibitors may be usefull for the treatment of human cardiac hypertrophy (Tsang et al., 2007, Drug Discovery Today 12, 112-124).

Metabolic diseases that may be treated with mTOR inhibitors comprise type 1 diabetes, type 2 diabetes, and obesity (Tsang et al., 2007. Drug Discovery Today 12, 112-124). Type 1 diabetes is caused by loss of insulin production due to destruction of pancreatic β-cells. Clinical studies using immunosuppressive regimen that contain rapamycin to prevent rejection of islet transplants have shown significant efficacy in type 1 diabetic patients. Type 2 diabetes arises when insulin secretion from pancreatic β-cells fails to compensate for the peripheral insulin resistance (or insensitivity to insulin) in skeletal muscle, liver and fat cells. Recent data indicate that sustained activation of mTOR signalling is a crucial event that renders insulin-receptors substrate (IRS) irresponsive to insulin. Moreover, it has been demonstrated that rapamycin restores the sensitivity of IRS to insulin (Shah et al., 2004. Curr. Biol. 14(18):1650-1656). Therefore, mTOR inhibitors are potentially useful in the management of type 2 diabetes. Obesity is a metabolic disease with a steadily increasing health risk worldwide. Recent evidence suggests that mTOR plays a role in lipid metabolism. During adipogenesis the expression of mTOR increases dramatically from barely detectable in preadipocytes to highly expressed in fully differentiated adipocytes, and rapamycin inhibits adipocyte differentiation (Yeh et al., 1995. Proc. Natl. Acad. Sci. U S A. 92(24):11086-90).

Recent reports suggest that mTOR inhibitors may be useful to treat neurodegenerative diseases such as Huntingtons's, Alzheimer's and Parkinson's disease. Huntingtons's disease is a neurodegenerative disorder caused by a mutant form of the protein huntingtin with abnormally long glutamine repeats at the amino-terminus. The mutant protein aggregates in neuronal cells and can cause nerve cell damage and toxicity. Rapamycin attenuates the accumulation of huntingtin and cell death, and protects against neurodegeneration in animal models of Huntington's disease (Ravikumar et al., 2004. Nat Genet. 36(6):585-95). In addition, rapamycin induces an autophagy response that has been suggested to play a role in the clearance of huntingtin aggregates.

Intracellular protein aggregates also occur in other neurodegenerative diseases, for example Alzheimer's disease. The Tau protein is frequently found in brains of Alzheimer's patients and is thought to contribute to the formation of neurofibrillary tangles (for example in tauopathies such as fronto-temporal dementia). In a fly model rapamycin reduces the concentration of tau protein and lowers the toxicity caused by tau accumulation (Berger et al., 2006. Hum. Mol. Genet. 15(3):433-42). Therefore, mTOR inhibitors may be useful in preventing the accumulation of toxic tau protein in Alzheimer's patients.

Parkinson's disease (PD) is a neurodegenerative disease associated with the accumulation and aggregation of misfolded proteins. Preventing aggregation or disaggregating misfolded proteins may provide a therapeutic benefit by slowing or preventing the progression of PD. The ubiquitin-proteasome system (UPS) is an important degradation mechanism acting on aggregated proteins. It was reported that rapamycin provides neuroprotection against dopaminergic neuronal cell death induced by the proteasome inhibitor lactacystin. It was suggested that the rapamycin effect is partially mediated by autophagy enhancement through enhanced degradation of misfolded proteins (Pan et al., 2008. Neurobiol. Dis. 32(1):16-25). Therefore compounds that can enhance autophagy may represent a promising strategy to treat PD patients.

In a further preferred embodiment, the disease or disorder associated with mTOR is an autophagy associated disease.

Therefore, another aspect of the present invention is a compound or a pharmaceutically acceptable salt thereof of any of the present invention for use in a method of treating or preventing an autophagy associated disease.

Autophagy is a lysosome-dependent process whereby proteins or damaged organelles within a cell are degraded (Mizushima et al., 2008. Nature 451(7182):1069-75). During this process an autophagosome with a double membrane encloses the component of the cell to be degraded. Then the autophagosome fuses with a lysosome which for example degrades proteins leading to the recycling of amino acids. Autophagy is primarily involved in the degradation of long-lived proteins, protein aggregates, and cellular organelles and other cellular components. In addition to its physiological function autophagy could be expoited for the treatment of a variety of diseases caused by misfolded proteins aggregates, for example neurodegenerative

diseases such as Huntington's, Alzheimer's or Parkinon's disease. Further autophagy associated diseases are described in WO-A2009/049242, incorporated herein with reference.

Autophagy inducing compound refers to a compound that induces autophagy in a cell. Autophagy associated disease refers to a disease that can be treated by the induction of autophagy. It has recently been shown that an ATP-competitive mTOR kinase inhibitor can induce autophagy (Thoreen et al., 2009. J. Biol. Chem. 284(12):8023-32). Interestingly, ATP competitive mTOR kinase inhibitors seem to induce autophagy more effectively than rapamycin in mammalian cells. Taken together, compounds of the present invention may be useful to induce autophagy in cells and to treat autophagy associated diseases.

In a further preferred embodiment, the disease or disorder is a viral infection.

Therefore, another aspect of the present invention is a compound or a pharmaceutically acceptable salt thereof of the present invention for use in a method of treating or preventing a viral infection.

All viruses require cellular ribosomes to translate their mRNAs. For example, human cytomegalovirus (HCMV) infection has been shown to activate the mTORC1 signaling pathway. Treatment of infected cells with Torin1, a mTOR inhibitor that targets the catalytic site of mTOR kinase, blocks the production of virus progeny. In addition, it was shown that Torin1 inhibits the replication of representative members of the alpha-, beta-, and gammaherpesvirus families, demonstrating the potential of mTOR kinase inhibitors as broad-spectrum antiviral agents (Moorman and Shenk, 2010. J. Virol. 84(10):5260-9). Further viral infections that may be treated or prevented by mTOR inhibitors are described in WO-A 2011/011716 incoporated herein with reference.

Yet another aspect of the present invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prophylaxis of diseases and disorders associated with mTOR.

Yet another aspect of the present invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating

or preventing an immunological, inflammatory, autoimmune, or allergic disorder or disease or a transplant rejection or a Graft-versus host disease.

Yet another aspect of the present invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing a proliferative disease, especially cancer.

Yet another aspect of the present invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing a cardiovascular disease, a metabolic disease or a neurodegenerative disease.

Yet another aspect of the present invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing an autophagy associated disease.

Yet another aspect of the present invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing a viral infection.

In the context of these uses of the invention, diseases and disorders associated with mTOR are as defined above.

Yet another aspect of the present invention is a method for treating, controlling, delaying or preventing in a mammalian patient in need thereof one or more conditions selected from the group consisting of diseases and disorders associated with mTOR, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to present invention or a pharmaceutically acceptable salt thereof.

Yet another aspect of the present invention is a method for treating, controlling, delaying or preventing in a mammalian patient in need thereof one or more conditions selected from the group consisting of an immunological, inflammatory, autoimmune, or allergic disorder or disease or a transplant rejection or a Graft-versus host disease, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to present invention or a pharmaceutically acceptable salt thereof.

Yet another aspect of the present invention is a method for treating, controlling, delaying or preventing in a mammalian patient in need thereof a proliferative disease, especially cancer, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to present invention or a pharmaceutically acceptable salt thereof.

Yet another aspect of the present invention is a method for treating, controlling, delaying or preventing in a mammalian patient in need thereof one or more conditions selected from the group consisting of a cardiovascular disease, a metabolic disease or a neurodegenerative disease, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to present invention or a pharmaceutically acceptable salt thereof.

Yet another aspect of the present invention is a method for treating, controlling, delaying or preventing in a mammalian patient in need thereof an autophagy associated disease, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to present invention or a pharmaceutically acceptable salt thereof.

Yet another aspect of the present invention is a method for treating, controlling, delaying or preventing in a mammalian patient in need thereof a viral infection, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to present invention or a pharmaceutically acceptable salt thereof.

In the context of these methods of the invention, diseases and disorders associated with mTOR are as defined above.

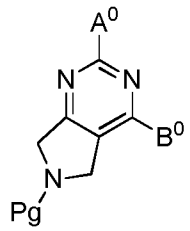
As used herein, the term "treating" or "treatment" is intended to refer to all processes, wherein there may be a slowing, interrupting, arresting, or stopping of the progression of a disease, but does not necessarily indicate a total elimination of all symptoms.

Preferred mammalian patients are human patients.

All embodiments discussed above with respect to the pharmaceutical composition of the invention also apply to the above mentioned first or second medical uses or methods of the invention.

In general compounds of the present invention may be prepared according to a method comprising the steps of

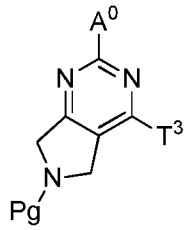
(a) reacting a compound of formula (II)



(II)

,

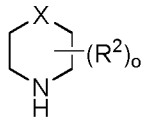
wherein Pg is a suitable protecting group (like tert.-butyloxycarbonyl) and A^0, B^0 are suitable leaving groups (like chloro) which may be the same or different with a compound of the formula X^0-T^3, wherein X^0 is a boronate ester or boronate acid and T^3 is defined as T^0 as defined above with the exception that the substituent $N(R^{13a})C(O)N(R^{13b}R^{13})$ or $N(R^{13a})C(O)OR^{13}$ is replaced by a nitro group or a suitably protected amino group (for example benzyloxycarbonyl), in a Suzuki reaction to yield a compound of formula (III)



(III)

;

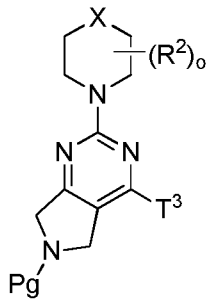
(b) reacting a compound of formula (III) with a compound of formula (IV)



(IV)

,

wherein X, R^2, o have the meaning as indicated above to yield a compound of formula (V)



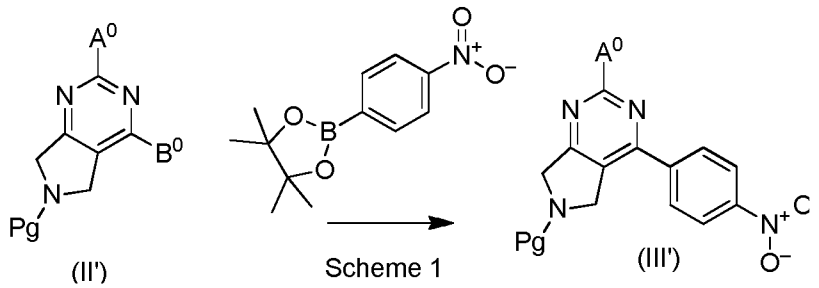
(V) ; and

(c_1) converting the nitro group (e.g. by reduction and reaction with an appropriate isocyanate or chloroformate) or the suitably protected amino group (e.g. by deprotection and reaction with an appropriate isocyanate or chloroformate) into substituent $N(R^{13a})C(O)N(R^{13b}R^{13})$ or $N(R^{13a})C(O)OR^{13}$ and subsequently removing the Pg protecting group to yield compounds of formula (I), wherein R^1 is H, optionally compounds of formula (I) wherein R^1 is H may be reacted with a compound of formula R^1-X^1, wherein X^1 is a suitable leaving group and R^1 has the meaning as indicated above (other than H) to give compounds of formula (I) wherein R^1 is other than H; or, alternatively

(c_2) removing the Pg protecting group and reacting the resulting compound with a compound of formula R^1-X^1, wherein X^1 is a suitable leaving group and R^1 has the meaning as indicated above (other than H), followed by converting the nitro group (e.g. by reduction and reaction with an appropriate isocyanate or chloroformate) or the suitably protected amino group (e.g. by deprotection and reaction with an appropriate isocyanate or chloroformate) into substituent $N(R^{13a})C(O)N(R^{13b}R^{13})$ or $N(R^{13a})C(O)OR^{13}$ to yield compounds of formula (I), wherein R^1 is other than H.

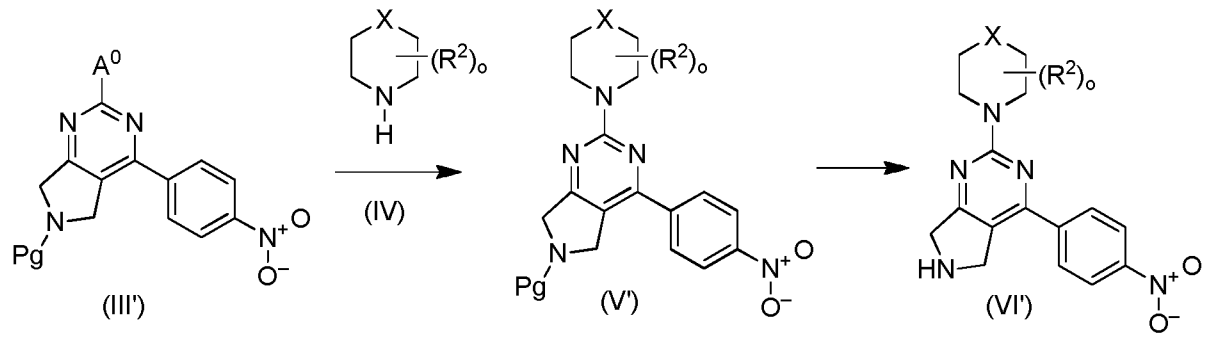
In a less preferred method step (b) is carried out before step (a).

More specifically, be way of example only, the method of preparation of a compound of the present invention may comprise the steps of



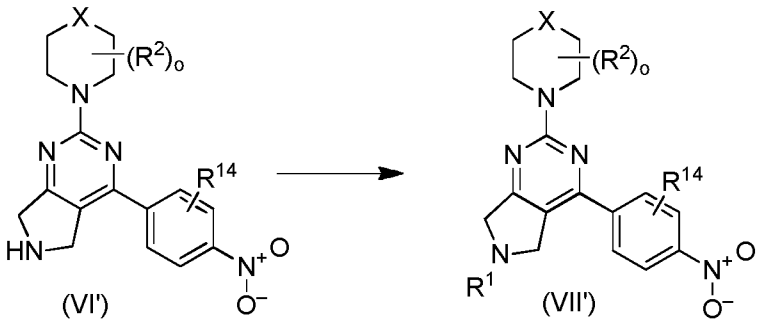
Scheme 1

Compounds of formula (II') where Pg represents a suitable protecting group (for example Boc) and A^0 and B^0 are suitable leaving groups (for example Cl) are commercially available or may be synthesised by one skilled in the art. Compounds of formula (III') can be synthesised by the reaction of compounds of formula (II') with an appropriate boronic acid or boronate ester derivative under Suzuki conditions. For example reaction with 4,4,5,5-tetramethyl-2-(4-nitrophenyl)-1,3,2-dioxaborolane gives compound of formula (III') wherein T^3 is 4-nitrophenyl. Suitable boronic acids or boronate esters are commercially available or may be synthesised by one skilled in the art.



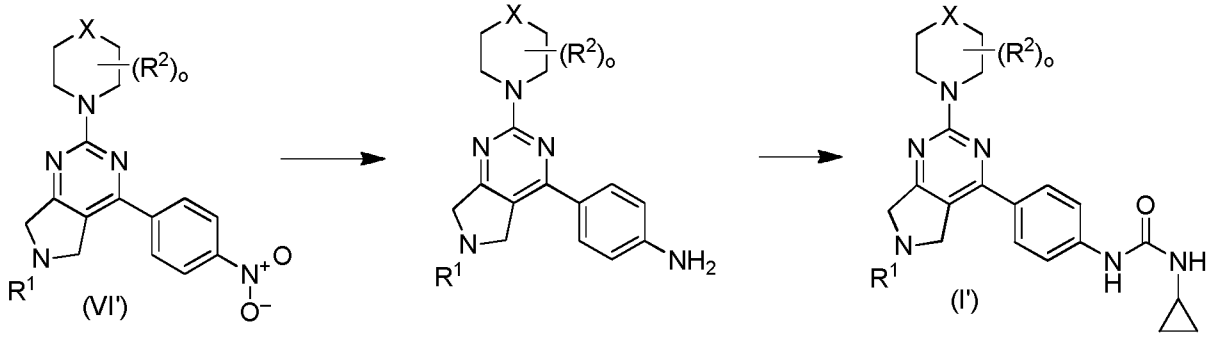
Scheme 2

Compounds of formula (III') can be reacted with an appropriately substituted morpholine or thiomorpholine usually in the presence of an organic tertiary amine base (for example triethylamine) in a range of possible solvents to give compounds of formula (V'). Subsequent deprotection to give compound of formula (VI') wherein R^1 is H. For example when Pg is Boc then deprotection can be achieved using methods well known to those skilled in the art (for example with HCl or TFA in organic solvent). Compounds of formula (VI'), wherein R^1 is H may be isolated in the form of salts or as free base.



Scheme 3

Compounds of formula (VI'), wherein R^1 is H can be derivatised using standard methods to generate a broad range of compounds of formula (VI') where R^1 is as defined above (except H). The unsubstituted compounds of formula (VI') (R^1 = H) can be reacted under appropriate conditions with alkyl halides to give compounds of formula (VI'), where R^1 is optionally substituted C_{1-6} alkyl. The unsubstituted compounds of formula (VI') can be reacted under appropriate conditions with aldehydes or ketones under reductive amination conditions to give respective substituted compounds of formula (VI'). Unsubstituted compounds of formula (VI') can be reacted under appropriate conditions with carboxylic acids or acid carboxylic chlorides to give compounds of formula (VI'), where R^1 is $C(O)R^3$ as defined above. Unsubstituted compounds of formula (VI') can be reacted under appropriate conditions with sulfonyl chlorides to give compounds of formula (VI') where R^1 is $S(O)_2R^3$ as defined above. Unsubstituted compounds of formula (VI') can be reacted under appropriate conditions with isocyanates to give compounds of formula (VI') where R^1 is $C(O)N(R^3R^{3a})$ as defined above. Unsubstituted compounds of formula (VI') can be reacted under appropriate conditions with chloroformates to give compounds of formula (VI') where R^1 is $C(O)OR^3$ as defined above.

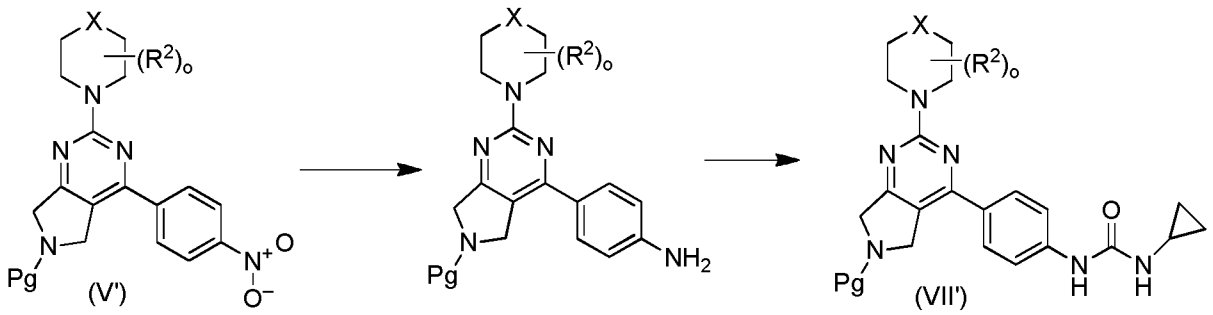


Scheme 4

Compounds of formula (VI') where T^3 is 4-nitrophenyl can be reduced to the aniline by for example reaction with hydrogen with palladium on charcoal catalyst in a suitable solvent. The

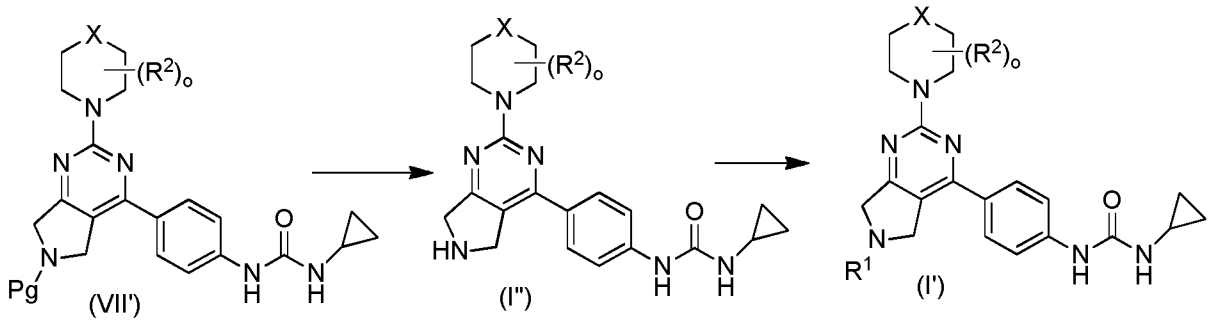
resulting aniline can then be converted by various methods to the urea. For example the aniline can be reacted with cyclopropyl isocyanate to form compounds of formula (I') wherein T^0 is phenyl substituted with cyclopropyl urea. Other methods of urea formation are also possible for example conversion to an intermediate phenyl carbamate and subsequent reaction with amines.

