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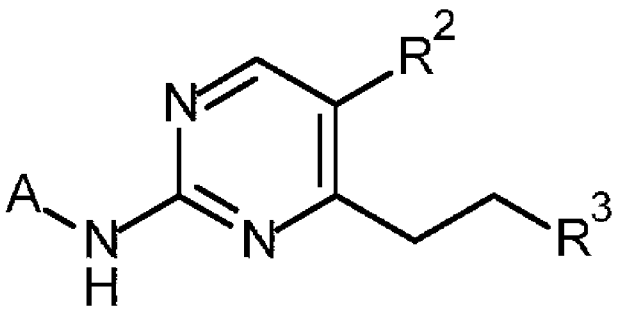



(I)

(57) Abstract: This invention relates to compounds of the formula (I):The invention also relates to processes for the preparation of the compound of the formula (I), pharmaceutical agents or compositions containing the compound or a method of using the compound for the treatment of proliferative diseases, such as cancer.

# INHIBITORS

This invention relates to 2,4,5-substituted pyrimidines that inhibit vascular endothelial growth factor receptor 3 (VEGFR3), also known as Fms related tyrosine kinase 4 (FLT4), processes for their preparation and pharmaceutical agents or compositions containing such compounds. This invention also relates to a method of using such compounds for the treatment of proliferative diseases, such as cancer, as well as the treatment of diseases ameliorated by the control and/or inhibition of lymphangiogenesis.

This invention relates to 2,4,5-substituted pyrimidines that inhibit focal adhesion kinase (FAK), processes for their preparation or pharmaceutical agents or compositions containing such compounds. This invention also relates to a method of using such compounds for the treatment of proliferative diseases, such as cancer.

## Background

Cancer remains a major cause of death in the 21st century. Consequently, considerable drug research and development effort is currently placed on the discovery of therapeutics that may provide life extending or curative options to cancer sufferers.

While there are many different varieties of cancer, each exhibiting a different array of genetic and growth properties, a common denominator among many solid cancer types is the ability to metastasise. Until the occurrence of metastasis, tumors are confined to one area of the body and may be controlled through surgical intervention and/or radiotherapy. However, metastasis causes cancer cells to spread to disparate parts of the body and while surgical intervention may remove the primary tumor lesion, removal of all metastatic lesions is very difficult to manage.

Tumor metastasis is a multistage process, involving the breakdown of extracellular matrix, invasion of local tissue parenchyma, intravasation into regional blood vessels and lymphatics, survival in the circulation and finally extravasation, survival and growth in secondary tissue sites (*Front. Biosci. (Elite Ed). 2012; 4: 1888-1897*).

Metastasis may occur through blood vessels or lymphatic vessels. Lymphatic vessels differ from blood vessels in several ways. Large collecting lymphatic vessels contain vascular smooth muscle cells in their wall, as well as valves, which prevent the backflow of lymph.

However, lymphatic capillaries, unlike typical blood capillaries, lack pericytes and continuous basal lamina and contain large inter-endothelial valve-like openings (*J. Theor. Med. 2003; 5: 59-66*). Due to their greater permeability, lymphatic capillaries are more effective than blood capillaries in allowing tumor cells to pass. Experimental evidence demonstrates that lymphangiogenesis (the formation of new lymphatic vessels) within a growing tumor lesion promotes metastasis through lymphatic vessels. The control of lymphangiogenesis presents an attractive therapeutic strategy for preventing lymph node metastasis (*J. Clin. Onc. 2007; 25: 4298-4307*).

The lymphatic system is comprised of capillaries and larger collecting vessels continuously lined by endothelial cells which return extravasated fluid and macromolecules from the interstitial space back to the blood circulation. Metastasis to regional lymph nodes via lymphatic vessels is a tumor progression process that is common to many cancer types. The extent of lymph node involvement is a major determinant for the staging of many types of cancer and is an important prognostic factor that is used as the basis for surgical and radiation treatment intervention of the affected lymph nodes.

Molecular signalling through binding of the growth factors VEGFC or VEGFD to their membrane receptor VEGFR3 has been shown to play a central role in the process of lymphangiogenesis (*Brit. J. Cancer 2006; 94: 1355-1360*). Stimulation of the VEGFR3 receptor occurs through the phosphorylation of its intracellular region and triggers a downstream signalling cascade that drives lymphatic endothelial cell proliferation, migration and differentiation leading to formation of lymphatic vessels (*Exp. Cell Res. 2006; 312: 575-583*). Increased expression of VEGFC or VEGFD has been shown to promote tumor associated lymphangiogenesis enabling lymphatic-mediated metastasis to regional lymph nodes. These observations have been reported for several different tumor types, including colorectal (*Oncol. Rep. 2009; 22: 1093-1100*) lung (*Ann. Oncol. 2010; 21: 223-231*), gastric (*Surgery 2009; 146: 896-905*), kidney (*Oncol. Rep. 2008; 20: 721-725*) prostate (*Clin. Cancer Res. 2004; 10: 5137-5144*) and ovarian (*Cancer 2004; 101: 1364-1374*). Blockade of VEGFC, VEGFD/VEGFR3 mediated signalling has been shown to inhibit lymphangiogenesis and suppress lymph node metastasis in several tumor experimental models in rodents (*Ann. N. Y. Acad. Sci. 2008; 113:, 225-234; Int. J. Cancer 2009; 125: 2747-2756*).

VEGFR3 is a transmembrane tyrosine kinase receptor that is broadly expressed in endothelial cells during embryogenesis (*Biochem. J. 2011; 437: 169-183*). In the latter stages of development VEGFR3 expression becomes restricted to developing lymphatic

vessels. In adults, VEGFR3 expression is primarily restricted to lymphatic endothelium and a subset of CD34+ hematopoietic cells. In addition, fenestrated capillaries and veins in certain endocrine organs, as well as monocytes, macrophages and some dendritic cells (DCs), continue to express VEGFR3 in adults. Disruption of the VEGFR3 gene in mouse embryos results in the failure of vascular network formation and death after embryonic day 9.5 (*Biochem. J. 2011; 437: 169-183*). This observation demonstrates that VEGFR3 plays an essential role in the development of embryonic vasculature. In cancer, VEGFR3 is overexpressed in lymphatic sinuses in metastatic lymph nodes and in lymphangiomas. Furthermore, in many instances cancer cells themselves express VEGFR3. VEGFR3 expressing cancer cells have been shown to be dependent on VEGFR3/VEGFC signalling for their proliferation (*Eur. J. Canc. 2011; 47: 2353 –2363*).

Based on the foregoing, it is apparent that inhibition of VEGFR3 signalling has strong potential as therapeutic strategy for mammalian subjects that have been diagnosed with a disease characterised by proliferation of endothelial cells that express this receptor. In the case of cancer, targeting VEGFR3 is likely to result in therapeutic benefit through suppression of lymphatic metastasis and suppression of growth in cancer cells that express VEGFR3.

Interestingly, and perhaps importantly from the view point of target selection within the VEGFR3 axis, in mice in which both the VEGFC and the VEGFD genes have been homozygously deleted, the blood vasculature develops normally, unlike the embryonic cardiovascular phenotype of VEGFR3 homozygous knockout mice: i.e. deletion of these two ligands is not the same as deletion of the receptor *(Mol. Cell. Biol. 2008; 28: 4843-4850*). These data raise the possibility that another ligand for VEGFR3 exists or that VEGFR3 may be able to act by an as-yet-unknown manner independent of its ligands VEGFC and VEGFD. The foregoing suggest that targeting VEGFR3 is more advantageous to blocking VEGFC/D-VEGFR3 signalling compared to targeting either VEGFC or VEGFD alone.

Whilst there are a number of studies reported involving tyrosine kinase inhibitors with various levels of VEGFR3 activity and selectivity (*Nat. Rev. Drug Discov. 2006; 5: 835-844; Mol. Cancer Ther. 2007; 6: 2012-2021; Cancer Res. 2009; 69: 8009-8016; Mol. Cancer Ther. 2012; 11: 1637-1649*) these studies have some limitations, resulting in part at least from inhibition at other tyrosine kinases.

Nonetheless, collectively these studies strengthen the conclusion that inhibition of VEGFR3 suppresses or reduces lymphangiogenesis and/or lymphogenic metastasis.

Accordingly, compounds that selectively inhibit VEGFR3 would be useful for the treatment of proliferative diseases, such as cancer.

As described above, VEGFR3 plays an important role in the control of lymphangiogenesis. Accordingly, inhibitors of VEGFR3 may have utility in the treatment of diseases other than cancer where control/inhibition of lymphangiogenesis has a therapeutic benefit. The lymphatic system plays a major role in chronic inflammatory diseases and in transplant rejection. Inhibition of lymphangiogenesis through suppression of VEGFR3 function may provide a viable therapeutic strategy in these conditions.