Alternatively from compounds of formula (V) the urea formation as described in scheme 4 above can be performed first



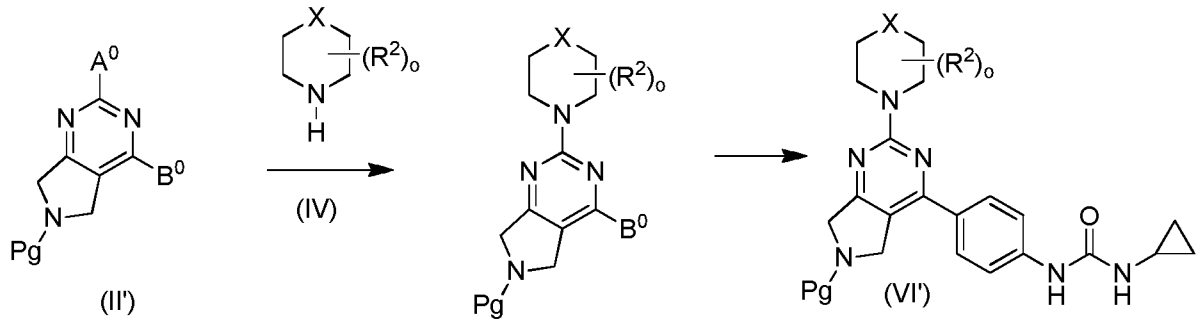
Scheme 5

For example taking compound (V') wherein T^3 is 4-nitrophenyl reducing to the aniline and converting to the urea as described for scheme 4 above gives compound (VII') wherein T^0 is phenyl substituted with cyclopropyl urea.



Scheme 6

Removal of the protection group gives compound of formula (I'') wherein R1 is H. For example when Pg is Boc then deprotection can be achieved using methods well known to those skilled in the art (for example with HCl or TFA in organic solvent). Compounds of formula (I), wherein R^1 is H may be isolated in the form of salts or as free base. Compound (I'') may be substituted as described for compound (VI) above or otherwise to give compound (I') wherein R1 is other than H.



Scheme 7

In an alternative route compound (II') can be reacted directly with a suitable morpholine or thiomorpholine (IV) (for example 3-S-Me morpholine) to yield as the minor isomer a compound of formula (VIII'). Suzuki reaction with a suitable boronate ester or boronic acid (for example 1-cyclopropyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea) gives compounds of formula (VI') wherein T^0 is phenyl substituted with cyclopropyl urea. Deprotection of compound (VI') as described above and optional addition of R^1 other than H gives products of formula (I) wherein R^1 is H or R^1 other than H respectively.

Compounds of the present invention may be prepared by one of the methods described above or in an analogous way as well as by using methods well known in the art. For a practitioner in the art it is clear the above reactions may comprise further protection and/or activation steps depending upon the chemical nature of further substitutents.

It will be appreciated that novel intermediates described herein form another embodiment of the present invention.

Examples

Abbreviations:

DCE	Dichloroethane
DCM	Dichloromethane
DIPEA	*N,N*-Diisopropylethylamine
DME	Ethylene Glycol di-methyl ether
DMF	*N,N*-Dimethylformamide
EDC	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
Et_3N	Triethylamine

EtOAc	Ethyl acetate
EtOH	Ethanol
H_2	Hydrogen Gas
H_2O	Water
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HCl	Hydrochloric Acid
HCO_2H	Formic Acid
MeCN	Acetonitrile
MeOH	Methanol
$MgSO_4$	Magnesium sulphate
MP-TsOH	Macroporous polystyrene resin with a p-toluenesulfonic acid functional group
Na_2CO_3	Sodium Carbonate
Na_2SO_4	Sodium Sulphate
$NaHCO_3$	Sodium Hydrogen Carbonate
NH_3	Ammonia
$Pd(PPh_3)_2Cl_2$	Bis(triphenylphosphine)palladium(II) chloride
$Pd(PPh_3)_2Cl_2$.DCM	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
petrol ether	petroleum ether bp 40-60 ^{0}C
SCX-II	Silica based sorbent with a chemically bonded propylsulfonic acid functional group.
STAB	Sodium triacetoxy borohydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

Analytical methods

1) Analysis performed on an Agilent 1100 system with following conditions.

Solvents: A= H_2O with 0.1% HCO_2H

B= MeCN with 0.1% HCO_2H

C= H_2O with 0.1% NH_3

D= MeCN with 0.1% NH_3

Temperature: 40°C

Wavelength: 254nm and 210nm

Mass spec data were gathered in positive electrospray ionisation mode from 150 and 700 amu.

Method A

Column: Phenomenex Gemini-C18, 4.6 x 150 mm, 5 microns

Gradient Conditions:

Time (min)	%A	%B
0.00	95.0	5.0
11.00	5.0	95.0
13.00	5.0	95.0
13.01	95.0	5.0
14.00	95.0	5.0

Flow Rate: 1 ml/min

Method B

Column: Phenomenex Gemini-C18, 3.0 x 30 mm, 3 microns

Gradient Conditions:

Time (min)	%A	%B
0.00	95.0	5.0
3.00	5.0	95.0
4.50	5.0	95.0
4.60	95.0	5.0
5.00	95.0	5.0

Flow Rate: 1.2 ml/min

Method C

Column: Phenomenex Gemini-C18, 3.0 x 30 mm, 3 microns

Gradient Conditions:

Time (min)	%C	%D
0.00	95.0	5.0
3.00	0.0	100.0
4.50	0.0	100.0

4.60	95.0	5.0
5.00	95.0	5.0

Flow Rate: 1.2 ml/min

2) Analysis performed on an Waters uPLC-SQD

Solvents: A= H_2O with 0.1% HCO_2H
B= MeCN with 0.1% HCO_2H
C= H_2O with 0.1% NH_3
D= MeCN with 0.1% NH_3

Temperature: 40°C

Wavelength: Photodiode array detection 210-400nm

The mass spec data were gathered in positive or negative mode, scanning for masses between 150 and 700amu.

Method D

Column: Waters Acquity UPLC BEH C18, 2.1 x 30 mm, 1.7 microns

Gradient Conditions:

Time (min)	%A	%B
0.00	95.0	5.0
0.20	95.0	5.0
1.00	5.0	95.0
1.50	5.0	95.0
1.70	95.0	5.0
2.70	95.0	5.0

Flow Rate: 0.5 ml/min

Method E

Column: Waters Acquity UPLC BEH C18, 2.1 x 30 mm, 1.7 microns

Gradient Conditions:

Time (min)	%C	%D
0.00	95.0	5.0
0.20	95.0	5.0
1.00	5.0	95.0
1.50	5.0	95.0

1.70	95.0	5.0
2.70	95.0	5.0

Flow Rate: 0.5 ml/min

3) Analysis performed on an Waters – ZQ prep system

Solvents: A= H_2O with 0.1% HCO_2H

B= (95% MeCN:5% H_2O) with 0.1% HCO_2H

Temperature: Room Temperature

Wavelength: Photodiode array detection 200-400nm

The mass spec data were gathered in positive or negative mode, scanning for masses between 150 and 700 amu using a 20V cone Voltage.

Method F

Column: Phenomenex Gemini NX C18 30 x 3mm 3µm

Gradient Conditions:

Time (min)	%A	%B
0.00	95.0	5.0
0.50	95.0	5.0
3.00	0.0	100.0
4.50	0.0	100.0
4.60	95.0	5.0
6.00	95.0	5.0

Flow Rate: 1.5 ml/min

4) Analysis performed on Agilent Technologies 1200 series with G6110A Quadrupole LC/MS

Solvents: A= MeOH

B= H_2O with 0.07% HCO_2H

Temperature: 25°C

Wavelength: Photodiode array detection

The mass spec Ion Source : API-ES.

Method G

Column : Ultimate AQ-C18, 3µm, 2.1×50mm

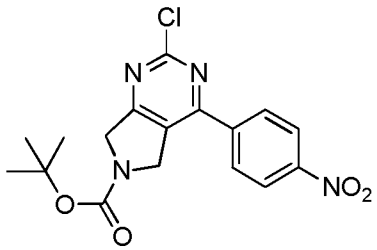
Gradient Conditions:

Time (min)	%A	%B
0	20	80
0.5	20	80
1.2	98	2
8	98	2
8.2	20	80
10	20	80

Flow Rate: 0.4 ml/min

Intermediate 1

tert-butyl 2-chloro-4-(4-nitrophenyl)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate

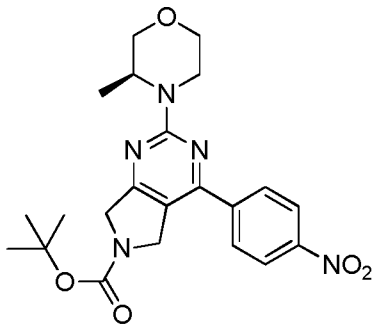


tert-butyl 2,4-dichloro-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (5g, 17.3 mmol), 4-nitrophenylboronic acid pinacol ester (3.17g, 19.0 mmol), $Pd(PPh_3)_2Cl_2$.DCM (706 mg, 0.87 mmol), and Na_2CO_3 (5.5g, 51.9 mmol) were dissolved in a mixture of DME:H_2O (4:1) (degassed prior to use) and stirred at 90^0C for 3h. The mixture was partitioned between H_2O and EtOAc. The organic layer was recovered, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The desired product was isolated by flash column chromatography (silica) using a gradient of 0-50% EtOAc in petrol ether yielding the title compound as a yellow solid (3.88g, 10.3 mmol, 60% yield).

LCMS (method B), ($M+H^+$) 377,379; Rt = 3.04 min.

Intermediate 2

(S)-tert-butyl 2-(3-methylmorpholino)-4-(4-nitrophenyl)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate



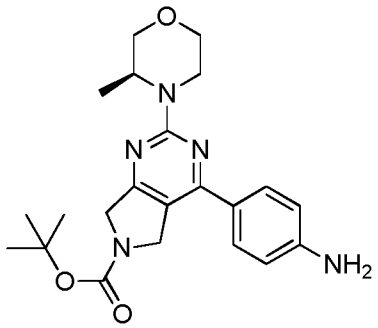
tert-butyl 2-chloro-4-(4-nitrophenyl)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (Intermediate 1) (2g, 5.3 mmol) was dissolved in dry DMF and stirred at 50^0C with 3S-methyl morpholine (1.07 mL, 10.6 mmol) and Et_3N (1.48 mL, 10.6 mmol) overnight. A further 1.07 mL of 3S-methyl morpholine and Et_3N (1.48 mL) were added and heating continued at 50^0C overnight. The mixture was cooled to room temperature and the solvent was removed *in vacuo*. The desired product was isolated by flash column chromatography (silica) using a gradient of 0-50% EtOAc in petrol ether yielding the title compound as a yellow solid (1.56g, 3.54 mmol, 67% yield).

^{1}H NMR (d_6-DMSO) 8.40-8.34 (m, 2H), 8.20-8.08 (m, 2H), 4.77 (s, 2H), 4.74-4.63 (br s, 1H), 4.47 (d, 2H), 4.33 (d, 1H), 3.95 (d, 1H), 3.75 (d, 1H), 3.60 (s, 1H), 3.50-3.39 (m. 1H), 3.27-3.16 (m, 1H), 1.46 (s, 9H), 1.22 (d, 3H).

LCMS (method B), ($M+H^+$) 442 Rt = 3.28 min.

Intermediate 3

(S)-tert-butyl 4-(4-aminophenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate



(S)-tert-butyl 2-(3-methylmorpholino)-4-(4-nitrophenyl)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (Intermediate 2) (1.56g, 3.54 mmol) was dissolved in EtOH and stirred with Pd/C (10%) (156 mg) at room temperature under H_2 overnight. The mixture was filtered through a celite 545 cake (pre conditioned by washing with MeOH) and washed with MeOH.

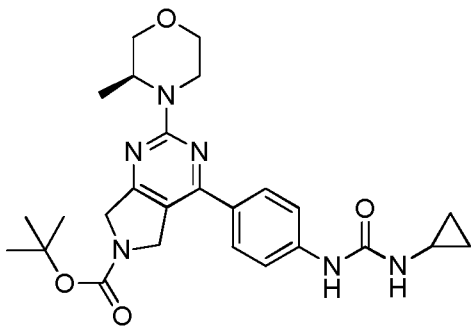
The solvent was removed *in vacuo* to yield the title compound as a bright yellow solid (1.16g, 2.82 mmol, 80% yield).

^{1}H NMR (d_6-DMSO) 7.70-7.61 (m, 2H), 6.65 (d, 2H), 5.74 (d, 2H), 4.73-4.65 (br s, 3H), 4.42-4.26 (m, 3H), 3.92 (d, 1H), 3.72 (d, 1H), 3.59 (d, 1H), 3.47-3.38 (m, 1H), 3.21-3.09 (m, 1H), 1.46 (s, 9H), 1.20 (d, 3H).

LCMS (method B), ($M+H^+$) 412 Rt = 2.81 min

Intermediate 4 (Example I4)

(S)-tert-butyl 4-(4-(3-cyclopropylureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate



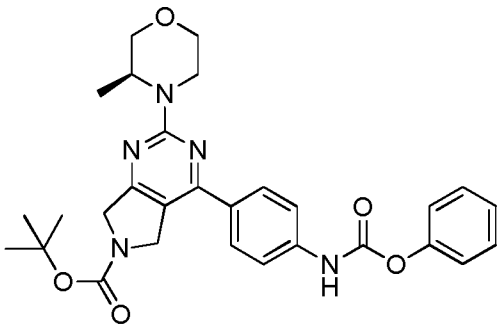
(S)-tert-butyl 4-(4-aminophenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (Intermediate 3) (1g, 2.43 mmol) was dissolved in dry DCM and stirred with cyclopropane isocyanate (310 μL, 3.66 mmol) at room temperature overnight. The solvent was removed *in vacuo* and the desired product was isolated by flash column chromatography (silica) using a gradient of 0-100% EtOAc in petrol ether yielding the title compound as a yellow gum (645mg, 1.30 mmol, 54% yield).

^{1}H NMR (d_6-DMSO) 8.63 (d, 1H), 7.86-7.75 (m, 2H), 7.56 (d, 2H), 6.49 (d, 1H), 4.79-4.63 (m, 3H), 4.45-4.27 (m, 3H), 4.00-3.89(m, 1H), 4.73 (d, 1H), 4.60 (d, 1H), 3.52-3.40 (m, 1H), 3.22-3.11 (m, 1H), 2.59-2.52 (m, 1H), 1.46 (s, 9H), 1.20 (d, 3H), 0.68-0.59 (m, 2H), 0.46-0.39 (m, 2H).

LCMS (method B), ($M+H^+$) 495 Rt = 2.85 min.

Intermediate 5 (Example I5)

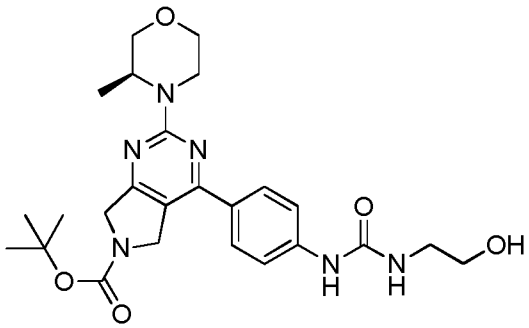
(S)-tert-butyl 2-(3-methylmorpholino)-4-(4-((phenoxycarbonyl)amino)phenyl)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate



(S)-tert-butyl 4-(4-aminophenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (Intermediate 3) (200mg, 0.49mmol) was dissolved in DCM and stirred with $NaHCO_3$ (61mg, 0.73 mmol) and phenyl chloroformate (92µL, 0.73mmol) at room temperature overnight. The solvent was removed *in vacuo* and the desired product was isolated by flash column chromatography (silica) using a gradient of 0-100% EtOAc in petrol ether yielding the title compound as a yellow gum (230mg, 0.43 mmol, 89% yield).
LCMS (method B), ($M+H^+$) 532 Rt = 3.33 min.

Intermediate 6 (Example I6)

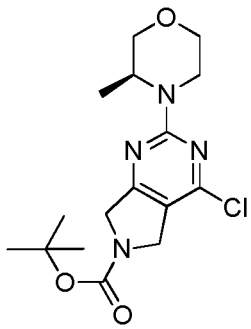
(S)-tert-butyl 4-(4-(3-(2-hydroxyethyl)ureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate



(S)-tert-butyl 2-(3-methylmorpholino)-4-(4-((phenoxycarbonyl)amino)phenyl)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (Intermediate 5) (115mg, 0.22 mmol) was dissolved in dry DMF and stirred with Et_3N (98 µL, 0.70 mmol) and ethanolamine (65 µL, 1.08 mmol) at 50^0C overnight. The solvent was removed *in vacuo* and the desired product was isolated by flash column chromatography (silica) using first, a gradient of 0-100% EtOAc in petrol ether, then 0-10% MeOH in EtOAc yielding the title compound as a yellow gum (54mg, 0.11 mmol, 51% yield).
LCMS (Method D), ($M+H^+$) 499 Rt = 1.05 min.

Intermediate 7

(S)-tert-butyl 4-chloro-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate

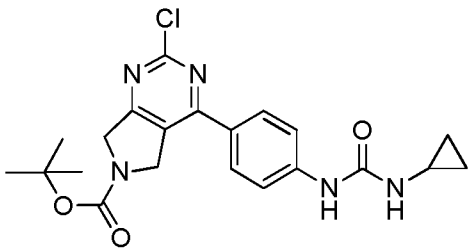


To a stirring solution of tert-butyl 2,4-dichloro-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (800 mg, 2.75 mmol) in DCM was added DIPEA (484 µL, 2.75 mmol) and 3S-methyl morpholine (312 mg, 3.09 mmol). The reaction mixture was heated at 30^{0}C overnight . The mixture was partitioned between DCM and saturated $NaHCO_3$ solution. The organic layer was recovered, dried via a hydrophobic frit and the solvent removed *in vacuo*. The title isomer was isolated by flash column chromatography (silica) using a gradient of 0-50% EtOAc in petrol ether (66.8 mg, 0.19 mmol, 6.8% yield).

LCMS (method B), ($M+H^+$) 355, 357 Rt = 3.22 min.