For example, preclinical studies have demonstrated that the expression of VEGFR3 in the cornea and ocular surface is modified during corneal neovascularisation and that VEGFR3 mediates corneal dendritic cell migration to lymph nodes and induction of immunity to corneal transplant. High-risk corneal transplantation, where grafting is performed on inflamed and highly vascularized host beds, has a very poor success rate, with rejection rates as high as 90% (*J. Leukoc Biol. 2003; 74: 172–178*). In preclinical models, treatment with a VEGFR3 antibody leads to significant suppression of corneal graft rejection (*Nat. Med. 2004; 10: 813 - 815*).

Choroidal neovascularization (CNV), the creation of new blood vessels in the choroid layer of the eye, leads to chronic inflammation which is implicated in the pathogenesis of age related macular degeneration (AMD) and is driven by factors which include uncontrolled expression of the vascular endothelial growth factor (VEGF) family members VEGFA and VEGFC (*J. Cell. Physiol. 2012; 227(1): 116-26*). Treatments for AMD have been developed that target VEGFA, for example the anti-VEGFA antibodies ranibizumab and bevacizumab and the anti-VEGF aptamer pegaptanib, but to date no treatments have been clinically evaluated that mediate effects through modulation of VEGFC and its cognate receptor VEGFR3.

Accordingly, compounds that inhibit VEGFR3 may be useful for the prevention and/or treatment of eye diseases, for example corneal graft rejection and age related macular degeneration.

Furthermore, there is increasing evidence that lymphatic vessels have an active role in chronic inflammation of the skin. Lymphatic endothelial cell proliferation and lymphatic hyperplasia have been described in chronic skin inflammation in mice and have been reported for skin lesions in psoriasis patients (*Blood 2004; 104: 1048–1057*).

Accordingly, compounds that inhibit VEGFR3 may be useful for the prevention and/or treatment of skin inflammations, such as skin lesions in patients with psoriasis.

Lymphangiogenesis has also been found to be associated with kidney transplant rejection. VEGFC producing macrophages induce formation of new lymphatics which induce and support the maintenance of an alloreactive immune response in renal transplants (*Nat. Med. 2006; 12: 230–234*).

Accordingly, compounds that inhibit VEGFR3 may be useful for the prevention and/or treatment of rejection in renal transplantation.

The ability of cells to perform their physiological function and maintain their position within organs is underpinned by their interaction with the extracellular matrix. Such interaction is mediated by focal adhesions that form the interface of interaction between cell and ECM proteins. Integrins located in the cell plasma membrane are an integral part of focal adhesions that are linked to the cell cytoskeleton and have the capacity to transmit signals enabling the extracellular matrix to influence cell function and behaviour. Several proteins and lipids co-localise with integrins within focal adhesions, including paxillin, zyxin, vinculin and FAK (focal adhesion kinase). Through its role in the regulation of focal adhesion formation and signalling, FAK is considered to be fundamental for cell migration and anchorage-dependent cell survival.

FAK is a 125 kDa ubiquitously expressed non-receptor tyrosine kinase that becomes phosphorylated upon integrin clustering at the cell surface. Phosphorylation renders FAK active and mediates downstream signalling events that influence a number of pathways including PI3K/Akt, ERK and JNK/MAPK leading to induction of gene transcription events that dictate cell movement, growth and survival under normal physiological circumstances but are also capable of driving tumor growth, resistance and metastasis in cancer pathological settings. FAK is a key component of protein complexes involving well-recognized signaling pathways in cancer, more specifically a signaling complex containing oncogenic proteins, such as the epidermal growth factor receptor (EGFR), human epidermal

growth factor receptor 2 (HER-2), MET (the hepatocyte growth factor receptor, encoded by c-Met ), and Src, and tumor suppressor proteins such as the transcription factor p53 and neurofibromin-1 (NF-1) places FAK at the center of cancer cell growth and regulation.

FAK has been implicated in nearly every aspect of cancer: invasion, metastasis, angiogenesis, epithelial mesenchymal transition (EMT), maintenance of cancer stem cells, and globally promoting tumor cell survival. Dysregulation of FAK expression and function has been implicated in the development and propagation of several malignancies through its role in enhancing tumor angiogenesis, tumor cell invasion and metastasis. Amplification of FAK expression has been described in a range of tumor types including Non-Small Cell Lung Cancer (NSCLC), pancreatic cancer, breast cancer, Head and Neck cancer, brain cancer, thyroid cancer, prostate cancer and acute myelogeneous leukemia. In these cases, high FAK expression was associated with a worse disease outcome.

FAK inhibitors evaluated in the clinic to-date target the ATP binding site in FAK aimed at inhibiting the kinase enzymatic activity. PF-562271 was the first inhibitor evaluated. A Phase I trial identified that a dose of 125 mg administered twice-per-day with food was well tolerated with 31 out of 99 treated patients experiencing stable disease. However, PF-562271 displayed nonlinear pharmacokinetics profile suggesting underlying issues with CYP450 enzyme metabolism.

Several new lines of investigation have provided experimental evidence enabling selection of cancer types and patient subpopulations that are more likely to respond to FAK inhibition. The tumor suppressor gene NF2 (encoding the Merlin protein) regulates FAK expression. Cancers in which NF2 is inactivated have a high expression level of FAK, leading to higher invasion rates. It has been shown that these cancer types are much more responsive to FAK inhibitors than those that have intact NF2. Recently it has been reported that KRAS mutant NSCLC, which often also have mutations at the CDKN2A locus, present as a highly aggressive tumour type which are resistant to therapy. It has been found that the RHOA-FAK signaling axis is a critical vulnerability in these tumour types and a specific opportunity exists for FAK inhibition as therapy. Attenuation of the p53 protein is one of the most common abnormalities in human tumours. Characterization of the FAK promoter demonstrated that p53 can bind and inhibit the FAK promoter activity *in vitro*. It was also demonstrated that p53 binds the FAK promoter-chromatin region *in vivo* and down-regulates FAK mRNA and protein levels. Furthermore many common p53 mutations blocked this transcriptional suppressor function of p53 against the FAK promoter. Finally a sample of

primary breast and colon cancers were analysed for p53 mutations and FAK expression, and showed that FAK expression was increased in tumours containing mutations of p53 compared to tumours with wild type p53. In addition, tumour-derived missense mutations in the DNA-binding domain (R282, R249, and V173) also led to increased FAK promoter activity.

Preclinical evidence points to the potential therapeutic utility in combining FAK inhibitors with other anti-cancer agents. In particular, FAK inhibition appears to curtail tumor growth and progression, increasing overall survival in animal models when combined with docetaxel, gemcitabine, 5-fluorouracil, temozolomide, sunitinib, oxaliplatin, doxorubicin or radiotherapy.

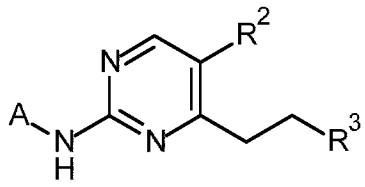
Inflammatory cytokines including TNF-α and IL-1β activate inflammatory gene expression via mitogen activated protein kinases (MAPKs) cascade and nuclear factor kappa B (NF-κB) activation. Inhibition of MAPK or NF-κB pathway significantly reduces inflammatory gene expression. Recent findings suggested that TNF-α activates MAPKs via FAK, and genetic and pharmacological FAK inhibition blocks inflammatory VCAM-1 expression. Although NF-κB is a critical player in inflammation signaling network, FAK inhibition does not block NF-κB activation but still does block VCAM-1 expression. Additionally, active MAPK expression in KD FAK cells did not rescue VCAM-1 expression. It turns out that FAK inhibition via a small molecule FAK inhibitor or genetic KD FAK promotes turnover of GATA4 transcription factor required for VCAM-1 expression. This is mediated by nuclear FAK scaffold function through interaction with GATA4 and ubiquitin E3 ligase CHIP. The finding suggests that FAK inhibition can provide anti-inflammatory effects via nuclear-localized FAK, but importantly, the inflammatory signaling pathway through FAK is not dependent of NF-κB activation. These observations support a role of FAK in inflammatory signaling.

**Summary**

The present inventors have discovered a particular class of compounds which are effective as VEGFR3 inhibitors. These compounds may exhibit selectivity for VEGFR3 over kinases such as VEGFR2. These compounds may exhibit FAK activity and accordingly improved *in vivo* efficacy for cancer. These compounds may exhibit improved selectivity for FAK over other kinases such as VEGFR2.

The present inventors have discovered a particular class of compounds which may exhibit improved pharmacokinetic and safety profiles. These compounds may have diminished activity on safety targets, such as hERG and/or CYP450s.