Intermediate 8

tert-butyl 2-chloro-4-(4-(3-cyclopropylureido)phenyl)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate



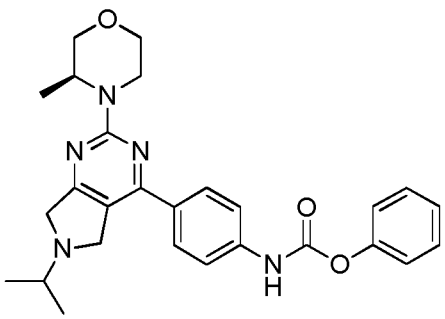
tert-butyl 2,4-dichloro-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (500 mg, 1.72 mmol), 1-cyclopropyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (521 mg, 1.72 mmol), Na_2CO_3 (457 mg, 4.31 mmol) and $Pd(PPh_3)_2Cl_2$.DCM (70 mg, 0.086 mmol) were stirred in a degassed mixture of 1,4-dioxane/H_2O (15:1) (6.4 mL) and heated in a microwave at 120 ^{0}C for 1 hr. The reaction mixture was partitioned between EtOAc and H_2O.

The organic layer was recovered and washed first with a saturated $NaHCO_3$ solution then brine. The organics were dried over Na_2SO_4, filtered and solvent removed *in vacuo*. The residue was purified by flash chromatography (silica) using a 20-50% EtOAc in petrol ether mixture as eluent, to yield the title compound as a cream solid (330 mg, 0.77 mmol, 45% yield).

LCMS (method D), $(M+H^+)$ 430 Rt = 1.11 min.

Intermediate 9 (Example I9)

(S)-phenyl (4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)carbamate

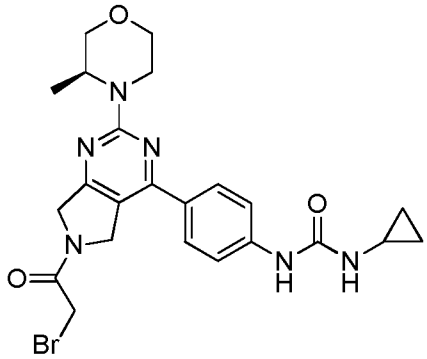


(S)-tert-butyl 2-(3-methylmorpholino)-4-(4-((phenoxycarbonyl)amino)phenyl)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (Intermediate 5) (700 mg, 1.32 mmol) was dissolved in 4M HCl in 1,4-dioxane and stirred at room temperature for 2.5 hours. The solvent was removed *in vacuo* to yield (S)-phenyl (4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)carbamate as the hydrochloride salt in quantitative yield. The product (650 mg, 1.37 mmol) was dissolved in DCE and stirred with acetone (205 µL, 2.78 mmol) and Et_3N (384 µL, 2.78 mmol) at room temperature for 2h. STAB (1.18g, 5.06 mmol) and a few drops of glacial acetic acid were added to the reaction mixture and stirring continued overnight. The mixture was partitioned between H_2O and EtOAc. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (silica) using a gradient of 0-100% EtOAc in petrol ether as eluent to yield the title compound (150 mg, 0.2 mmol, 23% yield).

LCMS (method G), $(M+H^+)$ 474 Rt = 7.56 min.

Intermediate 10 (Example I10)

(S)-1-(4-(6-(2-bromoacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea

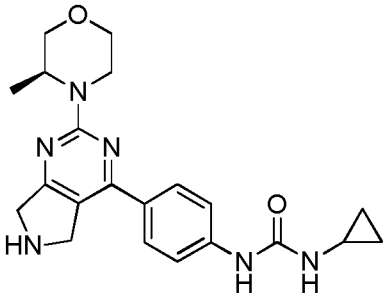


(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 1) (hydrochloride salt) (70mg, 0.16 mmol) was added to a stirring solution of Et_3N (45 μL, 0.32 mmol) in DCM. The mixture was stirred at 0 ^{0}C for 15 minutes before adding 2-bromoacetyl bromide (22 μL, 0.24 mmol) dropwise. The reaction mixture was stirred for 3 hours before partitioning between H_2O and DCM. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The product was purified by flash column chromatography (silica) using a mixture of DCM:MeOH (15:1) as eluent to yield the title compound (50 mg, 0.09 mmol, 60% yield).

LCMS (method G), ($M+H^+$) 515, 5174 Rt = 9.53 min.

Example 1

(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



(S)-tert-butyl 4-(4-(3-cyclopropylureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (Intermediate 4) (645 mg, 1.30 mmol) was dissolved in 4M HCl in dioxane and stirred at room temperature for 3h. The solvent was removed *in vacuo* to

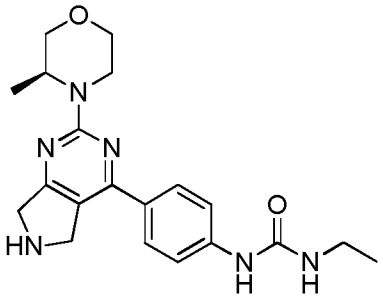
yield the desired hydrochloride salt in quantitative yields. A portion of the compound was purified by prep HPLC at high pH. The fractions were absorbed onto a SCX-2 cartidge and rinsed first with MeOH then 2M NH_3 in MeOH to release the product. The solvent was removed *in vacuo* to yield the title compound as a orange solid (630 mg, 1.46 mmol, quantitatitive yield).

^{1}H NMR (d_6-DMSO) 8.61 (s, 1H), 7.81 (d, 2H), 7.54 (d, 2H), 6.49 (d, 1H), 4.75-4.64 (m, 1H), 4.38-4.25 (m, 3H), 4.00-3.87(m, 3H), 3.73 (d, 1H), 3.65-3.57 (dd, 1H),3.48-3.39 (m, 1H), 3.22-3.12 (m, 1H), 2.60-2.52 (m, 1H), 1.20 (d, 3H), 0.68-0.61 (m, 2H), 0.45-0.39 (m, 2H).

LCMS (method A), ($M+H^+$) 395 Rt = 5.21 min

Example 2

(S)-1-ethyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



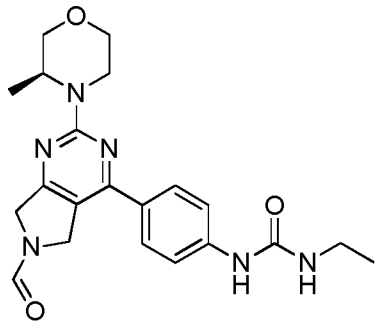
To a degassed solution of (S)-tert-butyl 4-chloro-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (Intermediate 7) (66.8 mg, 0.19 mmol) in DME:H_2O:EtOH (7:3:2) were added 1-ethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (65.6 mg, 0.23 mmol), $Pd(PPh_3)_2Cl_2$.DCM (6.63mg, 0.009 mmol) and Na_2CO_3 (30 mg, 0.28 mmol). The reaction mixture was stirred at 120 ^{0}C in a microwave for 30 minutes. The mixture was partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic layer was recovered, filtered through celite and then rinsed with brine. The EtOAc solution was absorbed onto a SCX-2 cartridge and rinsed first with MeOH (exposure time 30 mins), then 2M NH_3 in MeOH to elute the the partially deprotected product. The solvent was removed *in vacuo* and the material treated with 50% TFA in DCM to complete the deprotection. The product was absorbed onto a MP-TsOH cartidge and rinsed first with MeOH then 2M NH_3 in MeOH to release the product. The solvent was removed *in vacuo*. The compound was purified by prep HPLC first at low then at high pH. The fractions were absorbed onto a MP-TsOH cartidge and rinsed first with MeOH then 2M NH_3 in MeOH to release the product. The solvent was removed *in vacuo* to yield the title compound (5.4 mg, 0.014 mmol, 7.48%).

^{1}H NMR (d_6-DMSO) 8.77 (s, 1H), 7.80 (d, 2H), 7.54 (d, 2H), 6.22-6.18 (m, 1H), 4.74-4.63 (m, 1H), 4.39-4.26 (m, 1H), 4.03-3.88 (m, 1H), 3.63-3.56 (m, 1H), 3.47-3.39 (m, 3H), 3.25-3.07 (m, 5H), 2.67 (s, 1H), 2.33 (s, 1H), 1.19 (d, 3H), 1.05 (t, 3H).

LCMS (method A), ($M+H^+$) 383, Rt = 5.09 min.

Example 3

(S)-1-ethyl-3-(4-(6-formyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



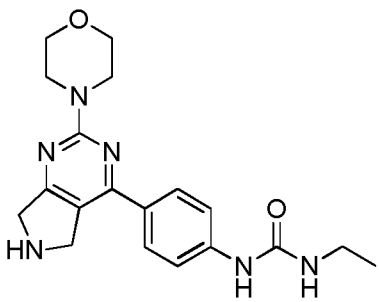
Product formed from Example 2 when concentrating HPLC fractions from MeCN, H_2O and HCO_2H solution with heat *in vacuo*. Purified by prep HPLC at high pH to yield the title compound (3.8 mg, 0.0093 mmol, 4.94% yield).

^{1}H NMR (d_6-DMSO) 8.83 (s, 1H), 8.37(s, 1H), 7.88-7.82 (m, 2H), 7.59-7.53 (m, 2H), 6.26-6.17 (m, 1H), 5.13-2-5.07 (m, 1H), 4.80-4.69 (m, 3H), 4.44 (s, 1H), 4.37-4.30 (m, 1H), 3.99-3.90 (m, 1H), 3.74 (d, 1H), 3.62-6.57 (m, 1H), 3.47-3.40 (m, 2H), 3.19-3.07 (m, 2H), 1.21 (d, 3H), 1.06 (t, 3H).

LCMS (method A), ($M+H^+$) 411, Rt = 8.05 min.

Example 4

1-ethyl-3-(4-(2-morpholino-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



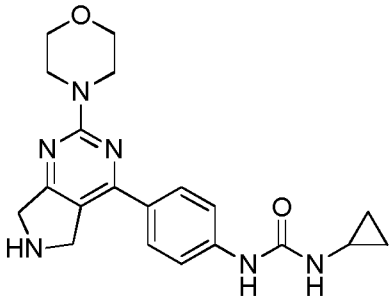
Method as described for Example 1, using morpholine and ethyl isocyanate as starting materials in the relevant steps. The solvent was removed *in vacuo*, and the compound was purified by trituration with a mixture of petrol ether:EtOAc (9:1). The bright yellow solid was filtered off to yield the title compound as the hydrochloride salt (115mg, 0.28 mmol, 75% yield).

^{1}H NMR (d_6-DMSO) 10.09-9.95 (m, 2H), 9.08 (s, 1H), 7.81 (d, 2H), 7.58 (d, 2H), 4.70 (t, 2H), 4.35 (t, 2H), 3.80 (t, 4H), 3.68 (t, 4H), 3.16-3.06 (q, 2H), 1.06 (t, 3H).

LCMS (method A), ($M+H^+$) 369, Rt = 4.70 min.

Example 5

1-cyclopropyl-3-(4-(2-morpholino-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



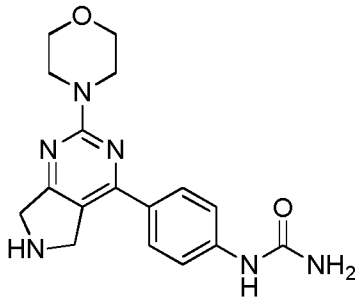
Method as described for Example 1 using morpholine as starting material in the relevant steps. Purification by prep. HPLC low pH to give a cream solid (8 mg, 0.021 mmol, 28% yield).

^{1}H NMR (d_6-DMSO) 8.66 (s, 1H), 8.17 (s, 1H), 7.82 (d, 2H), 7.54 (d, 2H), 6.52 (s, 1H), 4.31 (s, 2H), 3.94 (s, 2H), 3.72 (m, 8H), 2.59 – 2.53 (m, 1H), 0.71 – 0.55 (m, 2H), 0.48 – 0.35 (m, 2H).

LCMS (Method A), ($M+H^+$) 381, Rt= 5.02 min.

Example 6

1-(4-(2-morpholino-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



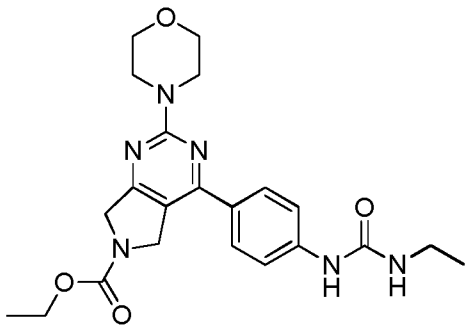
Isolated as a by product during purification by prep HPLC of example 5. Further purified by HPLC at low pH to give a cream solid (4.7 mg, 0.014 mmol, 16% yield).

^{1}H NMR (d_6-DMSO) 8.85 (s, 1H), 8.17 (s, 1H), 7.82 (d, 2H), 7.54 (d, 2H), 5.97 (s, 2H), 4.31 (s, 2H), 3.95 (s, 2H), 3.82 – 3.61 (m, 8H).

LCMS (Method A), ($M+H^+$) 341, Rt= 4.37 min.

Example 7

ethyl 4-(4-(3-ethylureido)phenyl)-2-morpholino-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate

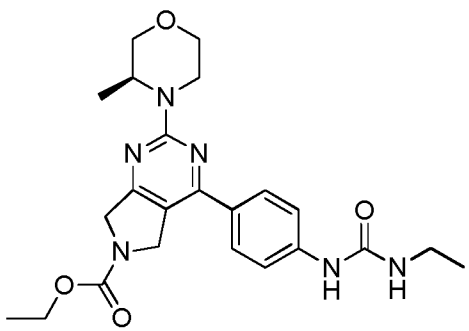


1-ethyl-3-(4-(2-morpholino-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea hydrochloride (Example 4) (100mg, 0.25 mmol) was dissolved in dry THF and stirred with $NaHCO_3$ (25mg, 0.29 mmol) and ethyl chloroformate (47 µL, 0.49 mmol) at room temperature for 2h. The solvent was removed *in vacuo* and the product purified by prep HPLC at low pH, yielding the title compound as a yellow solid (35.7mg, 0.08 mmol, 33%).

^{1}H NMR (d_6-DMSO) 8.80-8.75 (m, 1H), 7.87-7.78 (m, 2H), 7.55 (s, 2H), 6.25-6.18 (m, 1H), 4.80 (d, 2H), 4.45 (d, 2H), 4.17-4.08 (m, 2H), 3.80-3.73 (m, 4H), 3.73-3.63 (m, 4H), 3.16-3.06 (m, 2H), 1.28-1.21 (m, 3H), 1.06 (t, 3H).

Example 8

(S)-ethyl 4-(4-(3-ethylureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate



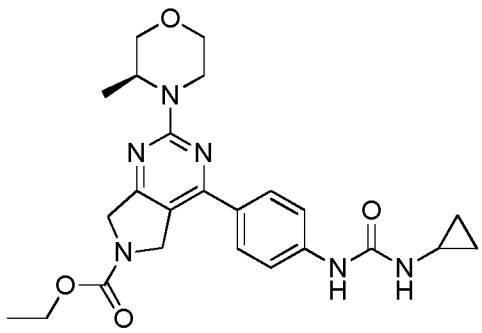
Method as described for Example 7 using (S)-1-ethyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea hydrochloride as starting material. The solvent was removed *in vacuo* and the product purified by prep HPLC at high pH to yield the title compound as a pale yellow solid (13.7 mg, 0.03 mmol, 23% yield).

^{1}H NMR (MeOD) 7.83 (t, 2H), 7.50 (d, 2H), 4.82-4.75 (m, 3H), 4.47 (d, 2H), 4.44-4.36 (m, 1H), 4.26-4.17 (m, 3H), 4.01-3.95 (m, 1H), 3.79 (d, 1H), 3.75-3.68 (m, 1H), 3.60-3.51 (m, 1H), 3.24-3.20 (qn, 2H), 3.19-3.12 (q, 2H), 1.36-1.31 (m, 3H), 1.29 (d, 3H), 1.17 (t, 3H).

LCMS (method A), ($M+H^+$) 455 Rt = 9.43 min

Example 9

(S)-ethyl 4-(4-(3-cyclopropylureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate



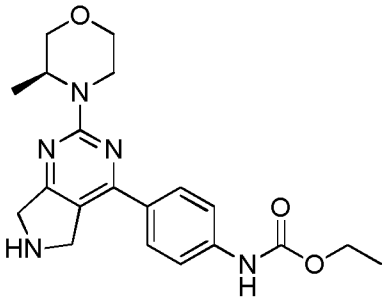
Method as described for Example 7 using (S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea as starting material. The reaction mixture was partitioned between EtOAc and H_2O. The organic layer was recovered, washed with brine dried with Na_2SO_4 and solvent removed *in vacuo*. The residue was purified by flash chromatography (silica) using 50-100% EtOAc in petrol ether as eluent to yield the title compound as a yellow solid. (3.8 mg, 0.008 mmol, 15% yield).

^{1}H NMR (d_6-DMSO) 8.65 (d, 1H), 7.83 (dd, 2H), 7.57 (d, 2H), 6.49 (s, 1H), 4.80 (d, 2H), 4.70 (d, 1H), 4.46 (d, 2H), 4.33 (d, 1H), 4.13 (qn, 2H), 3.93 (dd, 1H), 3.73 (d, 1H), 3.60 (dd, 1H), 3.44 (td, 1H), 3.19 (td, 1H), 2.61 – 2.53 (m, 1H), 1.29 – 1.19 (m, 6H), 0.70 – 0.60 (m, 2H), 0.46 – 0.35 (m, 2H).

LCMS (Method A), ($M+H^+$) 467, Rt= 9.39 min.

Example 10

(S)-ethyl (4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)carbamate



Step1: tert-butyl 2-chloro-4-(4-(3-cyclopropylureido)phenyl)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (Intermediate 8) (409 mg, 0.95 mmol), 3S-methyl morpholine (761 mg, 7.5 mmol) and DIPEA (0.83 mL, 4.75 mmol) were dissolved in EtOH (8 mL) and heated in a microwave at 120 ^{0}C for 24 hours. The reaction mixture was partitioned between EtOAc and H_2O. The organic layer was recovered, washed with brine dried with Na_2SO_4 and solvent removed *in vacuo*. The residue was purified by flash chromatography (silica) using a gradient of 20-50% EtOAc in petrol ether as eluent, to yield (S)-tert-butyl 4-(4-((ethoxycarbonyl)amino)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate as the minor product. (24 mg, 0.05 mmol, 5% yield).

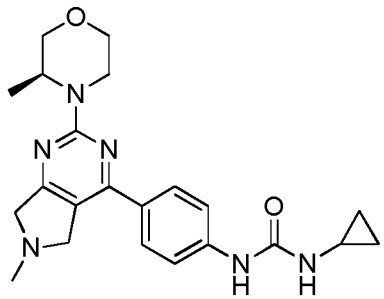
Step2: Method as per Example 1. Purified by prep HPLC at high pH to give the title compound (7.7 mg, 0.02 mmol, 40 % yield)

^{1}H NMR (d_6-DMSO) 9.88 (s, 1H), 7.85 (d, 2H), 7.60 (d, 2H), 4.70 (dd, 1H), 4.32 (d, 1H), 4.26 (s, 2H), 4.15 (q, 2H), 3.97 – 3.86 (m, 3H), 3.72 (d, 1H), 3.60 (dd, 1H), 3.44 (td, 2H), 3.17 (td, 1H), 1.26 (t, 3H), 1.19 (d, 3H).

LCMS (Method A), ($M+H^+$) 384, Rt= 5.60 min.

Example 11

(S)-1-cyclopropyl-3-(4-(6-methyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



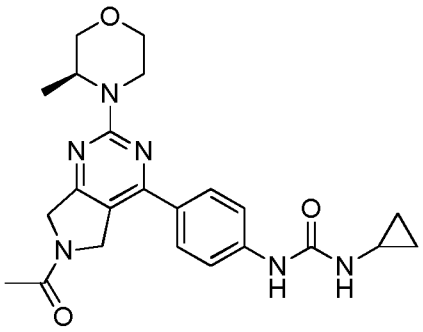
(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 1) (150 mg, 0.35 mmol), paraformaldehyde (20mg, 0.70 mmol) and Et_3N (97 µL, 0.70 mmol) were dissolved in DCE and stirred at room temperature for 1h. STAB (147 mg, 0.70 mmol) was added and the reaction mixture stirred at room temperature over 2 days. The mixture was partitioned between H_2O and DCM. The organic layer was recovered, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The desired product was isolated by flash column chromatography (silica) using a gradient of 0-20% MeOH in EtOAc (44 mg, 0.111 mmol, yield 31%).

^1H NMR (d_6-DMSO) 8.64 (s, 1H), 7.77 (d, 2H), 7.53 (d, 2H), 6.50 (d, 1H), 4.73-4.64 (m, 1H), 4.34-4.27 (m, 1H), 4.11-4.04 (br s, 1H), 4.02 (d, 2H), 3.92-3.88 (m, 1H), 3.51 (s, 3H), 3.63-3.56 (m, 1H), 3.48-3.39 (m, 1H), 3.19-3.10 (m, 3H), 2.58-2.53 (m, 1H), 1.19 (d, 3H), 0.67-0.60 (m, 2H), 0.44-0.38 (m, 2H).

LCMS (method A), ($M+H^+$) 409 Rt = 5.24 min

Example 12

(S)-1-(4-(6-acetyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea



To a stirred solution of (S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 1) (29 mg, 0.07 mmol) in DCM (1.5 mL) was added acetyl chloride (10 uL, 0.147 mmol) and Et_3N (20 uL, 0.147 mmol). The

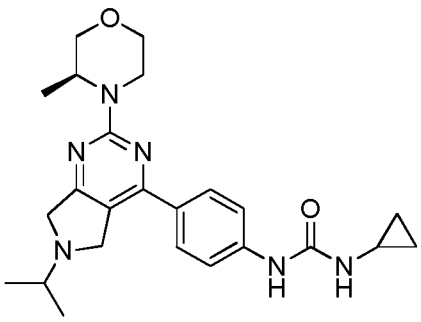
reaction mixture stirred at room temperature overnight. The reaction mixture was partitioned between DCM and H_2O. The organic layer was recovered, washed with brine and the solvent removed *in vacuo*. The crude product was purified by flash chromatography using a Biotage KP-NH cartridge 11g with a gradient of 0-5% MeOH in DCM as eluent to yield the title compound as a cream solid (3mg, 0.007 mmol, 10% yield).

^{1}H NMR (d_6-DMSO) 8.71 (d, 1H), 7.94 – 7.80 (m, 2H), 7.58 (dd, 2H), 6.54 (dd, 1H), 5.03 (s, 1H), 4.77 (s, 1H), 4.71 (s, 2H), 4.42 (s, 1H), 4.33 (d, 1H), 3.94 (d, 1H), 3.74 (d, 1H), 3.61 (d, 1H), 3.51 – 3.40 (m, 1H), 3.20 (td, 1H), 2.60 – 2.55 (m, 1H), 2.10 (d, 3H), 1.21 (d, 3H), 0.71 – 0.59 (m, 2H), 0.48 – 0.35 (m, 2H).

LCMS (Method A), ($M+H^+$) 437, Rt= 7.76 min.

Example 13

(S)-1-cyclopropyl-3-(4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



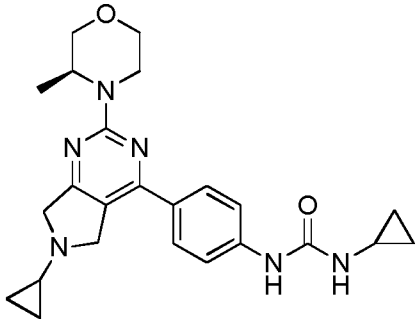
Method as described for Example 11 using acetone as starting material and DCM as solvent. Purified by prep HPLC at high pH to yield the title compound (25 mg, 0.06 mmol, 23% yield)

^{1}H NMR (d_6-DMSO) 8.61 (s, 1H), 7.80 (d, 2H), 7.54 (d, 2H), 6.48 (d, 1H), 4.68 (d, 1H), 4.31 (d, 1H), 4.05 (s, 2H), 3.92 (dd, 1H), 3.81 – 3.68 (m, 3H), 3.60 (dd, 1H), 3.44 (td, 1H), 3.16 (td, 1H), 2.78 (qn, 1H), 2.61 – 2.52 (m, 1H), 1.19 (d, 3H), 1.12 (d, 6H), 0.70 – 0.60 (m, 2H), 0.45 – 0.37 (m, 2H).

LCMS (Method A), ($M+H^+$) 437, Rt= 5.36 min.

Example 14

(S)-1-cyclopropyl-3-(4-(6-cyclopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



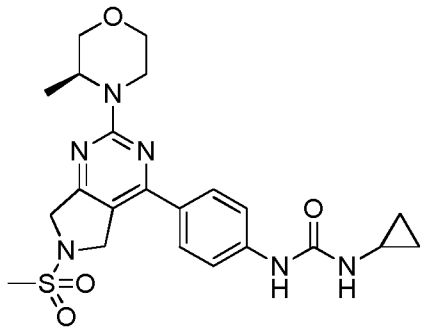
Method as described for Example 11 using cyclopropanone as starting material and DCM as solvent. Purified by prep HPLC at high pH to yield the title compound (14 mg, 0.03 mmol, 12% yield)

^{1}H NMR (d_6-DMSO) 8.62 (s, 1H), 7.78 (d, 2H), 7.54 (d, 2H), 6.48 (d, 1H), 4.77 – 4.61 (m, 1H), 4.30 (d, 1H), 4.22 – 4.12 (m, 2H), 3.92 (dd, 1H), 3.88 – 3.80 (m, 2H), 3.72 (d, 1H), 3.60 (dd, 1H), 3.49 – 3.38 (m, 1H), 3.22 – 3.10 (m, 1H), 2.60 – 2.54 (m, 1H), 2.16 – 2.07 (m, 1H), 1.19 (d, 3H), 0.69 – 0.61 (m, 2H), 0.53 – 0.36 (m, 6H). will

LCMS (Method A), ($M+H^+$) 435, Rt= 5.58 min.

Example 15

(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



To a stirred solution of (S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 1) (97 mg, 0.25 mmol) in MeCN:1,4-dioxane (3:2) was added Et_3N (103 uL, 0.74 mmol) and methane sulfonylchloride (57 uL, 0.74 mmol). The reaction mixture was stirred at room temperature overnight. Further methane sulfonylchloride (57 uL, 0.74 mmol) and Et_3N (103 uL, 0.74 mmol) were added and stirring was continued at room temperature overnight. The reaction mixture was partitioned between EtOAc and H_2O. A precipitate formed which was collected by filtration. The precipitate was

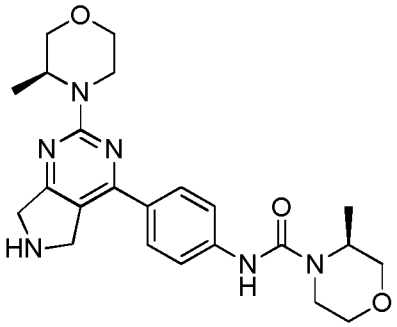
further purified by prep HPLC at high pH to yield the title compound as a pink solid (24 mg, 0.05 mmol, 20% yield).

^{1}H NMR (d_6-DMSO) 8.66 (s, 1H), 7.84 (d, 2H), 7.57 (d, 2H), 6.48 (d, 1H), 4.88 – 4.76 (m, 2H), 4.71 (dd, 1H), 4.49 (s, 2H), 4.33 (d, 1H), 3.94 (dd, 1H), 3.74 (d, 1H), 3.60 (dd, 1H), 3.44 (td, 1H), 3.20 (td, 1H), 3.06 (s, 3H), 2.60 – 2.53 (m, 1H), 1.22 (d, 3H), 0.69 – 0.61 (m, 2H), 0.45 – 0.37 (m, 2H).

LCMS (Method A), ($M+H^+$) 473, Rt= 8.50 min.

Example 16

(S)-3-methyl-N-(4-(2-((S)-3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)morpholine-4-carboxamide



Step1: tert-butyl 2-chloro-4-(4-(3-cyclopropylureido)phenyl)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (Intermediate 8) (50 mg, 0.116 mmol) and 3S-methyl morpholine (0.5 mL, 4.9 mmol) were heated in a microwave at 120 ^{0}C for 2 hours. The reaction mixture was partitioned between EtOAc and H_2O. The organic layer was recovered, washed with brine dried with Na_2SO_4 and solvent removed *in vacuo*. The residue was purified by flash chromatography (silica) using a gradient of 50-100% EtOAc in petrol ether as eluent followed by purification by prep HPLC at high pH, to yield tert-butyl 4-(4-((S)-3-methylmorpholine-4-carboxamido)phenyl)-2-((S)-3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate. (9 mg, 0.017 mmol, 15% yield).

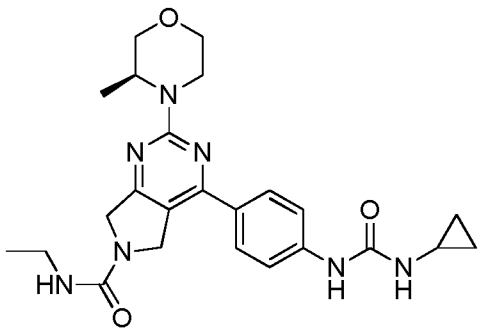
Step2: Method as per Example 1, to give the title compound (5 mg, 0.011 mmol, 71 % yield)

^{1}H NMR (d_6-DMSO) 8.70 (s, 1H), 7.81 (d, 2H), 7.62 (d, 2H), 4.70 (dd, 1H), 4.32 (d, 1H), 4.26 (s, 2H), 4.19 (dd, 1H), 4.00 – 3.82 (m, 4H), 3.79 – 3.69 (m, 2H), 3.69 – 3.60 (m, 2H), 3.60 – 3.52 (m, 2H), 3.50 – 3.40 (m, 2H), 3.23 – 3.10 (m, 2H), 1.20 (d, 6H).

LCMS (Method A), ($M+H^+$) 439, Rt= 5.27 min.

Example 17

(S)-4-(4-(3-cyclopropylureido)phenyl)-N-ethyl-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxamide



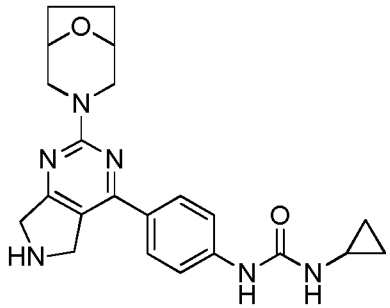
To a stirred solution of (S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 1) (134 mg, 0.34 mmol) in THF (2.5 mL) was added Et_3N (71 uL, 0.51 mmol) followed by ethyl isocyanate (32 uL, 0.40 mmol). The reaction mixture was heated at 50 ^{0}C with stirring for 4.5 hrs. The mixture was partitioned between EtOAc and H_2O. The organic layer was recovered, washed with brine and the solvent removed *in vacuo*. The material was purified by flash column chromatography (silica), using a gradient of 50-100% EtOAc in petrol ether as eluent to yield the title compound as a yellow solid (32 mg, 0.07 mmol, 20% yield).

^{1}H NMR (d_6-DMSO) 8.74 (s, 1H), 7.88 (d, 2H), 7.58 (d, 2H), 6.57 (d, 1H), 6.47 (t, 1H), 4.82 – 4.65 (m, 3H), 4.40 (s, 2H), 4.33 (d, 1H), 3.93 (dd, 1H), 3.73 (d, 1H), 3.61 (dd, 1H), 3.45 (td, 1H), 3.20 – 3.08 (m, 3H), 2.60 – 2.53 (m, 1H), 1.21 (d, 3H), 1.07 (t, 3H), 0.69 – 0.60 (m, 2H), 0.46 – 0.38 (m, 2H).

LCMS (Method A), ($M+H^+$) 466, Rt= 8.01 min.

Example 18

1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea



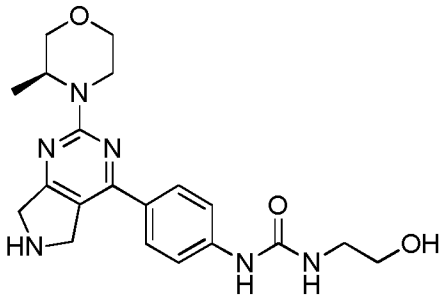
Method as described for Example 1, using 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride and cyclopropane isocyanate as starting materials in the relevant steps. The solvent was removed *in vacuo* and the product was absorbed onto a SCX-2 cartidge and rinsed first with MeOH then 2M NH_3 in MeOH to release the product. The material was further purified by trituration with a mixture of petrol ether:EtOAc (9:1). The pink solid was filtered off to yield the title compound (40 mg, 0.10 mmol, 67% yield).

^{1}H NMR (d_6-DMSO) 8.63 (s, 1H), 7.81 (d, 2H), 7.54 (d, 2H), 6.49 (s, 1H), 4.46-4.39 (br s, 2H), 4.33-4.24 (m, 4H), 3.94 (s, 2H), 3.08 (d, 2H), 2.59-2.53 (m, 1H), 1.85-1.76 (m, 2H), 1.72-1.64 (m, 2H), 0.67-0.60 (m, 2H), 0.44-0.38 (m, 2H).

LCMS (method A), ($M+H^+$) 407, Rt = 5.25 min.

Example 19

(S)-1-(2-hydroxyethyl)-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



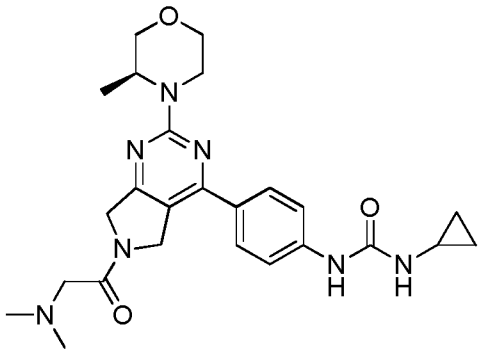
Method as described for Example 1 using (S)-tert-butyl 4-(4-(3-(2-hydroxyethyl)ureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (Intermediate 6) as starting material. The solvent was removed *in vacuo* and the product was absorbed onto a SCX-2 cartidge and rinsed first with MeOH then 2M NH_3 in MeOH to release the title compound as a orange solid (35mg, 0.09 mmol, 81% yield).

^{1}H NMR (d_6-DMSO) 8.90 (s, 1H), 7.81 (d, 2H), 7.51 (d, 2H), 6.33-6.25 (m, 1H), 4.83-4.66 (m, 2H), 4.41-4.27 (m, 3H), 4.01 (s, 2H), 3.97-3.88 (m, 1H), 3.73 (d, 1H), 3.49-3.39 (m, 4H), 3.21-3.12 (m, 4H), 1.18 (d, 3H).

LCMS (method A), ($M+H^+$) 399 Rt = 4.70 min

Example 20

(S)-1-cyclopropyl-3-(4-(6-(2-(dimethylamino)acetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



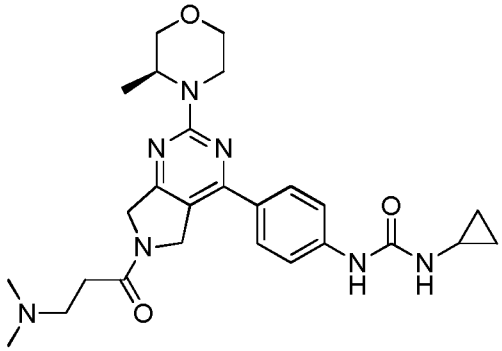
To a stirred solution of (S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 1) (55 mg, 0.14 mmol) and 2-(dimethylamino)acetic acid (14 mg, 0.14 mmol) in DCM:DMF (1.7:1) (2 mL) was added Et_3N (58 uL, 0.42 mmol) and EDC (32 mg, 0.17 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was partitioned between DCM and H_2O. The organic layer was recovered and the solvent removed *in vacuo*. The material was purified prep HPLC at low pH to yield the title compound (6 mg, 0.013 mmol, 9% yield).

^1H NMR (d_6-DMSO) 8.67 (s, 1H), 7.87 (d, 2H), 7.58 (dd, 2H), 6.51 (dd, 1H), 5.07 (s, 1H), 4.80 (d, 2H), 4.71 (s, 1H), 4.46 (s, 1H), 4.34 (d, 1H), 3.94 (d, 1H), 3.74 (d, 1H), 3.61 (d, 1H), 3.50 – 3.40 (m, 2H), 3.25 – 3.13 (m, 3H), 2.61 – 2.54 (m, 1H), 2.30 (s, 3H), 2.27 (s, 3H), 1.22 (d, 3H), 0.73 – 0.57 (m, 2H), 0.50 – 0.34 (m, 2H).

LCMS (Method A), ($M+H^+$) 480, Rt= 5.56 min.

Example 21

(S)-1-cyclopropyl-3-(4-(6-(3-(dimethylamino)propanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



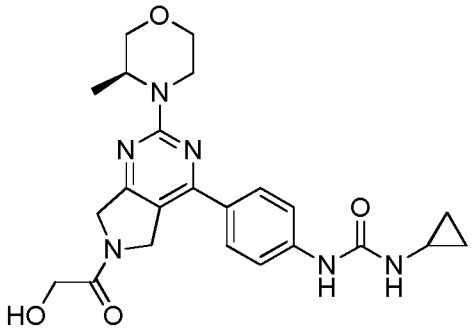
Method as per Example 20 using 3-(dimethylamino)propanoic acid hydrochloride as starting material. The material was purified prep HPLC at low pH to yield the title compound (28 mg, 0.057 mmol, 41% yield).

^{1}H NMR (d_6-DMSO) 8.75 (d, 1H), 7.87 (dd, 2H), 7.58 (dd, 2H), 6.59 (dd, 1H), 5.05 (s, 1H), 4.76 (d, 2H), 4.71 (s, 1H), 4.44 (s, 1H), 4.33 (d, 1H), 3.94 (d, 1H), 3.74 (d, 1H), 3.61 (d, 1H), 3.49 – 3.42 (m, 1H), 3.23 – 3.17 (m, 1H), 2.64 (s, 2H), 2.62 (d, 1H), 2.59 – 2.53 (m, 2H), 2.26 (s, 3H), 2.23 (s, 3H), 1.21 (d, 3H), 0.73 – 0.54 (m, 2H), 0.50 – 0.29 (m, 2H).

LCMS (Method A), ($M+H^+$) 494, Rt= 5.60 min.

Example 22

(S)-1-cyclopropyl-3-(4-(6-(2-hydroxyacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea

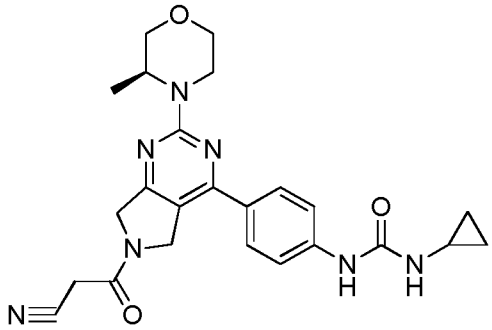


Method as per Example 20 using glycolic acid as starting material. The material was purified prep HPLC at low pH to yield the title compound (8 mg, 0.018 mmol, 13% yield). ^{1}H NMR (d_6-DMSO) 8.67 (s, 1H), 7.87 (d, 2H), 7.58 (dd, 2H), 6.49 (s, 1H), 4.96 (s, 1H), 4.83 (s, 1H), 4.78 (dt, 1H), 4.74 – 4.65 (m, 1H), 4.62 (s, 1H), 4.48 (s, 1H), 4.33 (d, 1H), 4.22 (d, 1H), 4.14 (d, 1H), 3.94 (dd, 1H), 3.74 (d, 1H), 3.61 (dd, 1H), 3.52 – 3.39 (m, 1H), 3.26 – 3.13 (m, 1H), 2.61 – 2.53 (m, 1H), 1.21 (d, 3H), 0.70 – 0.60 (m, 2H), 0.46 – 0.36 (m, 2H).