A first aspect provides compounds of the following formula (I) or isomers, salts, solvates or prodrugs thereof:



(I)

wherein:

A is an optionally substituted 5 to 10 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl group contains 1 to 4 heteroatoms selected from N, O and S;

A may optionally bear a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

wherein when A is a 9 or 10 membered heteroaryl group, the substitutent $R^{1A}$ must be present;

where $R^{1A}$ is selected from:

(i) $CH(R^{C1})NHZ^1$, where $R^{C1}$ is selected from H, $C_{1-3}$ alkyl, $C_{3-5}$ cycloalkyl and oxetanyl, and $Z^1$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(ii) $XNHZ^2$, where X is selected from $CF_2$, $CMe_2$, cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidine, and $Z^2$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(iii) a substituted 3-6 membered cycloalkyl; and

(iv) an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N, O and S;

each $R^{1B}$ is independently selected from $O\text{-}C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from $O\text{-}C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, $O\text{-}(C_{1-3}$ alkyl), $O\text{-}(CH_2)n\text{-}C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the $-C_2H_4-$ group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

$R^4$ is selected from:

(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

In some embodiments, the compounds of formula (I) or isomers, salts, solvates or prodrugs thereof as defined above with the proviso that the compound is not any of the following compounds or Boc-protected intermediates thereof:

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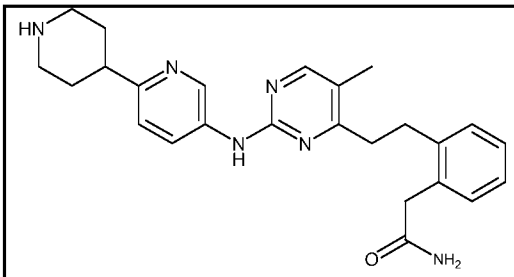
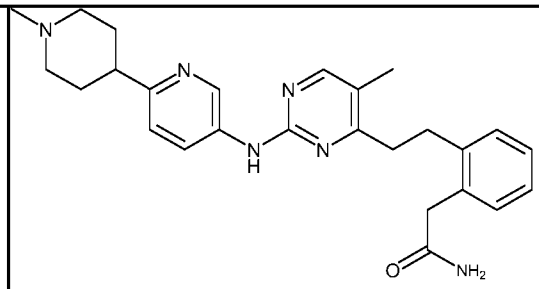
<td>  <br>2-(2-(2-(5-methyl-2-((6-(piperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (4)</td>
<td>  <br>2-(2-(2-(5-methyl-2-((6-(1-methylpiperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (5)</td>
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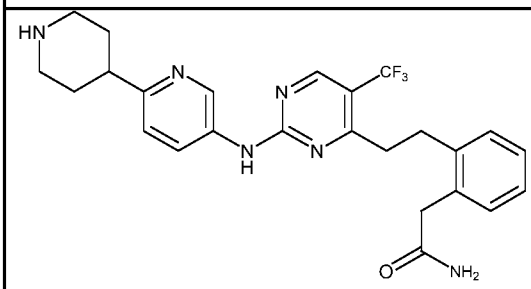
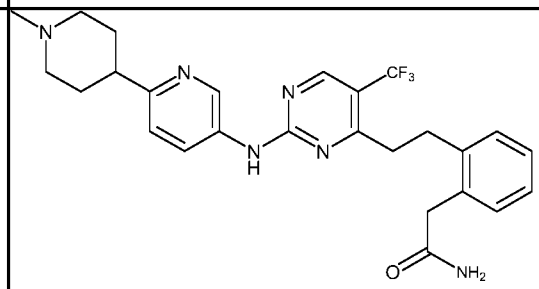
<td>  <br>2-(2-(2-(2-((6-(piperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (13)</td>
<td>  <br>2-(2-(2-(2-((6-(1-methylpiperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (14)</td>
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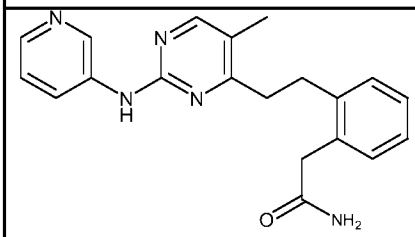
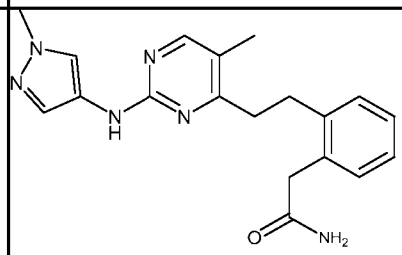
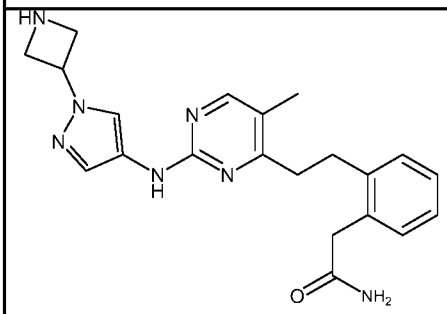
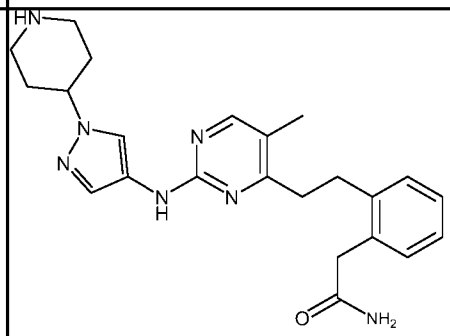
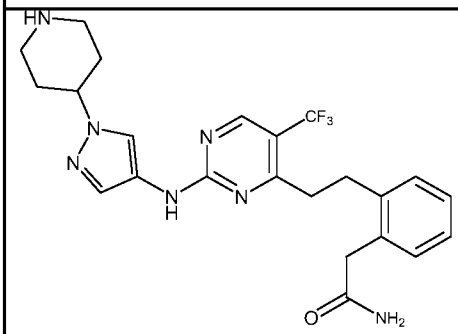
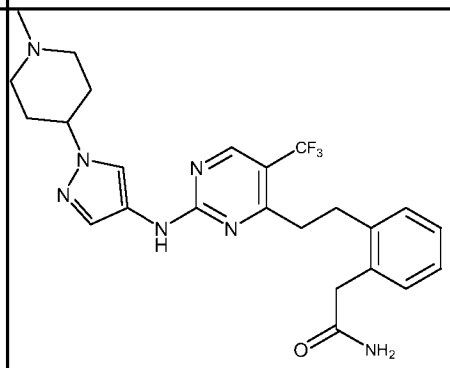
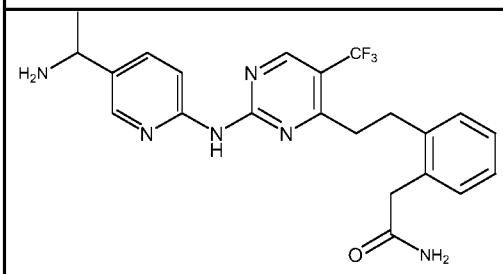
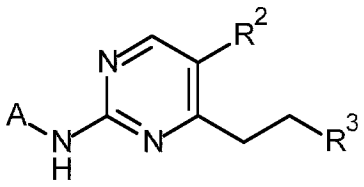
<td>  <br>2-(2-(2-(5-methyl-2-(pyridin-3-ylamino)pyrimidin-4-yl)ethyl)phenyl)acetamide (24)</td>
<td>  <br>2-(2-(2-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-</td>
</tr>
</table>

| | |
|---|---|
| | yl)ethyl)phenyl)acetamide (28) |
|  <br>*2-(2-(2-(2-((1-(azetidin-3-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (30)* |  <br>2-(2-(2-(5-Methyl-2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (33) |
|  <br>2-(2-(2-(2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (35) |  <br>2-(2-(2-(2-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (36) |
|  <br>2-(2-(2-(2-((6-(1-aminoethyl)pyridin-3-yl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (40) | |

A second aspect provides a compound of the formula (IC) or isomers, salts, solvates or prodrugs thereof:



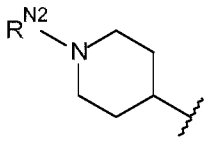
(IC)

wherein:

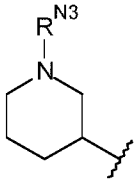
A is an optionally substituted 5 or 6 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl group contains 1 or 2 N heteroatoms;

A bears a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

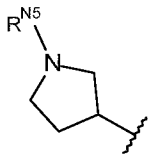
where $R^{1A}$ is selected from



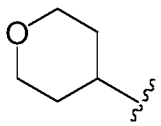
($R^{1A2}$)



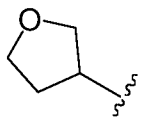
($R^{1A3}$)



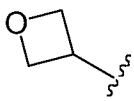
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

each of $R^{N2}$, $R^{N3}$ and $R^{N5}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1B}$ is independently selected from $O\text{-}C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from $O\text{-}C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, $O\text{-}(C_{1-3}$ alkyl), $O\text{-}(CH_2)n\text{-}C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$

either alpha or beta to the $-C_2H_4-$ group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

$R^4$ is selected from:

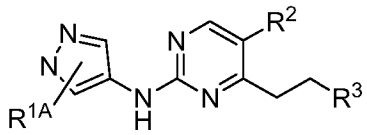
(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

In some embodiments of the preceding aspects, the group $R^{1B}$ is absent. In other words, the group A may optionally bear a substituent $R^{1A}$ and may optionally bear one or two substituents $R^{1C}$.

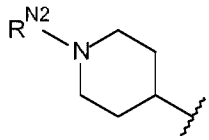
A third aspect provides a compound of formula (IE) or isomers, salts, solvates, or prodrugs thereof:



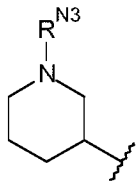
(IE)

wherein:

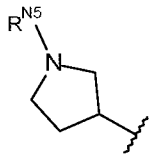
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



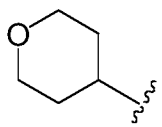
($R^{1A2}$)



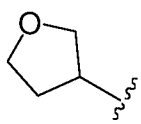
($R^{1A3}$)



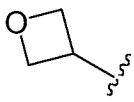
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

each of $R^{N2}$ and $R^{N5}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^{N3}$ is selected from H, $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the $-C_2H_4-$ group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

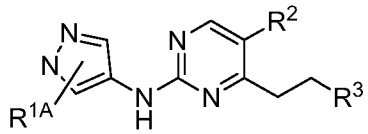
$R^4$ is selected from:

(i) $CH_2$-$C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

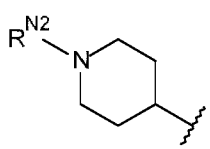
A fourth aspect provides a compound of formula (IG) or isomers, salts, solvates, or prodrugs thereof:



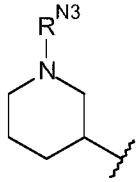
(IG)

wherein:

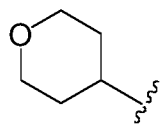
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



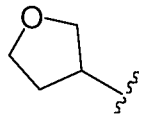
($R^{1A2}$)



($R^{1A3}$)



($R^{1A12}$)



($R^{1A13}$)

wherein:

$R^{N2}$ is independently selected from $C_{2-3}$ alkyl, $C_3$ alkenyl, and $C(=O)C_1$ alkyl;

$R^{N3}$ is $C_1$ alkyl;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

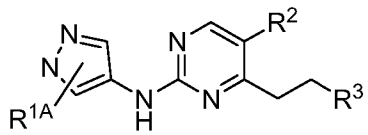
$R^4$ is selected from:

(i) $CH_2$-$C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

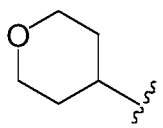
A fifth aspect provides a compound of formula (IH) or isomers, salts, solvates, or prodrugs thereof:



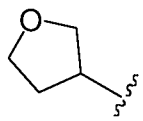
(IH)

wherein:

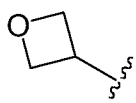
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the $-C_2H_4-$ group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

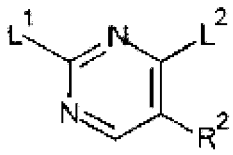
$R^4$ is selected from:

(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

A sixth aspect provides a process for the preparation of a compound of formula (I) or isomers, salts, solvates or prodrugs thereof, which comprises reacting a compound of formula F1



F1

with a compound of formula A-$NH_2$ to displace the group $L^1$ and with a compound of formula $HC\equiv R^3$ to displace the group $L^2$, or

with a compound of formula $HC\equiv R^3$ to displace the group $L^2$ and with a compound of formula A-$NH_2$ to displace the group $L^1$,

wherein A, $R^2$ and $R^3$ are as defined in formula (I) above and $L^1$ and $L^2$ are leaving groups.

A seventh aspect provides a pharmaceutical agent comprising a compound of the formula (I) or isomers, salts, solvates or prodrugs thereof.

There is also provided use of a compound of formula (I) or isomers, salts, solvates, protected forms or prodrugs thereof as a pharmaceutical agent.

There is further provided a compound of formula (I) or isomers, salts, solvates or prodrugs thereof for use as a pharmaceutical agent.

The pharmaceutical agent may be an anticancer agent, a lymphangiogenesis inhibitor, an antimetastasis agent or a VEGFR3 inhibitor.

The pharmaceutical agent may be an anticancer agent, an angiogenesis inhibitor, an antimetatstasis agent or a FAK inhibitor.

An eighth aspect provides a composition comprising a compound of formula (I) or an isomer, salt, solvate or prodrug thereof and a pharmaceutically acceptable carrier or diluent.

A ninth aspect provides a compound of formula (I) or an isomer, salt, solvate or prodrug thereof, agent of the seventh aspect or composition of the eighth aspect for use in a method of therapy.

A tenth aspect provides for the use of a compound of formula (I) or an isomer, salt, solvate or prodrug thereof, agent of the seventh aspect or composition of the eighth aspect in the preparation of a medicament for treating a disease or condition ameliorated by the inhibition of VEGFR3. The tenth aspect of the invention also provides a compound of formula (I), agent of the seventh aspect or composition of the eighth aspect for use in the method of treatment of a disease or condition ameliorated by the inhibition of VEGFR3.

An eleventh aspect provides for the use of a compound of formula (I) or an isomer, salt, solvate or prodrug thereof, agent of the seventh aspect or composition of the eighth aspect in the preparation of a medicament for treating cancer. The eleventh aspect of the invention also provides a compound of formula (I) or an isomer, salt, solvate or prodrug thereof, agent of the seventh aspect or composition of the eighth aspect for use in the method of treatment of cancer.

A twelfth aspect provides for the use of a compound of formula (I) or an isomer, salt, solvate or prodrug thereof, agent of the eighth aspect or composition of the ninth aspect in the preparation of a medicament for inhibiting, suppressing or reducing lymphangiogenesis. The thirteenth aspect of the invention also provides a compound of formula (I) or an isomer, salt, solvate or prodrug thereof, agent of the seventh aspect or composition of the eighth aspect for use in the method of inhibiting, supressing or reducing lymphangiogenesis.

A further aspect provides a compound of formula (I) or an isomer, salt, solvate or prodrug thereof, agent of the seventh aspect or composition of the eighth aspect for use in a method

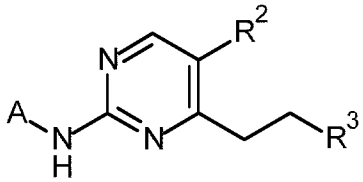
of treatment of the human or animal body, preferably in the form of a pharmaceutical composition.

Another aspect provides a method of inhibiting VEGFR3 *in vitro* or *in vivo*, comprising contacting a cell or cell lysates with an effective amount of a compound of formula (I) or an isomer, salt, solvate or prodrug thereof, agent of the seventh aspect or composition of the eighth aspect.

A still further aspect provides an anti-cancer treatment comprising a compound of formula (I) or an isomer, salt, solvate or prodrug thereof, agent of the seventh aspect or composition of the eighth aspect and an anti-tumour agent.

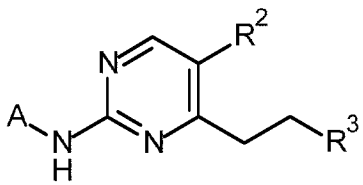
**Description**

The present invention provides compounds of the formula (I) or isomers, salts, solvates or prodrugs thereof:



Each of the groups A, $R^2$ and $R^3$ and the substituents $R^{1A}$, $R^{1B}$, $R^{1C}$ and $R^4$ will be discussed in more detail below. The embodiments of the invention or preferences expressed in the following description may be combined with one another as appropriate.