LCMS (Method A), ($M+H^+$) 453, Rt= 7.20 min.

Example 23

(S)-1-(4-(6-(2-cyanoacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea



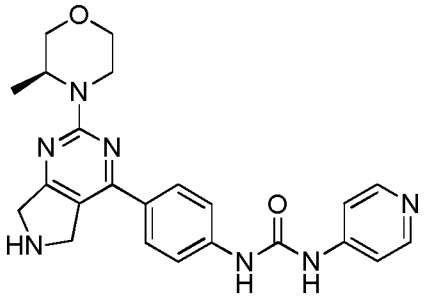
Method as per Example 20 using cyanoacetic acid as starting material. The material was purified prep HPLC at high pH to yield the title compound (7 mg, 0.015 mmol, 11% yield).

^{1}H NMR (d_6-DMSO) 8.70 (d, 1H), 7.86 (dd, 2H), 7.58 (dd, 2H), 6.53 (dd, 1H), 5.01 (s, 1H), 4.83 (s, 1H), 4.70 (s, 1H), 4.67 (s, 1H), 4.48 (s, 1H), 4.33 (d, 1H), 4.16 (s, 1H), 4.09 (s, 1H), 3.94 (dd, 1H), 3.74 (d, 1H), 3.60 (d, 1H), 3.51 – 3.39 (m, 1H), 3.20 (td, 1H), 2.61 – 2.53 (m, 1H), 1.21 (d, 3H), 0.71 – 0.58 (m, 2H), 0.50 – 0.30 (m, 2H).

LCMS (Method A), ($M+H^+$) 462, Rt= 7.98 min.

Example 24

(S)-1-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(pyridin-4-yl)urea



(S)-tert-butyl 2-(3-methylmorpholino)-4-(4-((phenoxycarbonyl)amino)phenyl)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate (Intermediate 5) (100 mg, 0.19 mmol) was dissolved in dry DMF and stirred with pyridin-4-amine (89 mg, 0.94 mmol) and Et_3N (85 µL, 0.61 mmol) at 80^{0}C in a microwave for 30 minutes. The solvent was removed *in vacuo* and the desired product was isolated by flash column chromatography (silica) using first, a

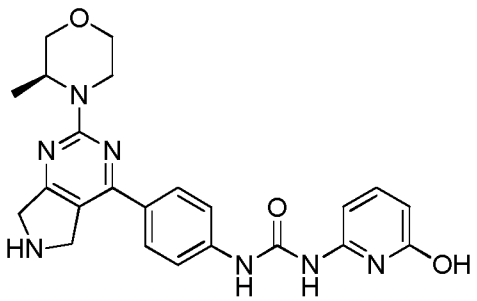
gradient of 0-100% EtOAc in petrol ether, then 0-10% MeOH in EtOAc yielding the desired product as a yellow solid (56.8 mg, 0.11 mmol, 57% yield). The solid was dissolved with 4M HCl in dioxane and stirred at room temperature for 2h. The solvent was removed *in vacuo* and the product was absorbed onto a SCX-2 cartidge and rinsed first with MeOH then 2M NH_3 in MeOH to release the title compound, solvent was removed *in vacuo* to give a dark brown solid (47.1 mg, 0.11 mmol, 100% yield).

^{1}H NMR (d_6-DMSO) 9.40 (s, 1H), 8.34 (d, 2H), 7.90 (t, 2H), 7.63 (t, 2H), 7.46 (d, 2H), 6.11 (s, 1H), 4.82-4.69 (br s, 1H), 4.76-4.66 (m, 1H), 4.46-4.42 (br s, 1H), 4.38-4.26 (m, 2H), 3.98-3.89 (m, 2H), 3.73 (d, 1H), 3.63-3.57 (m, 1H), 3.49-3.40 (m, 1H), 3.25-3.11 (m, 1H), 1.18 (d, 3H).

LCMS (method A), ($M+H^+$) 432 Rt = 4.14 min

Example 25

(S)-1-(6-hydroxypyridin-2-yl)-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



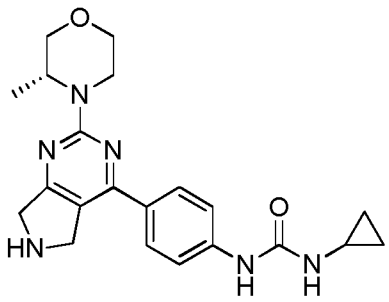
Method as described for Example 24 using 6-aminopyridin-2-ol as starting material. The solvent was removed *in vacuo* and the desired product was isolated by flash column chromatography using a gradient of 0-20% MeOH in EtOAc, yielding the desired product as a transparent solid. The solid was dissolved with 4M HCl in dioxane and stirred at room temperature for 3h. The solvent was removed *in vacuo* and the product was absorbed onto a SCX-2 cartidge and rinsed first with MeOH then 2M NH_3 in MeOH to release the title compound, solvent was removed *in vacuo* to give a brown solid (14.4 mg, 0.03mmol, 74% yield).

^{1}H NMR (d_6-DMSO) 10.67-10.56 (br s, 1H), 9.45-9.26 (br s, 1H), 7.88 (d, 2H), 7.74 (d, 2H), 7.56 (t, 1H), 6.78 (d, 2H), 6.22 (d, 2H), 4.74-4.67 (m, 1H), 4.38-4.27 (m, 3H), 3.98-3.89 (m, 3H), 3.73 (d, 1H), 3.64-3.57 (dd, 1H), 3.48-3.38 (m, 1H), 3.24-3.14 (m, 1H), 1.20 (d, 3H).

LCMS (method A), ($M+H^+$) 448 Rt = 5.01min

Example 26

(R)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



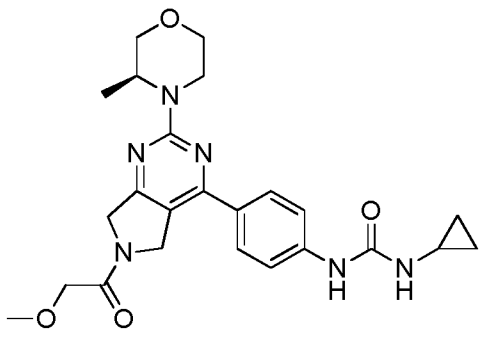
Method as described for Example 1 using (R)-3-methylmorpholine as starting material in the relevant steps. The solvent was removed *in vacuo* and the product was absorbed onto a SCX-2 cartidge and rinsed first with MeOH then 2M NH_3 in MeOH to release the title compound, solvent was removed *in vacuo* to give a dark red solid (41mg , 0.10 mmol, 70% yield).

^1H NMR (d_6-DMSO) 8.64 (s, 1H), 7.81 (d, 2H), 7.54 (d, 2H), 6.49-6.45 (br s, 1H), 4.76-4.66 (m, 1H), 4.37-4.27 (m, 3H), 3.99-3.87 (m, 3H), 3.73 (d, 1H), 3.63-3.56 (dd, 1H), 3.50-3.39 (m, 1H), 3.22-3.09 (m, 1H), 2.58-2.51 (m, 1H), 1.19 (d, 3H), 0.67-0.60 (m, 2H), 0.44-0.38 (m, 2H).

LCMS (method A), ($M+H^+$) 395 Rt = 5.18min

Example 27

(S)-1-cyclopropyl-3-(4-(6-(2-methoxyacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



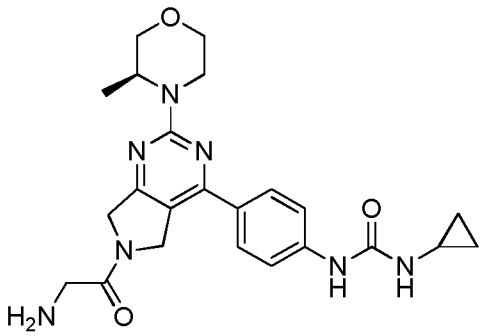
Method as for Example 20 using methoxyacetic acid as starting material. The material was purified by flash chromatography (silica) using 100% EtOAc followed by 10% MeOH in EtOAc as eluent to yield the title compound (3 mg, 0.006 mmol, 5% yield).

^{1}H NMR (d_6-DMSO) 8.65 (d, 1H), 7.86 (dd, 2H), 7.58 (d, 2H), 6.49 (dd, 1H), 4.97 (s, 1H), 4.83 (s, 1H), 4.77 – 4.67 (m, 1H), 4.65 (s, 1H), 4.48 (s, 1H), 4.33 (d, 1H), 4.24 (s, 1H), 4.15 (s, 1H), 3.94 (d, 1H), 3.74 (d, 1H), 3.61 (d, 1H), 3.51 – 3.41 (m, 1H), 3.35 (d, 3H), 3.20 (td, 1H), 2.60 – 2.53 (m, 1H), 1.21 (d, 3H), 0.75 – 0.58 (m, 2H), 0.50 – 0.35 (m, 2H).

LCMS (Method A), ($M+H^+$) 467, Rt= 7.73 min.

Example 28

(S)-1-(4-(6-(2-aminoacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea



Step1: Method as for Example 20 using N-(tert-Butoxycarbonyl)glycine as starting material. The material was used crude in step 2.

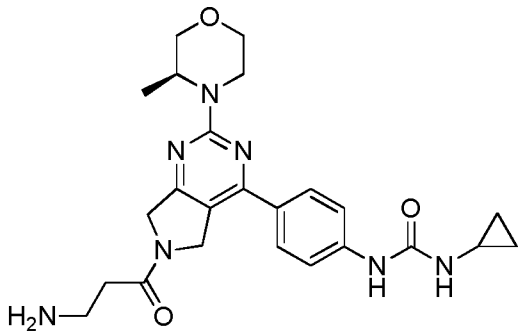
Step 2: Method as for Example 1 purified prep HPLC at high pH to yield the title compound (14 mg, 0.031 mmol, 22% yield).

^{1}H NMR (d_6-DMSO) 9.00 (d, 1H), 8.31 (s, 1H), 7.87 (dd, 2H), 7.59 (dd, 2H), 6.82 (dd, 1H), 5.00 (d, 1H), 4.84 (s, 1H), 4.76 – 4.68 (m, 1H), 4.67 (s, 1H), 4.49 (s, 1H), 4.34 (d, 1H), 3.94 (d, 1H), 3.74 (d, 2H), 3.63 (s, 1H), 3.59 (s, 1H), 3.54 (s, 1H), 3.49 – 3.40 (m, 1H), 3.24 – 3.15 (m, 1H), 2.60 – 2.53 (m, 1H), 1.22 (d, 3H), 0.68 – 0.60 (m, 2H), 0.45 – 0.38 (m, 2H).

LCMS (Method A), ($M+H^+$) 452, Rt= 5.24 min.

Example 29

(S)-1-(4-(6-(3-aminopropanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea



Step1: Method as for Example 20 using 3-((tert-butoxycarbonyl)amino)propanoic acid as starting material. The material was used crude in step 2.

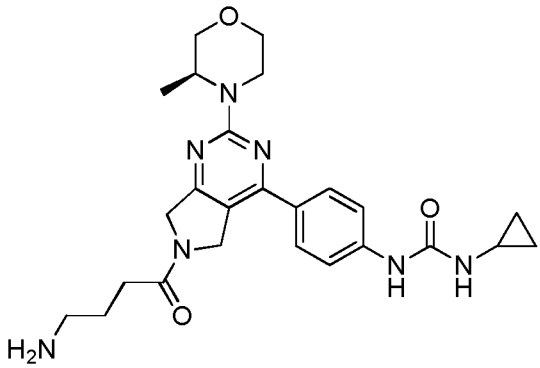
Step 2: Method as for Example 1 purified prep HPLC at high pH to yield the title compound (10 mg, 0.021 mmol, 15% yield).

^{1}H NMR (d_6-DMSO) 8.97 (d, 1H), 7.63 (t, 2H), 7.38 (dd, 2H), 6.79 (dd, 1H), 4.95 – 4.68 (m, 1H), 4.65 – 4.53 (m, 1H), 4.46 (s, 2H), 4.25 (s, 1H), 4.11 (d, 1H), 3.71 (d, 1H), 3.51 (d, 1H), 3.38 (d, 1H), 3.23 (t, 1H), 2.98 (t, 1H), 2.81 – 2.69 (m, 2H), 2.47 (t, 1H), 2.40 (t, 1H), 2.36 – 2.31 (m, 1H), 0.99 (d, 3H), 0.46 – 0.31 (m, 2H), 0.24 – 0.08 (m, 2H).

LCMS (Method A), ($M+H^+$) 466, Rt= 5.34 min.

Example 30

(S)-1-(4-(6-(4-aminobutanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea



Step1: Method as per Example 20 using 4-(tert-butoxycarbonylamino)butyric acid as starting material. The material was used crude in step 2.

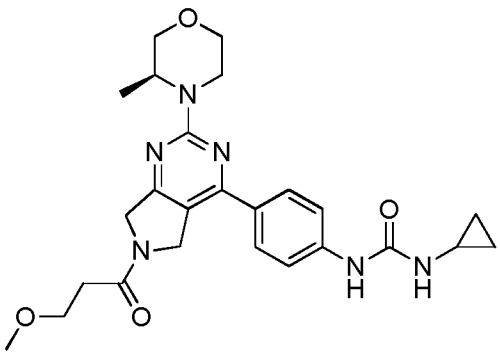
Step 2: Method as per Example 1 purified prep HPLC at high pH to yield the title compound (8 mg, 0.017 mmol, 12% yield).

^{1}H NMR (d_6-DMSO) 9.21 (d, 1H), 7.86 (dd, 2H), 7.60 (dd, 2H), 7.03 (dd, 1H), 5.14 – 4.93 (m, 1H), 4.79 (s, 1H), 4.69 (s, 2H), 4.45 (s, 1H), 4.33 (d, 1H), 3.94 (d1, H), 3.74 (d, 1H), 3.61 (d, 1H), 3.51 – 3.41 (m, 1H), 3.24 – 3.15 (m, 1H), 2.79 (q, 2H), 2.62 – 2.52 (m, 2H), 2.47 – 2.44 (m, 1H), 1.88 – 1.74 (m, 2H), 1.21 (d, 3H), 0.72 – 0.55 (m, 2H), 0.48 – 0.34 (m, 2H).

LCMS (Method A), ($M+H^+$) 480, Rt= 5.45 min.

Example 31

(S)-1-cyclopropyl-3-(4-(6-(3-methoxypropanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



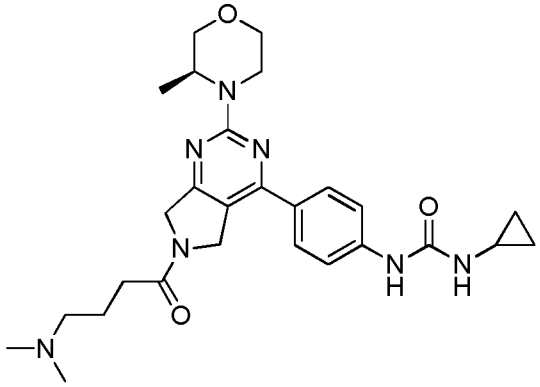
Method as per Example 20 using 3-methoxypropionic acid as starting material. The material was purified by flash chromatography (silica) using 100% EtOAc followed by 10% MeOH in EtOAc as eluent to yield the title compound (15 mg, 0.031 mmol, 22% yield).

^{1}H NMR (d_6-DMSO) 8.65 (s, 1H), 7.88 (dd, 2H), 7.57 (dd, 2H), 6.48 (s, 1H), 5.04 (s, 1H), 4.78 (s, 1H), 4.72 (s, 2H), 4.44 (s, 1H), 4.33 (d, 1H), 3.94 (d, 1H), 3.74 (d, 1H), 3.68 – 3.57 (m, 3H), 3.45 (t, 1H), 3.25 (d, 3H), 3.19 (td, 1H), 2.71 (t, 1H), 2.63 (t, 1H), 2.56 (m, 1H), 1.21 (d, 3H), 0.70 – 0.60 (m, 2H), 0.46 – 0.36 (m, 2H).

LCMS (Method A), ($M+H^+$) 481, Rt= 7.98 min.

Example 32

(S)-1-cyclopropyl-3-(4-(6-(4-(dimethylamino)butanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



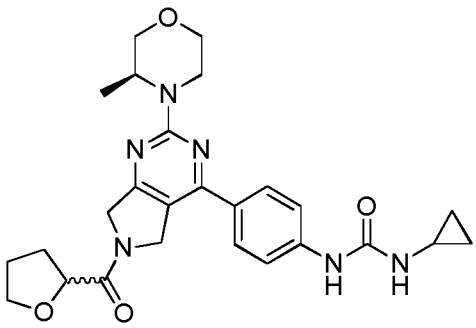
Method as per Example 20 using 4-(dimethylamino)butanoic acid hydrochloride as starting material. The material was purified by flash chromatography (Biotage KP-NH cartridge) using 10% MeOH in DCM as eluent to yield the title compound (18 mg, 0.035 mmol, 25% yield).

^{1}H NMR (d_6-DMSO) 8.64 (d, 1H), 7.87 (t, 2H), 7.57 (dd, 2H), 6.49 (dd, 1H), 5.01 (d, 1H), 4.78 (s, 1H), 4.69 (s, 2H), 4.44 (s, 1H), 4.33 (d, 1H), 3.94 (d, 1H), 3.74 (d, 1H), 3.61 (d, 1H), 3.45 (t, 1H), 3.19 (td, 1H), 2.61 – 2.53 (m, 1H), 2.45 (t, 1H), 2.37 (t, 1H), 2.27 (dd, 2H), 2.14 (s, 6H), 1.70 (qn, 2H), 1.21 (d, 3H), 0.72 – 0.59 (m, 2H), 0.47 – 0.36 (m, 2H).

LCMS (Method A), ($M+H^+$) 508, Rt= 5.42 min.

Example 33

1-cyclopropyl-3-(4-(2-((S)-3-methylmorpholino)-6-(tetrahydrofuran-2-carbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 1) (40 mg, 0.1mmol) was dissolved in DCM and stirred with DIPEA (50 mL, 0.30 mmol), HATU (53 mg, 0.14 mmol), and tetrahydrofuran-2-carboxylic acid (16.4mg, 0.14mmol) at room temperature overnight. The reaction mixture was partitioned between H_2O and DCM. The organic layer was recovered, dried over Na_2SO_4, filtered and the

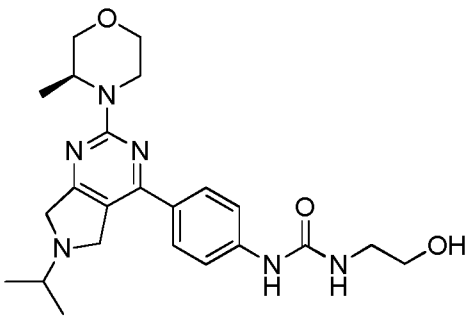
solvent removed *in vacuo*. The material was purified by flash column chromatography (silica) using a 15:1 mixture of DCM: MeOH as eluent, to yield the title compound (14mg, 0.03mmol, yield 28%).

^{1}H NMR (d_6-DMSO) 8.82-8.82 (br s, 1H), 7.85 (d, 2H), 7.60 (d, 2H), 7.05-6.89 (br s, 2H), 6.60 (d, 1H), 4.95-4.85 (m, 2H), 4.75-4.68 (m, 1H), 4.61-4.55 (br s, 2H), 4.38-4.30 (m, 1H), 3.98-3.91 (m, 1H), 3.75 (d, 1H), 3.63-3.56 (m, 1H), 3.49-3.38 (m, 1H), 3.27-3.16 (m, 1H), 2.69-2.64 (m, 1H) 2.58-2.54 (m, 1H), 2.33-2.31 (m, 1H), 2.04-1.94 (m, 3H), 1.23 (d,3H), 0.68-0.59 (m, 2H), 0.43-0.36(m, 2H).

LCMS (Method A) ($M+H^+$) 493 Rt = 5.58 min.

Example 34

(S)-1-(2-hydroxyethyl)-3-(4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea 2,2,2-trifluoroacetate



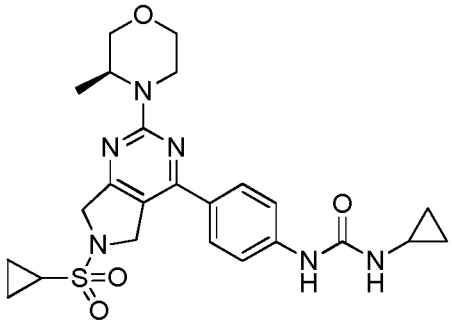
Method as described for Example 11 using (S)-1-(2-hydroxyethyl)-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 19) hydrochloride salt and acetone as starting materials. The reaction mixture was partitioned between H_2O and EtOAc. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The material was purified by prep HPLC to yield the title compound.

^{1}H NMR (MeOD) 7.83 (d, 2H), 7.57 (d, 2H), 4.9 (br s, 2H), 4.57 (s, 2H), 4.51-4.43 (m, 1H), 4.03-3.96 (m, 1H), 3.82-3.75 (m, 2H), 3.75-3.68 (m, 1H), 3.68-3.63 (m, 2H), 3.60-3.51 (m, 1H), 3.39-3.34 (m, 3H), 1.49 (d, 6H), 1.31 (d, 3H).

LCMS (Method A) ($M+H^+$) 441 Rt = 5.00 min.

Example 35

(S)-1-cyclopropyl-3-(4-(6-(cyclopropylsulfonyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



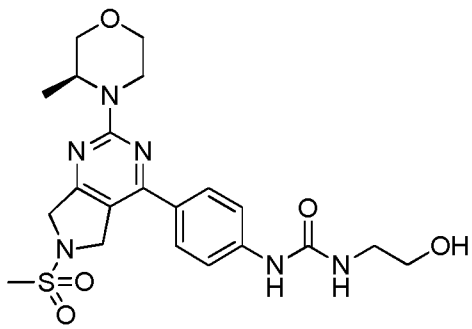
Method as described for Example 15 using cyclopropanesulfonyl chloride as starting material. The reaction mixture was partitioned between H_2O and EtOAc. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The material was purified by prep HPLC to yield the title compound.

^{1}H NMR ($CDCl_3$) 7.82 (d, 2H), 7.56 (d, 2H), 7.04-7.00 (m, 1H), 4.93-4.85 (m, 3H), 4.58 (s, 2H), 4.50-4.39 (m, 1H), 4.04-3.96 (m, 1H), 3.83-3.77 (m, 1H), 3.77-3.69 (m, 1H), 3.60-3.50 (m, 2H), 2.69-2.58 (m, 1H), 2.44-2.36 (m, 1H), 1.39-1.12 (m, 3H), 1.08-0.95 (m, 2H), 0.95-0.84 (m, 4H), 0.78-0.66 (m, 2H).

LCMS (Method A) ($M+H^+$) 499 Rt = 9.15min.

Example 36

(S)-1-(2-hydroxyethyl)-3-(4-(2-(3-methylmorpholino)-6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



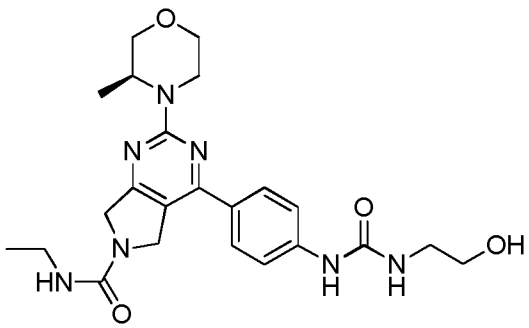
Method as described for Example 15 using (S)-1-(2-hydroxyethyl)-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 19) hydrochloride salt as starting material. The reaction mixture was partitioned between H_2O and EtOAc. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The material was purified by treatment with a relevant sulphonyl chloride trapping resin in methanol to yield the title compound after filtration of the resin and removal of the solvent *in vacuo*.

^{1}H NMR (d_6-DMSO) 8.93 (s, 1H), 7.84 (d, 2H), 7.55 (d, 2H), 6.29 (t, 1H), 4.86-4.77 (m, 2H), 4.74-4.66 (m, 1H), 4.48 (s, 2H), 4.37-4.27 (m, 1H), 3.96-3.89 (m, 1H), 3.74 (d, 1H), 3.61 (d, 1H), 3.48-3.42 (m, 3H), 3.20-3.13 (m, 3H), 3.06 (s, 3H), 1.21 (d, 3H).

LCMS (Method F) ($M+H^+$) 476 Rt = 2.07 min.

Example 37

(S)-N-ethyl-4-(4-(3-(2-hydroxyethyl)ureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxamide



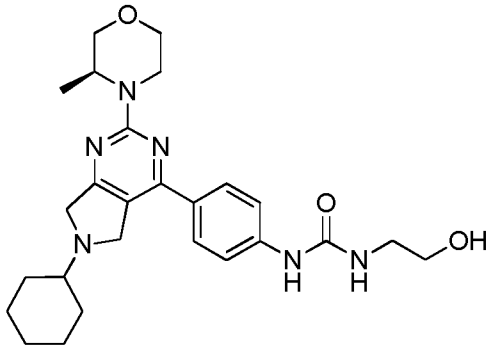
Method as described for Example 17 using (S)-1-(2-hydroxyethyl)-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 19) hydrochloride salt as starting material. The reaction mixture was partitioned between H_2O and EtOAc. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The material was purified by treatment with a relevant isocyanate trapping resin in methanol to yield the title compound after filtration of the resin and removal of the solvent *in vacuo*.

^{1}H NMR (d_6-DMSO) 8.93 (s, 1H), 7.86 (d, 2H), 7.55 (d, 2H), 6.47 (t, 1H), 6.30 (t, 1H), 4.77 (t, 1H), 4.75-4.66 (m, 3H), 4.39 (s, 2H), 4.36-4.26 (m, 1H), 3.96-3.89 (m, 1H), 4.73 (d, 1H), 3.64-3.56 (m, 1H), 3.45-3.39 (m, 3H), 3.24-3.0+9 (m, 5H), 1.21 (d, 3H), 1.07 (t, 3H).

LCMS (Method F) ($M+H^+$) 470 Rt = 2.02 min.

Example 38

(S)-1-(4-(6-cyclohexyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea



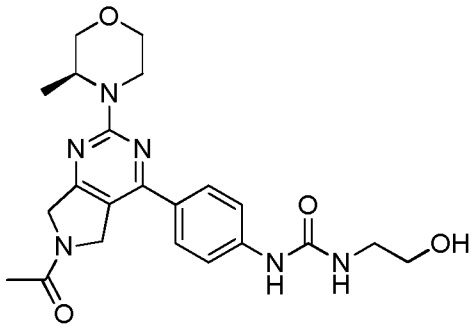
Method as described for Example 11 using (S)-1-(2-hydroxyethyl)-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 19) hydochloride salt and cyclohexanone as starting materials. The solvent was removed *in vacuo*. The residue was re-dissolved in EtOAc and partitioned with H_2O. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The material was purified by prep HPLC to yield the title compound.

^{1}H NMR (MeOD) 7.82 (d, 2H), 7.53 (d, 2H), 4.71-4.54 (br s, 4H), 4.45-4.36 (m, 3H), 4.07 (s, 2H), 4.02-3.95 (m, 1H), 3.80 (d, 1H), 3.74-3.64 (m, 1H), 3.65 (t, 2H), 3.59-3.51 (m, 1H), 3.34 (d, 3H), 2.86-2.75 (m, 1H), 2.21-2.10 (m, 2H), 1.91-1.82 (m, 2H), 1.75-1.66 (m, 1H), 1.42-1.20 (m, 5H).

LCMS (Method F) ($M+H^+$) 481 Rt = 1.82 min.

Example 39

(S)-1-(4-(6-acetyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea



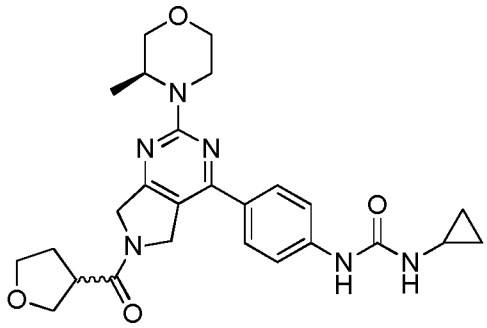
Method as described for Example 12 using (S)-1-(2-hydroxyethyl)-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 19) hydochloride salt as starting material. A precipitate was formed. The precipitate was filtered and washed with EtOH and Et_2O to yield the title compound.

^{1}H NMR (d_6-DMSO) 7.92 (s, 1H), 7.90-7.82 (m, 2H), 7.58-7.52 (m, 2H), 6.34-6.26 (m, 1H), 5.06-4.96 (m, 1H), 4.80-4.72 (m, 2H), 4.72-4.63 (br s, 1H), 4.42 (s, 1H), 4.36-4.29 (m, 1H), 3.97-3.89 (m, 1H), 3.76-3.70 (m, 1H), 3.65-3.56 (m, 1H), 3.49-3.39 (m, 3H), 3.22-3.12 (m, 3H), 2.09 (d, 3H), 1.21 (d, 3H).

LCMS (Method F) ($M+H^+$) 441 Rt = 1.98 min.

Example 40

1-cyclopropyl-3-(4-(2-((S)-3-methylmorpholino)-6-(tetrahydrofuran-3-carbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea 2,2,2-trifluoroacetate



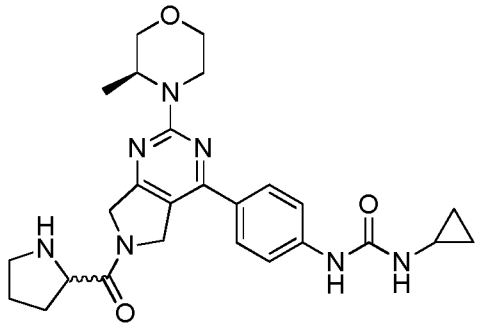
Method as described for Example 33 using tetrahydrofuran-3-carboxylic acid as starting material. The reaction mixture was partitioned between H_2O and DCM. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The material was purified by prep HPLC to yield the title compound.

^{1}H NMR ($CDCl_3$) 7.96-7.82 (dd, 2H), 7.68-7.55 (dd, 2H), 7.14-7.11 (br s, 1H), 5.630-5.20 m, 1H), 5.05-4.95 (m, 1H), 4.76-4.70 (m, 1H), 4.67 (s, 1H), 4.50-4.41 (m, 1H), 4.19-4.11 (m, 1H), 4.07-3.88 (m, 4H), 3.88-3.74 (m, 2H), 3.66-3.56 (m, 1H), 3.41-3.28 (m, 1H), 2.72-2.59 (m, 1H), 2.33-2.14 (m, 2H), 1.35 (d, 3H), 1.31-1.26 (m, 2H), 0.98-0.86 (m, 2H), 0.79-0.74 (m, 2H).

LCMS (Method F) ($M+H^+$) 493 Rt = 2.15 min.

Example 41

1-cyclopropyl-3-(4-(2-((S)-3-methylmorpholino)-6-(pyrrolidine-2-carbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea hydrochloride



.

Step 1: Method as described for Example 33 using 1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid as starting material.

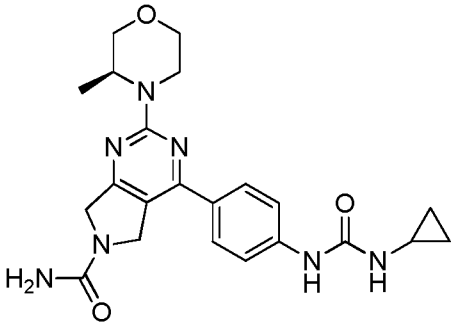
Step 2: Method as described for Example 1 using tert-butyl 2-(4-(4-(3-cyclopropylureido)phenyl)-2-((S)-3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidine-6-carbonyl)pyrrolidine-1-carboxylate as starting material. The solvent was removed *in vacuo* to yield the title compound.

^{1}H NMR (MeOD) 8.01-7.86 (dd, 2H), 7.67-7.56 (dd, 2H), 5.36-4.97 (m, 3H), 4.85-4.64 (m, 3H), 4.43-4.33 (m, 1H), 4.10-4.01 (m, 1H), 3.87-3.81 (m, 1H), 3.81-3.73 (m, 1H), 3.66 (s, 1H), 3.60 (s, 1H), 3.55-3.38 (m, 3H), 2.76-2.55 (m, 2H), 2.22-2.03 (m, 1H), 1.40 (t, 3H), 0.79-0.72 (m, 2H), 0.58-0.50 (m, 2H).

LCMS (Method F) ($M+H^+$) 492 Rt = 1.88 min.

Example 42

(S)-4-(4-(3-cyclopropylureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxamide 2,2,2-trifluoroacetate



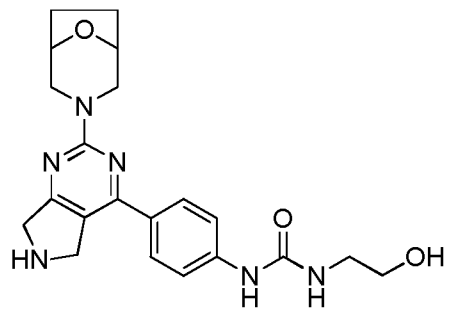
(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea (Example 1) hydrochloride salt (40 mg, 0.09mmol), was dissolved in DMF and sodium isocyanate (12mg, 0.18 mmol) added to the stirring mixture. Acetic acid (1mL) was added dropwise to the reaction mixture and stirring was continued overnight at room temperature. The reaction mixture was quenched with H_2O and saturated $NaHCO_3$ solution was used to raise the pH to greater then 7.0. The mixture was partitioned with EtOAc. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude material was purified by prep HPLC to yield the title compound (14 mg, 0.03mmol, yield 17%).

^{1}H NMR (MeOD) 7.92 (d, 2H), 7.56 (d, 2H), 4.52 (s, 2H), 4.47-4.37 (m, 1H), 4.03-3.95 (m, 1H), 3.81 (d, 1H), 3.76-3.70 (m, 1H), 3.62-3.53 (m, 1H), 3.34 (s, 2H), 2.64-2.56 (m, 1H), 1.31 (d, 3H), 0.79-0.72 (m, 2H), 0.55-0.49 (m, 2H).

LCMS (Method F) ($M+H^+$) 438 Rt = 2.05 min.

Example 43

1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea hydrochloride



In the first instance the method followed was as described for Intermediates 1 to 3 using 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride as starting material in the relevant steps. Subsequent steps were as described for Intermediates 5 & 6 and the final deprotection as per

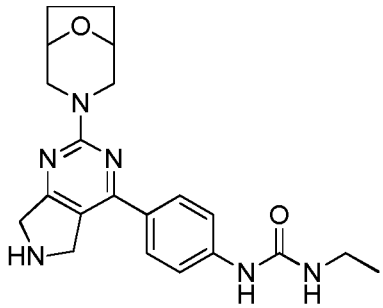
Example 1. The solvent was removed *in vacuo* and the crude material azeotroped with toluene. The solvent was then removed *in vacuo* to yield the title compound.

^{1}H NMR (MeOD) 7.92 (d, 2H), 7.56 (d, 2H), 4.52 (s, 2H), 4.46-4.39 (dd, 1H), 4.02-3.97 (dd, 1H), 3.81 (d, 1H), 3.76-3.70 (dd, 1H), 3.63-3.53 (m, 1H), 3.35 (s, 2H), 2.64-2.56 (m, 1H), 1.31 (d, 3H),0.79-0.72 (m, 2H), 0.56-0.48 (m, 2H).

LCMS (Method F) ($M+H^+$) 411 Rt = 1.73 min.

Example 44

1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-ethylurea hydrochloride



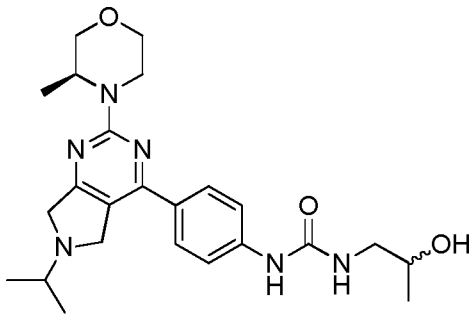
Method as described for Intermediates 1 to 4, using 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride and ethyl isocyanate as starting materials in the relevant steps. Followed by deprotection as for Example 1**.** The solvent was removed *in vacuo* and the crude material azeotroped with toluene. The solvent was then removed *in vacuo* to yield the title compound.

^{1}H NMR (MeOD) 7.83 (d, 2H), 7.56 (d, 2H), 4.57-4.36 (m, 6H), 3.60 (s, 2H), 3.27-3.18 (m, 4H), 1.99-1.92 (m, 2H), 1.83-1.75 (m, 2H), 1.34-1.27 (m, 2H), 1.17 (t, 3H).

LCMS (Method F) ($M+H^+$) 395 Rt = 1.80 min.

Example 45

1-(2-hydroxypropyl)-3-(4-(6-isopropyl-2-((S)-3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea



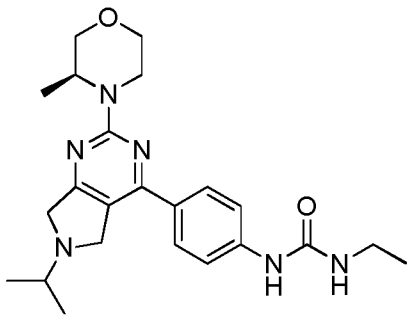
Method as described for Intermediate 6 using (S)-phenyl (4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)carbamate (Intermediate 9) and 1-aminopropan-2-ol as starting materials. The mixture was partitioned between H_2O and EtOAc. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The material was purified by treatment with a relevant trapping resin in methanol to yield the title compound after filtration of the resin and removal of the solvent *in vacuo*.

^{1}H NMR (d_6-DMSO) 8.88 (s, 1H), 7.80 (d, 2H), 7.52 (d, 2H), 6.26 (t, 1H), 4.79 (d, 1H), 4.71-4.65 (m, 1H), 4.34-4.26 (m, 1H), 4.05 (s, 2H), 3.95-3.88 (dd, 1H), 3.78-3.64 (m, 4H), 3.63-3.56 (dd, 1H), 3.48-3.39 (m, 1H), 3.20-3.10 (m, 2H), 2.98-2.88 (m, 1H), 2.84-2.72 (m, 1H), 1.25-1.21 (m, 1H), 1.18 (d, 3H), 1.11 (d, 6H), 1.05 (d, 3H).

LCMS (Method F) ($M+H^+$) 455 Rt = 1.82 min.

Example 46

(S)-1-ethyl-3-(4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea 2,2,2-trifluoroacetate



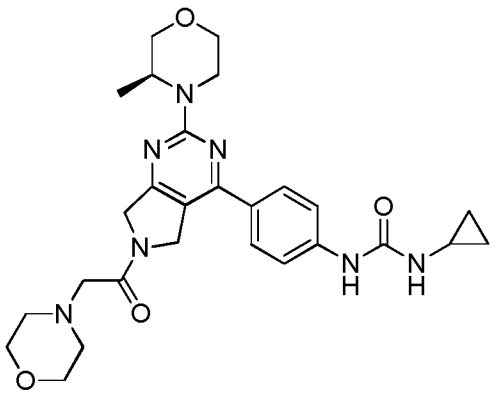
Method as described for Intermediate 6 using (S)-phenyl (4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)carbamate (Intermediate 9) and ethyl amine (2M solution in THF) as starting materials. The solvent was removed *in vacuo*. The residue was re-dissolved in EtOAc and partitioned with H_2O. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The material was purified by prep HPLC to yield the title compound.