In some embodiments, there is provided compounds of the following formula (I) or isomers, salts, solvates or prodrugs thereof:



(I)

wherein:

A is an optionally substituted 5 to 10 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl group contains 1 to 4 heteroatoms selected from N, O and S;

A may optionally bear a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

wherein when A is a 9 or 10 membered heteroaryl group, the substitutent $R^{1A}$ must be present;

where $R^{1A}$ is selected from:

(i) $CH(R^{C1})NHZ^1$, where $R^{C1}$ is selected from H, $C_{1-3}$ alkyl, $C_{3-5}$ cycloalkyl and oxetanyl, and $Z^1$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(ii) $XNHZ^2$, where X is selected from $CF_2$, $CMe_2$, cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidine, and $Z^2$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(iii) a substituted 3-6 membered cycloalkyl; and

(iv) an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N, O and S;

each $R^{1B}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the $-C_2H_4-$ group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

$R^4$ is selected from:

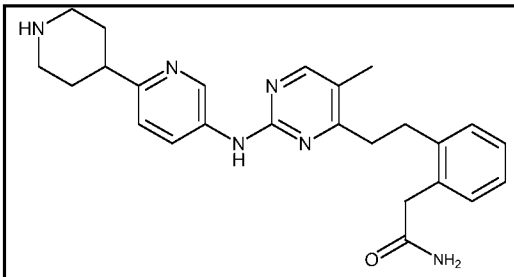
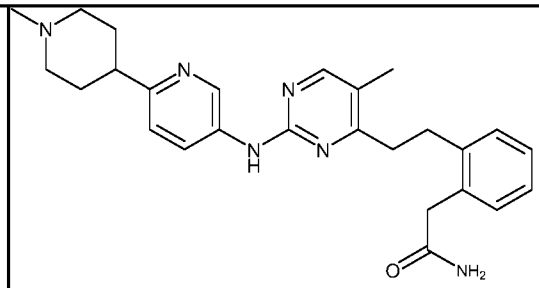
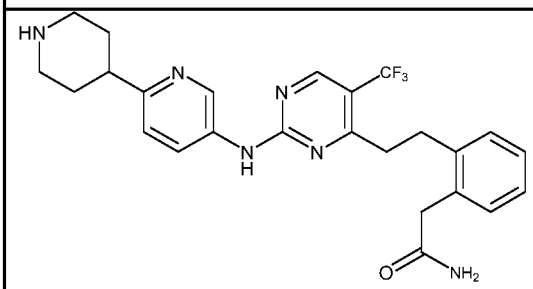
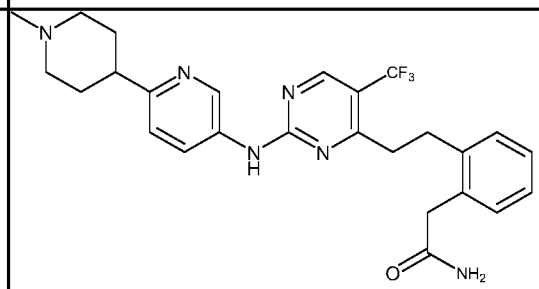
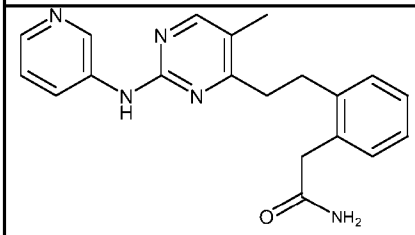
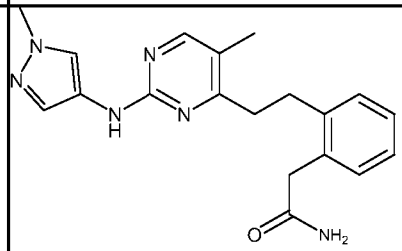
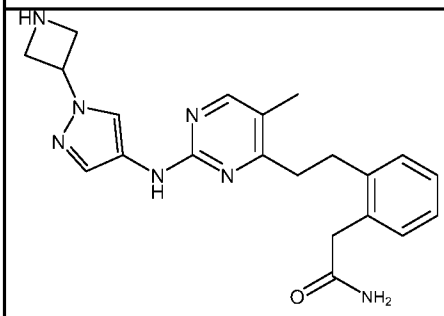
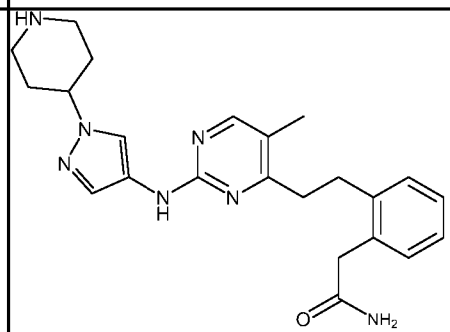
(i) $CH_2$-$C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

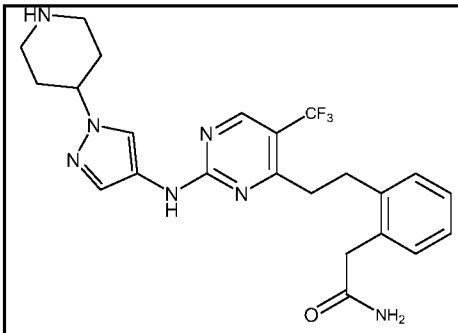
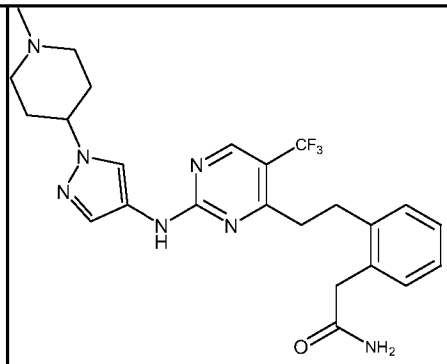
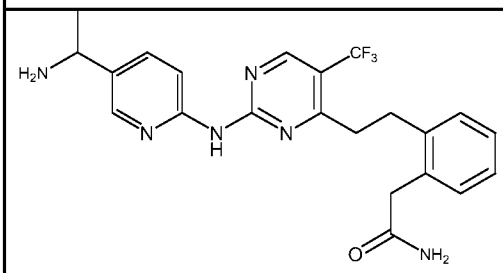
(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

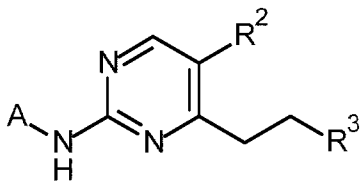
*Proviso*

In some embodiments, the following compounds and Boc-protected intermediates thereof are disclaimed from the present application:

| | |
|---|---|
|  <br>2-(2-(2-(5-methyl-2-((6-(piperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (4) |  <br>2-(2-(2-(5-methyl-2-((6-(1-methylpiperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (5) |
|  <br>*2-(2-(2-(2-((6-(piperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (13)* |  <br>2-(2-(2-(2-((6-(1-methylpiperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (14) |
|  <br>2-(2-(2-(5-methyl-2-(pyridin-3-ylamino)pyrimidin-4-yl)ethyl)phenyl)acetamide (24) |  <br>2-(2-(2-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (28) |
|  <br>*2-(2-(2-(2-((1-(azetidin-3-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (30)* |  <br>2-(2-(2-(5-Methyl-2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (33) |

| | |
|---|---|
|  2-(2-(2-(2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (35) |  2-(2-(2-(2-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (36) |
|  2-(2-(2-(2-((6-(1-aminoethyl)pyridin-3-yl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (40) | |

In some embodiments, there is provided compounds of the following formula (IA) or isomers, salts, solvates or prodrugs thereof:



(IA)

wherein:

A is a substituted 5 to 10 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl group contains 1 to 4 heteroatoms selected from N, O and S;

A bears a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

where $R^{1A}$ is selected from:

(i) $CH(R^{C1})NHZ^1$, where $R^{C1}$ is selected from H, $C_{1-3}$ alkyl, $C_{3-5}$ cycloalkyl and oxetanyl, and $Z^1$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(ii) $XNHZ^2$, where X is selected from $CF_2$, $CMe_2$, cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidine, and $Z^2$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(iii) a substituted 3-6 membered cycloalkyl; and

(iv) an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N, O and S;

each $R^{1B}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

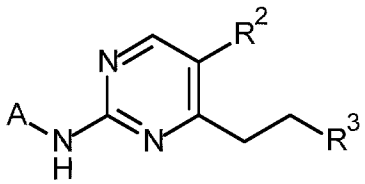
$R^4$ is selected from:

(i) $CH_2$-$C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

In some embodiments, there is provided compounds of the following formula (IA1) or isomers, salts, solvates or prodrugs thereof:



(IA1)

wherein:

A is a substituted 5 to 10 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl group contains 1 to 4 heteroatoms selected from N, O and S;

A bears a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

where $R^{1A}$ is selected from:

(iii) a substituted 3-6 membered cycloalkyl; and

(iv) an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N, O and S;

each $R^{1B}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

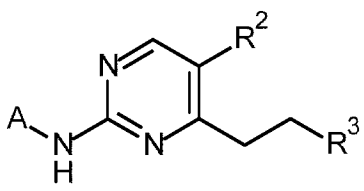
$R^4$ is selected from:

(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

In some embodiments, there is provided of the following formula (IB) or isomers, salts, solvates or prodrugs thereof:



(IB)

wherein:

A is an optionally substituted 5- or 6-membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl ring system contains 1 to 4 heteroatoms selected from N, O and S;

A may optionally bear a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

where $R^{1A}$ is selected from:

(i) $CH(R^{C1})NHZ^1$, where $R^{C1}$ is selected from H, $C_{1-3}$ alkyl, $C_{3-5}$ cycloalkyl and oxetanyl, and $Z^1$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(ii) $XNHZ^2$, where X is selected from $CF_2$, $CMe_2$, cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidine, and $Z^2$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(iii) a substituted 3-6 membered cycloalkyl; and

(iv) an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N, O and S;

each $R^{1B}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

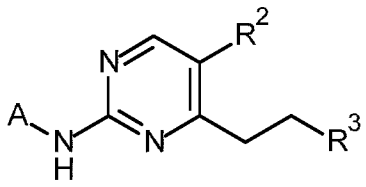
$R^4$ is selected from:

(i) $CH_2$-$C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

In some embodiments, there is provided of the following formula (IB1) or isomers, salts, solvates or prodrugs thereof:



(IB1)

wherein:

A is an optionally substituted 5- or 6-membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl ring system contains 1 to 4 heteroatoms selected from N, O and S;

A may optionally bear a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

where $R^{1A}$ is selected from:

(iii) a substituted 3-6 membered cycloalkyl; and

(iv) an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N, O and S;

each $R^{1B}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

$R^4$ is selected from:

(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

In some embodiments, the compounds of the first aspect are of formula (I) as defined above wherein when

A is substituted pyridinyl,

$R^2$ is $CF_3$ or $CH_3$,

$R^3$ is substituted phenyl and bears a substituent $R^4$ alpha to the $–C_2H_4$- group,

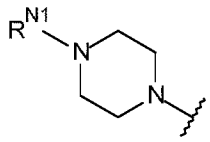
$R^4$ is $–CH_2$-C(O)-$NH_2$

A bears a substituent $R^{1A}$ selected from:

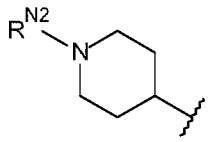
(i) $CH(R^{C1})NHZ^1$, where $R^{C1}$ is selected from H, $C_{2-3}$ alkyl, $C_{3-5}$ cycloalkyl and oxetanyl, and $Z^1$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(ii) $XNHZ^2$, where X is selected from $CF_2$, $CMe_2$, cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidine, and $Z^2$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me; and

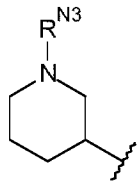
(iii) a substituted 3-6 membered cycloalkyl selected from:



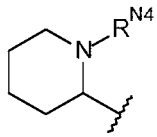
($R^{1A1}$)



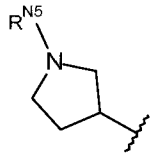
($R^{1A2}$)



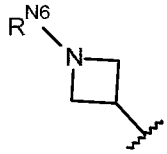
($R^{1A3}$)



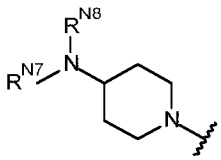
($R^{1A4}$)



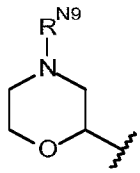
($R^{1A5}$)



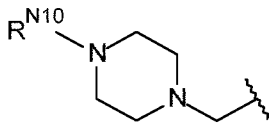
($R^{1A6}$)



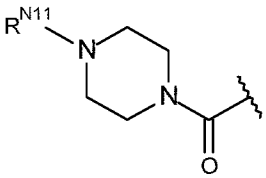
($R^{1A7}$)



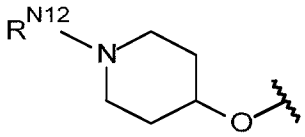
($R^{1A8}$)



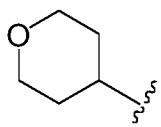
($R^{1A9}$)



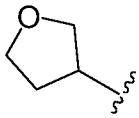
($R^{1A10}$)

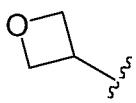


($R^{1A11}$)



($R^{1A12}$)





($R^{1A13}$) ($R^{1A14}$)

wherein:

$R^{N2}$ is independently selected from $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

each of $R^{N1}$, $R^{N3}$, $R^{N4}$, $R^{N5}$, $R^{N6}$, $R^{N9}$, $R^{N10}$, $R^{N11}$ and $R^{N12}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups; and.

each of $R^{N7}$ and $R^{N8}$ is independently selected from H and methyl.

In some embodiments, the compounds of formula (IB) are as defined above wherein when

A is substituted pyrazolyl,

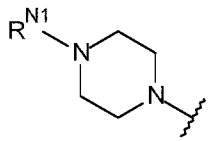
$R^2$ is $CF_3$ or $CH_3$,

$R^3$ is substituted phenyl and bears a substituent $R^4$ alpha to the $–C_2H_4$- group,

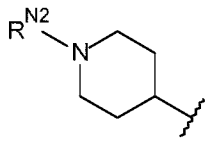
$R^4$ is $–CH_2$-C(O)-$NH_2$

A bears a substituent $R^{1A}$ selected from:

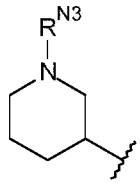
(iii) a substituted 3-6 membered cycloalkyl selected from:



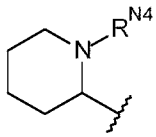
($R^{1A1}$)



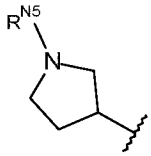
($R^{1A2}$)



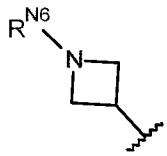
($R^{1A3}$)



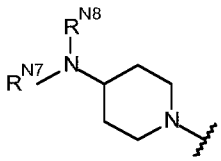
($R^{1A4}$)



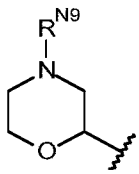
($R^{1A5}$)



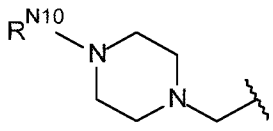
($R^{1A6}$)



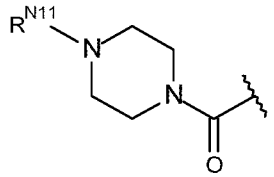
($R^{1A7}$)



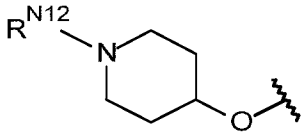
($R^{1A8}$)



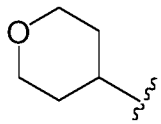
($R^{1A9}$)



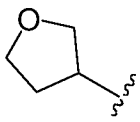
($R^{1A10}$)



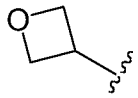
($R^{1A11}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

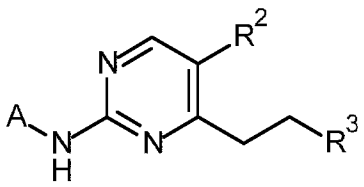
$R^{N2}$ is independently selected from $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^{N6}$ is independently selected from $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

each of $R^{N1}$, $R^{N3}$, $R^{N4}$, $R^{N5}$, $R^{N9}$, $R^{N10}$, $R^{N11}$ and $R^{N12}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups; and.

each of $R^{N7}$ and $R^{N8}$ is independently selected from H and methyl.

In some embodiments, there is provided a compound of the formula (IC) or isomers, salts, solvates or prodrugs thereof:



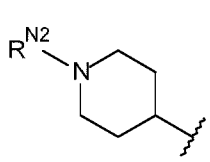
(IC)

wherein:

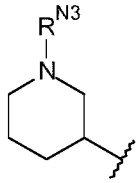
A is an optionally substituted 5 or 6 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl group contains 1 or 2 N heteroatoms;

A bears a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

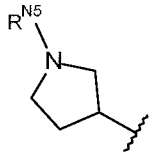
where $R^{1A}$ is selected from



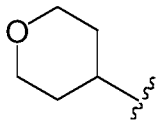
($R^{1A2}$)



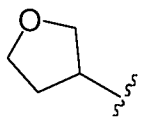
($R^{1A3}$)



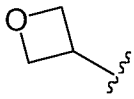
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

each of $R^{N2}$, $R^{N3}$, and $R^{N5}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1B}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

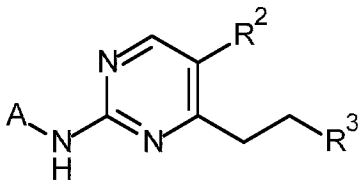
$R^4$ is selected from:

(i) $CH_2$-$C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

In some embodiments, there is provided a compound of the formula (ID) or isomers, salts, solvates or prodrugs thereof:

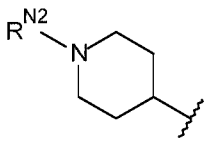


(ID)

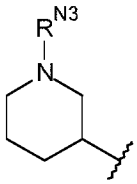
wherein:

A is an optionally substituted 5 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl group contains 1 or 2 N heteroatoms; A bears a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

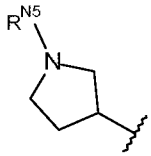
where $R^{1A}$ is selected from



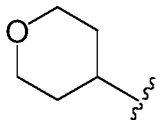
($R^{1A2}$)



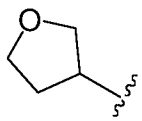
($R^{1A3}$)



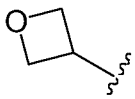
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

$R^{N2}$ is independently selected from $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

each of $R^{N3}$ and $R^{N5}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1B}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the $-C_2H_4-$ group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

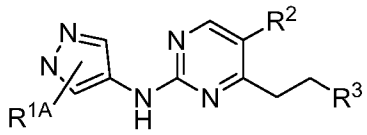
$R^4$ is selected from:

(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

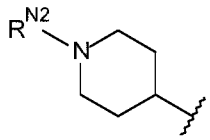
In some embodiments, there is provided a compound of formula (IE) or isomers, salts, solvates, or prodrugs thereof:



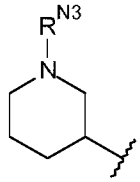
(IE)

wherein:

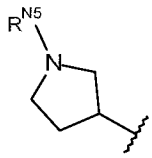
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



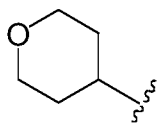
($R^{1A2}$)



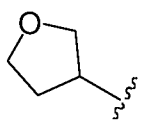
($R^{1A3}$)



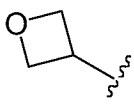
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

each of $R^{N2}$ and $R^{N5}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^{N3}$ is selected from H, $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

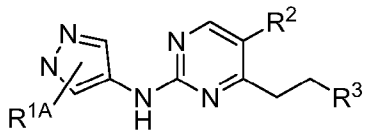
$R^4$ is selected from:

(i) $CH_2$-$C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

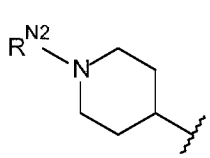
In some embodiments, there is provided a compound of formula (IF) or isomers, salts, solvates, or prodrugs thereof:



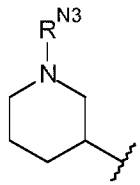
(IF)

wherein:

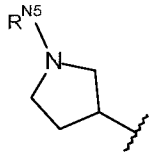
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



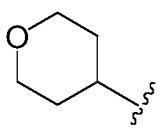
($R^{1A2}$)



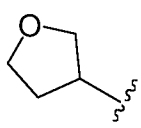
($R^{1A3}$)



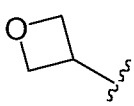
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

$R^{N2}$ is independently selected from $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^{N3}$ is selected from H, $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^{N5}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the $-C_2H_4-$ group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

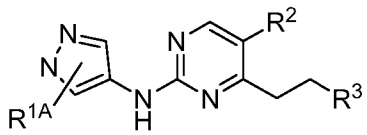
$R^4$ is selected from:

(i) $CH_2$-$C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

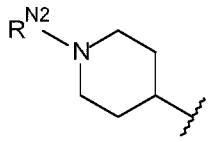
In some embodiments, there is provided a compound of formula (IG) or isomers, salts, solvates, or prodrugs thereof:



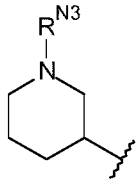
(IG)

wherein:

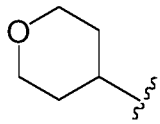
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



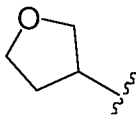
($R^{1A2}$)



($R^{1A3}$)



($R^{1A12}$)



($R^{1A13}$)

wherein:

$R^{N2}$ is selected from $C_{2-3}$ alkyl, $C_3$ alkenyl, and $C(=O)C_1$ alkyl;

$R^{N3}$ is $C_1$ alkyl;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the $-C_2H_4-$ group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

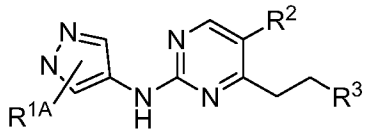
$R^4$ is selected from:

(i) $CH_2$-$C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

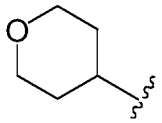
In some embodiments, there is provided a compound of formula (IH) or isomers, salts, solvates, or prodrugs thereof:



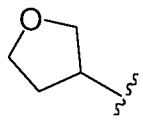
(IH)

wherein:

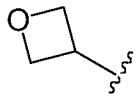
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

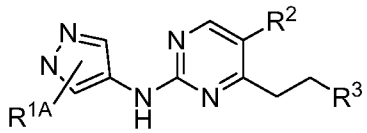
$R^4$ is selected from:

(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

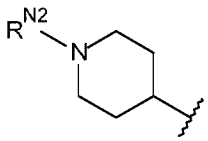
In some embodiments, there is provided a compound of formula (IJ) or isomers, salts, solvates, or prodrugs thereof:



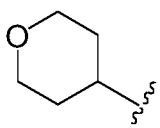
(IJ)

wherein:

the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



($R^{1A2}$)



($R^{1A12}$)

wherein:

$R^{N2}$ is selected from $C_3$ alkyl and $C_3$ alkynyl;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-($CH_2$)n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

$R^4$ is selected from:

(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

**Further Embodiments**

The following embodiments and preferences relate to the compounds of formula (I), (IA), (IA1), (IB), (1B1), (IC), (ID), (IE), (IF), (IG), (IH) and (IJ), as defined in the first to fifth aspects, above. Each of these embodiments and preferences may be combined with one another as appropriate.

*A*

A is a substituted 5 to 10 membered heteroaryl group. The heteroaryl group is linked to the NH group through an aromatic ring carbon atom, and the heteroaryl group contains 1 to 4 heteroatoms selected from N, O and S.

A is a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an heteroaromatic compound (i.e. a compound having at least one heteroaromatic ring), which moiety has from 5 to 10 ring atoms. Preferably, each ring has from 5 to 7 ring atoms.

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

$N_1$: pyrrole (azole) (5-membered), pyridine (azine) (6-membered), azepine (7-membered), azocine (8-membered);

$O_1$: furan (oxole) (5-membered); pyran (6-membered); oxepine (7-membered); oxocine (8-membered); oxonine (9-membered), oxecine (10-membered);

$S_1$: thiophene (thiole) (5-membered), thiopyran (6-membered), thiepine (7-membered), thiocine (8-membered);
$N_1O_1$: oxazole (5-membered), isoxazole (5-membered), isoxazine (6-membered);
$N_2O_1$: oxadiazole (furazan) (5-membered);
$N_3O_1$: oxatriazole (5-membered);
$N_1S_1$: thiazole (5-membered), isothiazole (5-membered);
$N_2$: imidazole (1,3-diazole) (5-membered), pyrazole (1,2-diazole) (5-membered), pyridazine (1,2-diazine) (6-membered), pyrimidine (1,3-diazine) (6-membered) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (6-membered), diazepine (7-membered);
$N_3$: triazole (5-membered), triazine (6-membered); and,
$N_4$: tetrazole (5-membered).

Examples of heteroaryl groups which comprise fused rings, include, but are not limited to, those derived from:
9-membered (with 2 fused rings) derived from benzofuran ($O_1$), isobenzofuran ($O_1$), indole ($N_1$), isoindole ($N_1$), indolizine ($N_1$), indoline ($N_1$), isoindoline ($N_1$), purine ($N_4$) (e.g., adenine, guanine), benzimidazole ($N_2$), indazole ($N_2$), benzoxazole ($N_1O_1$), benzisoxazole ($N_1O_1$), benzodioxole ($O_2$), benzofurazan ($N_2O_1$), benzotriazole ($N_3$), benzothiofuran ($S_1$), benzothiazole ($N_1S_1$), benzothiadiazole ($N_2S$);
10-membered (with 2 fused rings) derived from chromene ($O_1$), isochromene ($O_1$), chroman ($O_1$), isochroman ($O_1$), benzodioxan ($O_2$), quinoline ($N_1$), isoquinoline ($N_1$), quinolizine ($N_1$), benzoxazine ($N_1O_1$), benzodiazine ($N_2$), pyridopyridine ($N_2$), quinoxaline ($N_2$), quinazoline ($N_2$), cinnoline ($N_2$), phthalazine ($N_2$), naphthyridine ($N_2$), pteridine ($N_4$).

Thus, when A is a 5 to 10 membered heteroaryl group, it may be selected from any of the groups listed above.