^{1}H NMR (MeOD) 7.83 (d, 2H), 7.57 (d, 2H), 4.85-4.78 (m, 1H), 4.57 (s, 2H), 4.50-4.44 (m, 1H), 4.03-3.97 (dd, 1H), 3.84-3.76 (m, 2H), 3.73.-3.67 (dd, 1H), 3.60-3.51 (m, 1H), 3.30-3.20 (q, 2H), 1.49 (d, 6H), 1.31 (d, 3H), 1.17 (t, 3H).

LCMS (Method F) ($M+H^+$) 425 Rt = 1.87 min.

Example 47

(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6-(2-morpholinoacetyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea 2,2,2-trifluoroacetate



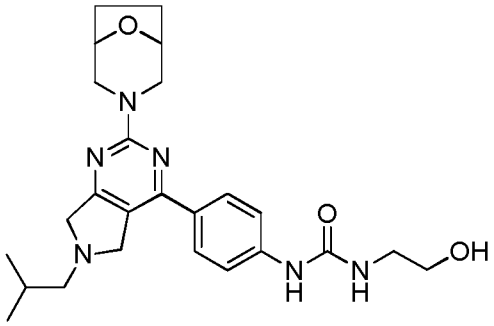
(S)-1-(4-(6-(2-bromoacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea (Intermediate 10) (50mg, 0.009 mmol) was dissolved in THF with Et_3N (27 µL, 0.19 mmol) and morpholine (14 µL, 0.16 mmol). The reaction mixture was stirred at 50^{0}C overnight. The solvent was removed *in vacuo*. The crude material was dissolved in DCM and extracted with H_2O. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The material was purified by flash column chromatography (silica) using a mixture of DCM:MeOH (15:1) as eluent. The product was then further purified by prep HPLC to yield the title compound (8mg, 0.02 mmol, 16% yield).

^{1}H NMR (MeOD) 7.89 (d, 2H), 7.60-7.54 (m, 2H), 5.05 (s, 1H), 4.99-4.94 (m, 2H), 4.83-4.76 (m, 2H), 4.65 (d, 2H), 4.47-4.37 (m, 2H), 4.33 (s, 1H), 4.09-3.90 (m, 4H), 3.82 (d, 1H), 3.76-3.68 (m, 1H), 3.63-3.51 (m, 1H), 3.35 (s, 1H), 1.31 (d, 7H), 0.81-0.72 (m, 2H), 0.56-0.49 (m, 2H).

LCMS (Method F) ($M+H^+$) 522 Rt = 1.85 min.

Example 48

1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6-isobutyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea 2,2,2-trifluoroacetate



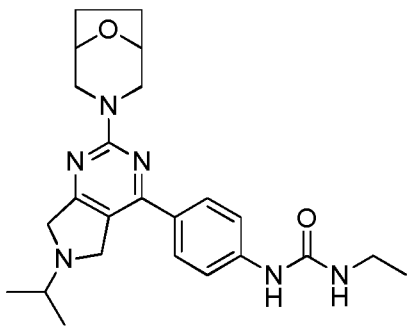
Method as described for Example 11 using 1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea hydrochloride (Example 43) and isobutyraldehyde as starting materials. The solvent was removed *in vacuo* and the dry residue re-dissolved in EtOAc and partitioned with H_2O. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude material was then purified by prep HPLC to yield the title compound.

^{1}H NMR (MeOD) 7.81 (d, 2H), 7.57 (d, 2H), 4.61-4.53 (br s, 2H), 4.51-4.37 (m, 4H), 3.65 (t, 2H), 3.39-3.33 (m, 4H), 3.24-3.18 (m, 1H), 2.28-2.16 (m, 1H), 2.02-1.90 (m, 2H), 1.81-1.75 (m, 2H), 1.36-1.26 (m, 2H), 1.11 (d, 6H).

LCMS (Method F) ($M+H^+$) 467 Rt = 1.78 min.

Example 49

1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6-isopropyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-ethylurea 2,2,2-trifluoroacetate



Method as decribed for Example 11 using 1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-ethylurea (Example 44) hydrochloride salt and acetone as starting materials. The solvent was removed *in vacuo* and the dry residue

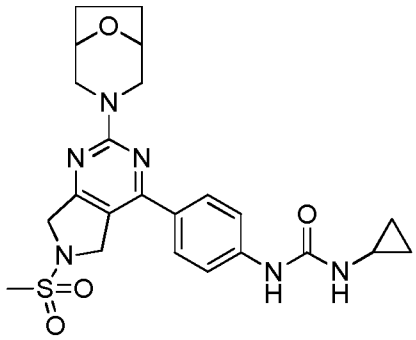
re-dissolved in EtOAc and partitioned with H_2O. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude material was purified by prep HPLC to yield the title compound.

^{1}H NMR (MeOD) 7.82 (d, 2H), 7.57 (d, 2H), 4.55 (s, 2H), 4.50-4.38 (m, 4H), 3.84-3.74 (m, 1H), 3.53-3.45 (q, 1H), 3.29-3.16 (m, 4H), 1.99-1.89 (m, 2H), 1.82-1.74 (m, 2H), 1.48 (d, 6H), 1.20-1.13 (m, 4H).

LCMS (Method F) ($M+H^+$) 437 Rt = 1.82 min.

Example 50

1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea



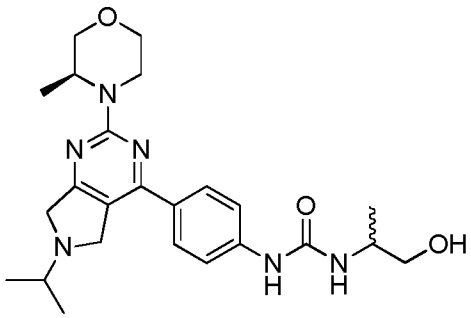
Method as described for Example 15 using 1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea (Example 18) hydrochloride salt as starting material. The mixture was partitioned between H_2O and DCM. The organic layer was recovered, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude material was then purified by prep HPLC to yield the title compound.

^{1}H NMR (MeOD+$CDCl_3$) 7.83 (d, 2H), 7.54 (d, 2H), 4.53-4.43 (m, 3H), 4.39 (d, 2H), 3.26-3.16 (m, 3H), 2.98 (s, 2H), 2.64-2.55 (m, 1H), 2.01-1.88 (m, 2H), 1.88-1.79 (m, 2H), 1.29 (d, 2H), 0.79-0.70 (m, 2H), 0.57-0.48 (m, 2H).

LCMS (Method F) ($M+H^+$) 485 Rt = 2.22 min.

Example 51

1-(1-hydroxypropan-2-yl)-3-(4-(6-isopropyl-2-((S)-3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea 2,2,2-trifluoroacetate



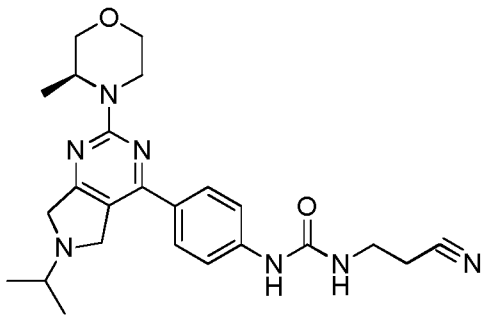
Method as described for Intermediate 6 using (S)-phenyl (4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)carbamate (Intermediate 9) and 2-aminopropan-1-ol as starting materials. The solvent removed *in vacuo* and the crude material was purified by prep HPLC to yield the title compound.

^{1}H NMR (MeOD) 7.83 (d, 2H), 7.56 (d, 2H), 4.863-4.77 (m, 2H), 4.57 (s, 2H), 4.47 (s, 2H), 4.04-3.96 (dd, 1H), 3.92-3.83 (m, 1H), 3.83-3.76 (m, 2H), 3.74-3.67 (dd, 1H), 3.54 (d, 3H), 1.49 (d, 6H), 1.31 (d, 3H), 1.20 (d, 3H).

LCMS (Method F) ($M+H^+$) 455 Rt = 1.78 min.

Example 52

(S)-1-(2-cyanoethyl)-3-(4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea 2,2,2-trifluoroacetate



Method as described for Intermediate 6 using (S)-phenyl (4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)carbamate (Intermediate 9) and 3-aminopropanenitrile as starting materials. The solvent removed *in vacuo* and the crude material was purified by prep HPLC to yield the title compound.

^{1}H NMR (MeOD) 7.85 (d, 2H), 7.59 (d, 2H), 4.57 (s, 2H), 4.48 (d, 1H), 4.03-3.96 (dd, 1H), 3.85-3.75 (m, 2H), 3.74-3.68 (dd, 1H), 3.59-3.53 (dd, 1H), 3.50 (t, 2H), 3.35 (s, 1H), 2.71 (t, 2H), 1.49 (d, 6H), 1.31 (d, 3H).

LCMS (Method F) ($M+H^+$) 450 Rt = 1.80 min.

Biological Assays

Determination of the effect of the compounds according to the invention on mTOR

The compounds of the present invention as described were tested in the mTOR kinobeads assay as described below. Briefly, test compounds (at various concentrations) and the affinity matrix (1:1 mixture of beads with immobilized phenylthiazole ligand 1 and beads with immobilized phenylmorpholin-chromen ligand; WO 2009/098021) were added to cell lysate aliquots and allowed to bind to the proteins in the lysate sample. After the incubation time the beads with captured proteins were separated from the lysate. Bound proteins were then eluted and the presence of mTOR, PI3Kα, PI3Kβ, PI3Kγ, PI3Kδ and DNA-dependent protein kinase (DNA-PK) was detected and quantified using a specific antibody in a dot blot procedure and the Odyssey infrared detection system. Dose response curves for individual kinases were generated and IC_{50} values calculated. Kinobeads assays for PI3 kinases (WO-A 2008/015013) and for kinase selectivity profiling (WO 2009/098021) have been previously described.

Washing of affinity matrix

The affinity matrix was washed two times with 15 ml of 1x DP buffer containing 0.2% NP40 (IGEPAL® CA-630, Sigma, #I3021) and then resupended in 5.5 ml of 1x DP buffer containing 0.2% NP40 (10% beads slurry).

5xDP buffer: 250 mM Tris-HCl pH 7.4, 25% Glycerol, 7.5 mM $MgCl_2$, 750 mM NaCl, 5 mM Na_3VO_4, filter the 5x-lysis buffer through 0.22 µm filter and store in aliquots at -80°C. The 5xDP buffer is diluted to 1xDP buffer containing 1 mM DTT and 25 mM NaF.

Preparation of test compounds

Stock solutions of test compounds were prepared in DMSO. In a 96 well plate 30 µl solution of diluted test compounds at 5 mM in DMSO were prepared. Starting with this solution a 1:3 dilution series (9 steps) was prepared. For control experiments (no test compound) a buffer containing 2% DMSO was used. Compound Pi-103 (Calbiochem catalogue number 528100) served as a positive control.

Cell culture and preparation of cell lysates

Jurkat cells (ATCC catalogue number TIB-152 Jurkat, clone E6-1) and Ramos cells (ATCC number CRL-1596) were grown in 1 litre Spinner flasks (Integra Biosciences, #182101) in suspension in RPMI 1640 medium (Invitrogen, #21875-034) supplemented with 10% Fetal Bovine Serum (Invitrogen) at a density between 0.15 x 10^6 and 1.2 x 10^6 cells/ml. Cells were

harvested by centrifugation, washed once with 1 x PBS buffer (Invitrogen, #14190-094) and cell pellets were frozen in liquid nitrogen and subsequently stored at -80°C.

Cells were homogenized in a Potter S homogenizer in lysis buffer: 50 mM Tris-HCl, 0.8% NP40, 5% glycerol, 150 mM NaCl, 1.5 mM $MgCl_2$, 25 mM NaF, 1 mM sodium vanadate, 1 mM DTT, pH 7.5. One complete EDTA-free tablet (protease inhibitor cocktail, Roche Diagnostics, 1873580) per 25 ml buffer was added. The material was dounced 10 times using a mechanized POTTER S, transferred to 50 ml falcon tubes, incubated for 30 minutes on ice and spun down for 10 min at 20,000 g at 4°C (10,000 rpm in Sorvall SLA600, precooled). The supernatant was transferred to an ultracentrifuge (UZ)-polycarbonate tube (Beckmann, 355654) and spun for 1 hour at 100.000 g at 4°C (33.500 rpm in Ti50.2, precooled). The supernatant was transferred again to a fresh 50 ml falcon tube, the protein concentration was determined by a Bradford assay (BioRad) and samples containing 50 mg of protein per aliquot were prepared. The samples were immediately used for experiments or frozen in liquid nitrogen and stored frozen at -80°C.

Dilution of cell lysate

Cell lysate (approximately 50 mg protein per plate) was thawed in a water bath at room temperature and then kept on ice. To the thawed cell lysate 1xDP 0.8% NP40 buffer containing protease inhibitors (1 tablet for 25 ml buffer; EDTA-free protease inhibitor cocktail; Roche Diagnostics 1873580) was added in order to reach a final protein concentration of 5mg/ml total protein. For the kinobeads experiment a 1:1 mix of Jurkat and Ramos cell lysates was used. The diluted cell lysate was stored on ice.

Incubation of lysate with test compound and affinity matrix

To a 96 well filter plate (Multiscreen HTS, BV Filter Plates, Millipore #MSBVN1250) were added per well: 50 µl affinity matrix (10% beads slurry), 3 µl of compound solution, and 100 µl of cell diluted lysate. Plates were sealed and incubated for two hours in a cold room on a Thermoxer with shaking (750 rpm). Afterwards the plate was washed twice with 230 µl washing buffer (1xDP 0.4% NP40). The filter plate was placed on top of a collection plate (Greiner bio-one, PP-microplate 96 well V-shape, 65120) and the beads were then eluted with 20 µl of sample buffer (100 mM Tris, pH 7.4, 4% SDS, 0.00025% Bromophenol blue, 20% glycerol, 50 mM DTT). The eluate was frozen qickly at -80°C and stored at -20°C.

Detection and quantification of eluted kinases

The kinases in the eluates were detected and quantified by spotting on Nitrocellulose membranes and using a first antibody directed against the kinase of interest and a fluorescently labeled secondary antibody (anti-mouse or anti-rabbit IRDye™ antibodies from Rockland). The Odyssey Infrared Imaging system from LI-COR Biosciences (Lincoln, Nebraska, USA) was operated according to instructions provided by the manufacturer

(Schutz-Geschwendener et al., 2004. Quantitative, two-color Western blot detection with infrared fluorescence. Published May 2004 by LI-COR Biosciences, www.licor.com).

After spotting of the eluates the nitrocellulose membrane (BioTrace NT; PALL, #BTNT30R) was first blocked by incubation with Odyssey blocking buffer (LICOR, 927-40000) for one hour at room temperature. Blocked membranes were then incubated for 16 hours at 25°C with the first antibody diluted in Odyssey blocking buffer (LICOR #927-40000). Afterwards the membrane was washed three times for 10 minutes with PBS buffer containing 0.1% Tween 20 at room temperature. Then the membrane was incubated for 60 minutes at room temperature with the detection antibody (IRDye™ labelled antibody from Rockland) diluted in Odyssey blocking buffer (LICOR #927-40000). Afterwards the membrane was washed three times for 10 minutes each with 1 x PBS buffer containng 0.1% Tween 20 at room temperature. Then the membrane was rinsed once with PBS buffer to remove residual Tween 20. The membrane was kept in PBS buffer at 4°C and then scanned with the Odyssey instrument. Fluorescence signals were recorded and analysed according to the instructions of the manufacturer.

Table 1: Sources and dilutions of antibodies

Target kinase	Primary antibody (dilution)	Temperature of primary incubation	Secondary antibody (dilution)
PI3Kα	Cell Signalling Technologies 4255 (1 in 100)	25°C	Anti-Rabbit (1 in 2500)
PI3Kβ	Millipore 04-400 (1 in 1000)	25°C	Anti-Rabbit (1 in 2500)
PI3K δ	Santa Cruz SC7176 (1 in 1000)	4°C	Anti-Rabbit (1 in 2500)
PI3Kγ	Jena Bioscience ABD-026L (1 in 100)	25°C	Anti-Mouse (1 in 2500)
mTOR	Cell Signalling Technologies 2972 (1 in 500)	25°C	Anti-Rabbit (1 in 5000)
DNAPK	Calbiochem NA57 (1 in 1000)	4°C	Anti-Mouse (1 in 5000)

As shown in Table 2, the selectivity of compounds of the invention was further determined versus DNA-dependent protein kinase (DNA-PK), PI3Kα, PI3Kβ, PI3Kδ, and PI3Kγ.

Table 2: Inhibition values (IC_{50} in μM) as determined in the kinobeads assay

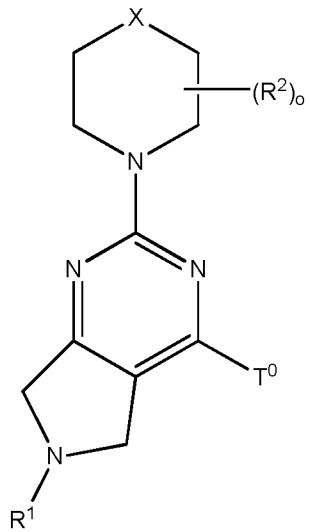
(Activity level: A ≤ 0.1μM, 0.1 < B ≤ 1μM, 1 < C ≤ 10μM, 10 < D ≤ 100μM, E > 100μM)

Example	mTor	PI3Kα	PI3Kβ	PI3Kδ	PI3Kγ	DNA-PK
1	B	D	D	D	D	E
2	B	D	D	D	D	D
3	B	D	D	D	D	E
4	B	C	D	D	D	D
5	B	D	D	D	D	D
6	B	C	C	C	C	D
7	C	E	E	E	E	E
8	D	E	E	E	E	E
9	C	E	E	E	E	E
10	D	D	E	E	E	E
11	B	D	D	D	D	D
12	C	D	D	D	E	E
13	B	E	E	E	E	E
14	C	E	E	E	E	E
15	B	E	E	E	E	E
16	C	E	E	E	E	E
17	C	D	E	E	E	E
18	B	E	E	E	E	D
19	A	C	D	D	C	D
20	C	E	D	D	E	E
21	C	E	D	D	E	E
22	B	D	D	C	D	E
23	B	D	D	D	E	E
24	C	D	D	D	D	E
25	B	C	C	D	C	E
26	B	E	D	D	E	E
27	C	D	D	D	E	E
28	C	D	D	D	D	E
29	C	D	D	D	D	E
30	C	D	D	D	E	E
31	B	E	D	D	E	E
32	C	E	C	D	D	D

33	C	E	D	D	E	E
34	B	D	D	D	D	E
35	C	E	E	E	E	E
36	B	D	D	D	C	E
37	B	C	D	D	D	D
38	C	E	E	E	E	E
39	B	D	D	C	D	D
40	C	D	D	D	E	E
41	C	D	D	D	D	E
42	B	D	D	D	E	E
43	A	E	E	E	E	C
44	B	E	D	D	E	D
45	C	D	E	E	E	E
46	C	E	E	E	E	E
47	C	E	D	E	E	E
48	C	E	E	E	E	E
49	C	E	E	E	E	E
50	C	E	E	E	E	E
51	C	E	E	E	E	E
52	C	E	E	E	E	E

Patent Claims

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt, prodrug or metabolite thereof, wherein

X is O; or S;

R^1 is H; $C(O)R^3$; $C(O)OR^3$; $C(O)N(R^3R^{3a})$; $S(O)_2N(R^3R^{3a})$; $S(O)N(R^3R^{3a})$; $S(O)_2R^3$; $S(O)R^3$; T^1; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^4, which are the same or different;

R^3, R^{3a} are independently selected from the group consisting of H; T^1; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^4, which are the same or different;

R^4 is halogen; CN; $C(O)OR^5$; OR^5; $C(O)R^5$; $C(O)N(R^5R^{5a})$; $S(O)_2N(R^5R^{5a})$; $S(O)N(R^5R^{5a})$; $S(O)_2R^5$; $S(O)R^5$; $N(R^5)S(O)_2N(R^{5a}R^{5b})$; $N(R^5)S(O)N(R^{5a}R^{5b})$; SR^5; $N(R^5R^{5a})$; NO_2; $OC(O)R^5$; $N(R^5)C(O)R^{5a}$; $N(R^5)S(O)_2R^{5a}$; $N(R^5)S(O)R^{5a}$; $N(R^5)C(O)N(R^{5a}R^{5b})$; $N(R^5)C(O)OR^{5a}$; $OC(O)N(R^5R^{5a})$; or T^1;

R^5, R^{5a}, R^{5b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

T^1 is C_{3-7} cycloalkyl; 4 to 7 membered heterocyclyl; 8 to 11 membered heterobicyclyl; phenyl; naphthyl; indenyl; or indanyl, wherein T^1 is optionally substituted with one or more R^6, which are the same or different;

R^6 is halogen; CN; $C(O)OR^7$; OR^7; oxo (=O), where the ring is at least partially saturated; $C(O)R^7$; $C(O)N(R^7R^{7a})$; $S(O)_2N(R^7R^{7a})$; $S(O)N(R^7R^{7a})$; $S(O)_2R^7$; $S(O)R^7$; $N(R^7)S(O)_2N(R^{7a}R^{7b})$; $N(R^7)S(O)N(R^{7a}R^{7b})$; SR^7; $N(R^7R^{7a})$; NO_2; $OC(O)R^7$; $N(R^7)C(O)R^{7a}$; $N(R^7)S(O)_2R^{7a}$; $N(R^7)S(O)R^{7a}$; $N(R^7)C(O)N(R^{7a}R^{7b})$; $N(R^7)C(O)OR^{7a}$; $OC(O)N(R^7R^{7a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^8, which are the same or different;

R^7, R^{7a}, R^{7b} are independently selected from the group consisting of H; C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^8 is halogen; CN; $C(O)OR^9$; OR^9; $C(O)R^9$; $C(O)N(R^9R^{9a})$; $S(O)_2N(R^9R^{9a})$; $S(O)N(R^9R^{9a})$; $S(O)_2R^9$; $S(O)R^9$; $N(R^9)S(O)_2N(R^{9a}R^{9b})$; $N(R^9)S(O)N(R^{9a}R^{9b})$; SR^9; $N(R^9R^{9a})$; NO_2; $OC(O)R^9$; $N(R^9)C(O)R^{9a}$; $N(R^9)S(O)_2R^{9a}$; $N(R^9)S(O)R^{9a}$; $N(R^9)C(O)N(R^{9a}R^{9b})$; $N(R^9)C(O)OR^{9a}$; or $OC(O)N(R^9R^{9a})$;

R^9, R^{9a}, R^{9b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

o is 1; 2; 3; or 4;

Each R^2 is independently selected from the group consisting of H; halogen; CN; $C(O)OR^{10}$; OR^{10a}; oxo (=O); $C(O)R^{10}$; $C(O)N(R^{10}R^{10a})$; $S(O)_2N(R^{10}R^{10a})$; $S(O)N(R^{10}R^{10a})$; $S(O)_2R^{10}$; $S(O)R^{10}$; $N(R^{10})S(O)_2N(R^{10a}R^{10b})$; $N(R^{10})S(O)N(R^{10a}R^{10b})$; SR^{10}; $N(R^{10}R^{10a})$; NO_2; $OC(O)R^{10}$; $N(R^{10})C(O)R^{10a}$; $N(R^{10})S(O)_2R^{10a}$;

$N(R^{10})S(O)R^{10a}$; $N(R^{10})C(O)N(R^{10a}R^{10b})$; $N(R^{10})C(O)OR^{10a}$; $OC(O)N(R^{10}R^{10a})$; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{11}, which are the same or different;

Optionally two R^2 are joined to form together with the ring to which they are attached an 8 to 11 membered heterobicycle.

R^{10}, R^{10a}, R^{10b} are independently selected from the group consisting of H; C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{11} is halogen; CN; $C(O)OR^{12}$; OR^{12}; $C(O)R^{12}$; $C(O)N(R^{12}R^{12a})$; $S(O)_2N(R^{12}R^{12a})$; $S(O)N(R^{12}R^{12a})$; $S(O)_2R^{12}$; $S(O)R^{12}$; $N(R^{12})S(O)_2N(R^{12a}R^{12b})$; $N(R^{12})S(O)N(R^{12a}R^{12b})$; SR^{12}; $N(R^{12}R^{12a})$; NO_2; $OC(O)R^{12}$; $N(R^{12})C(O)R^{12a}$; $N(R^{12})S(O)_2R^{12a}$; $N(R^{12})S(O)R^{12a}$; $N(R^{12})C(O)N(R^{12a}R^{12b})$; $N(R^{12})C(O)OR^{12a}$; or $OC(O)N(R^{12}R^{12a})$;

R^{12}, R^{12a}, R^{12b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

T^0 is phenyl; or 5 to 6 membered aromatic heterocycle, wherein T^0 is substituted with $N(R^{13a})C(O)N(R^{13b}R^{13})$ or $N(R^{13a})C(O)OR^{13}$ and optionally further substituted with one or more R^{14}, which are the same or different;

R^{14} is halogen; CN; $C(O)OR^{15}$; OR^{15}; $C(O)R^{15}$; $C(O)N(R^{15}R^{15a})$; $S(O)_2N(R^{15}R^{15a})$; $S(O)N(R^{15}R^{15a})$; $S(O)_2R^{15}$; $S(O)R^{15}$; $N(R^{15})S(O)_2N(R^{15a}R^{15b})$; $N(R^{15})S(O)N(R^{15a}R^{15b})$; SR^{15}; $N(R^{15}R^{15a})$; NO_2; $OC(O)R^{15}$; $N(R^{15})C(O)R^{15a}$; $N(R^{15})S(O)_2R^{15a}$; $N(R^{15})S(O)R^{15a}$; $N(R^{15})C(O)N(R^{15a}R^{15b})$; $N(R^{15})C(O)OR^{15a}$; $OC(O)N(R^{15}R^{15a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{13a}, R^{13b}, R^{15}, R^{15a}, R^{15b} are independently selected from the group consisting of H; C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{13} is H; T^2; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{16}, which are the same or different;

R^{16} is halogen; CN; $C(O)OR^{17}$; OR^{17}; $C(O)R^{17}$; $C(O)N(R^{17}R^{17a})$; $S(O)_2N(R^{17}R^{17a})$; $S(O)N(R^{17}R^{17a})$; $S(O)_2R^{17}$; $S(O)R^{17}$; $N(R^{17})S(O)_2N(R^{17a}R^{17b})$; $N(R^{17})S(O)N(R^{17a}R^{17b})$; SR^{17}; $N(R^{17}R^{17a})$; NO_2; $OC(O)R^{17}$; $N(R^{17})C(O)R^{17a}$; $N(R^{17})S(O)_2R^{17a}$; $N(R^{17})S(O)R^{17a}$; $N(R^{17})C(O)N(R^{17a}R^{17b})$; $N(R^{17})C(O)OR^{17a}$; $OC(O)N(R^{17}R^{17a})$; or T^2;

R^{17}, R^{17a}, R^{17b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

Optionally R^{13}, R^{13b} are joined to form together with the nitrogen atom to which they are attached an at least the nitrogen atom as ring heteroatom containing 4 to 7 membered heterocyclyl ring; or 8 to 11 membered heterobicyclyl ring, wherein the 4 to 7 membered heterocyclyl ring; and the 8 to 11 membered heterobicyclyl ring are optionally substituted with one or more R^{18}, which are the same or different;

T^2 is C_{3-7} cycloalkyl; 4 to 7 membered heterocyclyl; 8 to 11 membered heterobicyclyl; phenyl; naphthyl; indenyl; or indanyl, wherein T^2 is optionally substituted with one or more R^{18}, which are the same or different;

R^{18} is halogen; CN; $C(O)OR^{19}$; OR^{19}; oxo (=O), where the ring is at least partially saturated; $C(O)R^{19}$; $C(O)N(R^{19}R^{19a})$; $S(O)_2N(R^{19}R^{19a})$; $S(O)N(R^{19}R^{19a})$; $S(O)_2R^{19}$; $S(O)R^{19}$; $N(R^{19})S(O)_2N(R^{19a}R^{19b})$; $N(R^{19})S(O)N(R^{19a}R^{19b})$; SR^{19}; $N(R^{19}R^{19a})$; NO_2; $OC(O)R^{19}$; $N(R^{19})C(O)R^{19a}$; $N(R^{19})S(O)_2R^{19a}$; $N(R^{19})S(O)R^{19a}$; $N(R^{19})C(O)N(R^{19a}R^{19b})$; $N(R^{19})C(O)OR^{19a}$; $OC(O)N(R^{19}R^{19a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more R^{20}, which are the same or different;

R^{19}, R^{19a}, R^{19b} are independently selected from the group consisting of H; C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{20} is halogen; CN; $C(O)OR^{21}$; OR^{21}; $C(O)R^{21}$; $C(O)N(R^{21}R^{21a})$; $S(O)_2N(R^{21}R^{21a})$; $S(O)N(R^{21}R^{21a})$; $S(O)_2R^{21}$; $S(O)R^{21}$; $N(R^{21})S(O)_2N(R^{21a}R^{21b})$; $N(R^{21})S(O)N(R^{21a}R^{21b})$; SR^{21}; $N(R^{21}R^{21a})$; NO_2; $OC(O)R^{21}$; $N(R^{21})C(O)R^{21a}$; $N(R^{21})S(O)_2R^{21a}$; $N(R^{21})S(O)R^{21a}$; $N(R^{21})C(O)N(R^{21a}R^{21b})$; $N(R^{21})C(O)OR^{21a}$; or $OC(O)N(R^{21}R^{21a})$;

R^{21}, R^{21a}, R^{21b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

2. The compound of claim 1, wherein X is O.

3. The compound of claim 1 or 2, wherein R^1 is H; $C(O)R^3$; $S(O)_2R^3$; optionally substituted C_{1-6} alkyl; $C(O)OR^3$; $C(O)NHR^3$; or optionally substituted T^1.

4. The compound of claim 3, wherein R^1 is H.

5. The compound of any one of claims 1 to 3, wherein R^3 is H; optionally substituted C_{1-6} alkyl; or optionally substituted T^1.

6. The compound of any one of claims 1 to 5, wherein o is 1 or 2.

7. The compound of any one of claims 1 to 6, wherein R^2 is H; or methyl.

8. The compound of any one of claims 1 to 7, wherein o is 1, R^2 is methyl and the ring carbon to which the methyl group is attached has (S)-configuration.

9. The compound of any one of claims 1 to 6, wherein X is O and two R^2 are joined to form together with the morpholine ring to which they are attached an 8-oxa-3-azabicyclo[3.2.1]octan-3-yl residue.

10. The compound of any one of claims 1 to 9, wherein T^0 is phenyl; pyridine; pyrimidine; pyridazine; or pyrazine and wherein T^0 is substituted with $N(R^{13a})C(O)N(R^{13b}R^{13})$ and optionally further substituted with one or more R^{14}, which are the same or different.

11. The compound of claim 10, wherein T^0 is phenyl and wherein T^0 is substituted with $N(R^{13a})C(O)N(R^{13b}R^{13})$ and optionally further substituted with one or more R^{14}, which are the same or different.

12. The compound of any of claims 1 to 11, wherein T^0 is only substituted with $N(R^{13a})C(O)N(R^{13b}R^{13})$.

13. The compound of any one of claims 1 to 12, wherein R^{13a} is H.

14. The compound of any one of claims 1 to 13, wherein R^{13b} is H or R^{13b}, R^{13} are joined to form together with the nitrogen to which they are attached an optionally substituted morpholine ring.

15. The compound of any one of claims 1 to 14, wherein R^{13} is H; optionally substituted C_{1-6} alkyl; optionally substituted C_{3-7} membered cycloalkyl; or optionally substituted pyridine.

16. The compound of any one of claims 1 to 15, wherein R^{13a}, R^{13b} are H and R^{13} is CH_2CH_2OH.

17. A compound of claim 1 selected from the group consisting of

(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-ethyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-ethyl-3-(4-(6-formyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
1-ethyl-3-(4-(2-morpholino-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
1-cyclopropyl-3-(4-(2-morpholino-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
1-(4-(2-morpholino-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

ethyl 4-(4-(3-ethylureido)phenyl)-2-morpholino-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate;

(S)-ethyl 4-(4-(3-ethylureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate;

(S)-ethyl 4-(4-(3-cyclopropylureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylate;

(S)-ethyl (4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)carbamate;

(S)-1-cyclopropyl-3-(4-(6-methyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-(4-(6-acetyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;

(S)-1-cyclopropyl-3-(4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-cyclopropyl-3-(4-(6-cyclopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-3-methyl-N-(4-(2-((S)-3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)morpholine-4-carboxamide;

(S)-4-(4-(3-cyclopropylureido)phenyl)-N-ethyl-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxamide;

1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;

(S)-1-(2-hydroxyethyl)-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-cyclopropyl-3-(4-(6-(2-(dimethylamino)acetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-cyclopropyl-3-(4-(6-(3-(dimethylamino)propanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-cyclopropyl-3-(4-(6-(2-hydroxyacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-(4-(6-(2-cyanoacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;

(S)-1-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(pyridin-4-yl)urea;

(S)-1-(6-hydroxypyridin-2-yl)-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(R)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-cyclopropyl-3-(4-(6-(2-methoxyacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-(4-(6-(2-aminoacetyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;

(S)-1-(4-(6-(3-aminopropanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;

(S)-1-(4-(6-(4-aminobutanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;

(S)-1-cyclopropyl-3-(4-(6-(3-methoxypropanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-cyclopropyl-3-(4-(6-(4-(dimethylamino)butanoyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

1-cyclopropyl-3-(4-(2-((S)-3-methylmorpholino)-6-(tetrahydrofuran-2-carbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-(2-hydroxyethyl)-3-(4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-cyclopropyl-3-(4-(6-(cyclopropylsulfonyl)-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-1-(2-hydroxyethyl)-3-(4-(2-(3-methylmorpholino)-6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

(S)-N-ethyl-4-(4-(3-(2-hydroxyethyl)ureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxamide;

(S)-1-(4-(6-cyclohexyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea;

(S)-1-(4-(6-acetyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea;

1-cyclopropyl-3-(4-(2-((S)-3-methylmorpholino)-6-(tetrahydrofuran-3-carbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;

1-cyclopropyl-3-(4-(2-((S)-3-methylmorpholino)-6-(pyrrolidine-2-carbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-4-(4-(3-cyclopropylureido)phenyl)-2-(3-methylmorpholino)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxamide;
1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea;
1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-ethylurea;
1-(2-hydroxypropyl)-3-(4-(6-isopropyl-2-((S)-3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-ethyl-3-(4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-cyclopropyl-3-(4-(2-(3-methylmorpholino)-6-(2-morpholinoacetyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6-isobutyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-(2-hydroxyethyl)urea;
1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6-isopropyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-ethylurea;
1-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)-3-cyclopropylurea;
1-(1-hydroxypropan-2-yl)-3-(4-(6-isopropyl-2-((S)-3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea;
(S)-1-(2-cyanoethyl)-3-(4-(6-isopropyl-2-(3-methylmorpholino)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)phenyl)urea; and
pharmaceutically acceptable salts, prodrugs or metabolites thereof.

18. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof of any one of the claims 1 to 17 together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

19. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 17 for use as a medicament.

20. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 17 for use in a method of treating or preventing a disease or disorder associated with mTOR.

21. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 17 for use in a method of treating or preventing an immunological, inflammatory, autoimmune, or allergic disorder or disease or a transplant rejection or a Graft-versus host disease.

22. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 17 for use in a method of treating or preventing a proliferative disease, especially cancer.

23. A compound or a pharmaceutically acceptable salt thereof of any of claims 1 to 17 for use in a method of treating or preventing a cardiovascular disease, a metabolic disease or a neurodegenerative disease.

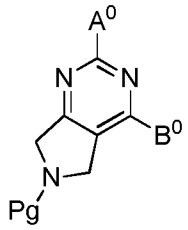
24. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 17 for use in a method of treating or preventing autophagy associated diseases.

25. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 17 for use in a method of treating or preventing a viral infection.

26. A method for treating, controlling, delaying or preventing in a mammalian patient in need thereof one or more conditions selected from the group consisting of diseases and disorders associated with mTOR, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound of any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof.

27. A method for the preparation of a compound of any one of the claims 1 to 17, comprising the steps of

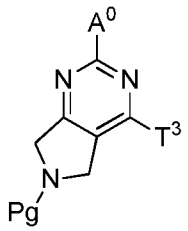
(a) reacting a compound of formula (II)



(II)

,

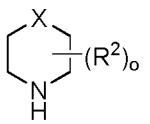
wherein Pg is a suitable protecting group and A^0, B^0 are suitable leaving groups which may be the same or different with a compound of the formula X^0-T^3, wherein X^0 is a boronate ester or boronate acid and T^3 is defined as T^0 as defined in any one of claims 1 to 17 with the exception that the substituent $N(R^{13a})C(O)N(R^{13b}R^{13})$ or $N(R^{13a})C(O)OR^{13}$ is replaced by a nitro group or a suitably protected amino group, in a Suzuki reaction to yield a compound of formula (III)



(III)

;

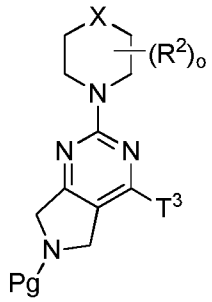
(b) reacting the compound of formula (III) with a compound of formula (IV)



(IV)

,

wherein X, R^2, o have the meaning as indicated in any one of claims 1 to 17 to yield a compound of formula (V)



(V) ; and

(c_1) converting the nitro group or the suitably protected amino group into substituent $N(R^{13a})C(O)N(R^{13b}R^{13})$ or $N(R^{13a})C(O)OR^{13}$ and subsequently removing the Pg protecting group to yield compounds of formula (I), wherein R^1 is H; and optionally compounds of formula (I) wherein R^1 is H may be reacted with a compound of formula R^1-X^1, wherein X^1 is a suitable leaving group and R^1 has the meaning as indicated in any of claims 1 to 17 (but other than H) to give compounds of formula (I) wherein R^1 is other than H; or, alternatively

(c_2) removing the Pg protecting group and reacting the resulting compound with a compound of formula R^1-X^1, wherein X^1 is a suitable leaving group and R^1 has the meaning as indicated above (other than H), followed by converting the nitro group or the suitably protected amino group into substituent $N(R^{13a})C(O)N(R^{13b}R^{13})$ or $N(R^{13a})C(O)OR^{13}$ to yield compounds of formula (I), wherein R^1 is other than H.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/055953

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61P37/00 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/120994 A2 (WYETH LLC [US]; VERHEIJEN JEROEN CUNERA [US]; ZASK ARIE [US]; AYRAL-KA) 21 October 2010 (2010-10-21) cited in the application page 1 claims 19,20 pages 1,14,48 claim 10 -----	1-27
Y	WO 2010/103094 A1 (CELLZOME LTD [GB]; LYNCH ROSEMARY [GB]; CANSFIELD ANDREW [GB]; NIBLOCK) 16 September 2010 (2010-09-16) cited in the application claims 1,17-24 example 34; table 4 -----	1-27

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 August 2012	27/08/2012

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/055953

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010120994 A2	21-10-2010	NONE	
WO 2010103094 A1	16-09-2010	CA 2755061 A1	16-09-2010
		EP 2406258 A1	18-01-2012
		US 2012065202 A1	15-03-2012
		WO 2010103094 A1	16-09-2010