The 5 to 10 membered heteroaryl group contains 1 to 4 heteroatoms selected from N, O and S. In some embodiments the 5 to 10 membered heteroaryl ring system contains 1 or 2 heteroatoms selected from N, O and S. In some embodiments the heteroatoms are N atoms.

In some embodiments, A is a 5 or 6 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom.

In some embodiments, the 5 or 6 membered heteroaryl ring system contains 1 to 4 heteroatoms selected from N, O and S. In some embodiments the 5 or 6 membered

heteroaryl ring system contains 1 or 2 heteroatoms selected from N, O and S. In other embodiments the heteroatoms are N atoms.

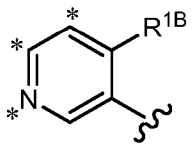
In some embodiments, A is a 5 or 6 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl ring system contains 1 or 2 N heteroatoms.

In some embodiments, A is selected from the group consisting of pyrrole, pyridine, imidazole, pyrazole, pyridazine, pyrimidine or pyrazine.
In some embodiments, when A is a 5 to 10 membered heteroaryl group, A is substituted.

In embodiments where A is a 5 to 8 membered heteroaryl group, A may be unsubstituted.

In embodiments where A is a 5 to 10 membered heteroaryl group, A may be substituted with a substituent $R^{1A}$, one or two substituents $R^{1B}$ and one or two further substituents $R^{1C}$. It will be appreciated that A may be substituted with any combination of the substituents $R^{1A}$, $R^{1B}$, and $R^{1C}$.

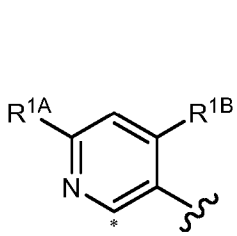
By way of example, when A is substituted pyridine, A may bear one or two substituents $R^{1B}$ which are alpha to the NH group. In other words, when present the $R^{1B}$ group is *ortho* to the NH group, therefore, A has the structure:

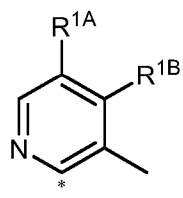


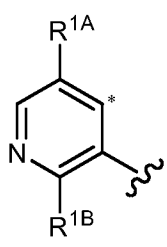
($A^1$)

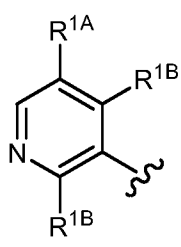
The $R^{1B}$ group cannot be *beta* or *gamma* to the connection point to the rest of the compound (i.e., it cannot be in the asterixed positions).

A may optionally bear a substituent $R^{1A}$ which is not alpha to the NH group. Accordingly, the $R^{1A}$ group can either be *meta* or *para*, and so A can, for example, have the structures:





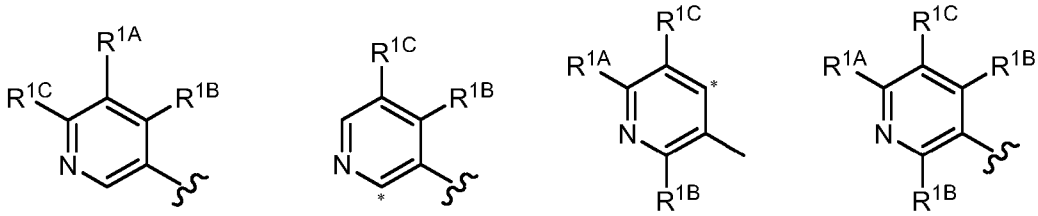




($A^2$) ($A^3$) ($A^4$) ($A^5$)

where the $R^{1A}$ group cannot be *alpha* to the connection point to the rest of the compound (i.e., it cannot be in the positions that are asterixed or occupied by $R^{1B}$).

A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group. Accordingly, the $R^{1C}$ group can either be *meta* or *para*, and so A can, for example, have the structures:



($A^6$) ($A^7$) ($A^8$) ($A^9$)

where the $R^{1C}$ group cannot be *alpha* to the connection point to the rest of the compound (i.e., it cannot be in the positions that are asterixed or occupied by $R^{1B}$).

In other examples, if A is a 5-membered heteroaryl or a 7 to 10 membered heteroaryl, the $R^{1A}$ group is *meta* to the -NH- group. Thus, when A is a 5-membered heteroaryl, the $R^{1A}$ group is *beta* to the -NH- group.

In some embodiments, A is substituted with a substituent $R^{1A}$, optionally one or two substituents $R^{1B}$, and $R^{1C}$ is absent.

In some embodiments, A bears a substituent $R^{1A}$. In other words, A is substituted with a substituent $R^{1A}$, and $R^{1B}$ and $R^{1C}$ are absent.

*$R^{1A}$*

According to the first aspect of the invention, $R^{1A}$ is selected from:

(i) $CH(R^{C1})NHZ^1$, where $R^{C1}$ is selected from H, $C_{1-3}$ alkyl, $C_{3-5}$ cycloalkyl and oxetanyl, and $Z^1$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(ii) $XNHZ^2$, where X is selected from $CF_2$, $CMe_2$, cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidine, and $Z^2$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me; and

(iii) a substituted 3-6 membered cycloalkyl ;

(iv) an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N, O and S.

According to the first aspect of the invention, A is a 5 to 10 membered heteroaryl group and the substituent $R^{1A}$ must be present when A is a 9 or 10 membered heteroaryl group. In some embodiments, when A is a 5 to 8 membered heteroaryl group, $R^{1A}$ may optionally be present. In other words, when A is a 5 to 8 membered heteroaryl group, $R^{1A}$ may be absent.

In some embodiments, $R^{1A}$ is selected from:

(iii) a substituted 3-6 membered cycloalkyl ; and

(iv) an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N, O and S.

In some embodiments, $R^{1A}$ is an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N, O and S.

In some embodiments, when present, $R^{1A}$ is selected from any one of the following structures:

$CH_2NHZ^1$;

$CH(CH_3)NHZ^1$;

$CH(C_2H_5)NHZ^1$;

$CH(C_3H_7)NHZ^1$;

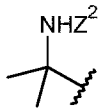
CH(cyclopropyl)$NHZ^1$;

CH(cyclobutyl)$NHZ^1$;

CH(cyclopentyl)$NHZ^1$;

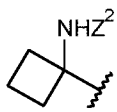
CH(oxetanyl)$NHZ^1$;

$CF_2NHZ^2$;

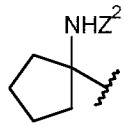



($R^{1X1}$)

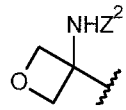

($R^{1X2}$)




($R^{1X3}$)




($R^{1X4}$)




($R^{1X5}$)

wherein, each of $Z^1$ and $Z^2$ is independently selected from H, $C(=O)OC_{1-3}$ alkyl (i.e. C(=O)O-methyl, C(=O)O-ethyl, C(=O)O-prop-1-yl and C(=O)O-prop-2-yl) and C(=O)Me;

substituted cyclopropyl,

substituted cyclobutyl,

substituted cyclopentyl,

substituted cyclohexyl,

optionally substituted azetidinyl,

optionally substituted pyrrolidinyl,

optionally substituted piperidinyl,
optionally substituted oxetanyl,
optionally substituted tetrahydrofuranyl,
optionally substituted tetrahydropyranyl,
optionally substituted thietanyl,
optionally substituted thiolanyl,
optionally substituted thianyl,
optionally substituted morpholinyl,
optionally substituted dioxanyl, and
optionally substituted piperazinyl.

In some embodiments, when $R^{1A}$ is a substituted 3-6 membered cycloalkyl, the cycloalkyl group has one or two substituents. The substituents may be selected from $C_{1-3}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkyl(CN), $CO(C_{1-3}$ alkyl), OH, $OC_{1-3}$ alkyl, $NH_2$, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $NHCOC_{1-3}$ alkyl, $CONH_2$, $CONHC_{1-3}$ alkyl, $CON(C_{1-3}$ alkyl$)_2$, cyano, =O and $C_{3-5}$ cycloalkyl, where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups.

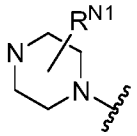
In some embodiments, when $R^{1A}$ is a substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N, O and S, the heterocycle may have one or two substituents. The substituents may be selected from $C_{1-3}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkyl(CN), $CO(C_{1-3}$ alkyl), $NH_2$, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $NHCOC_{1-3}$ alkyl, $CONH_2$, $CONHC_{1-3}$ alkyl, $CON(C_{1-3}$ alkyl$)_2$, =O and $C_{3-5}$ cycloalkyl, where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups.

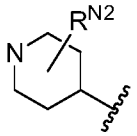
In some embodiments, $R^{1A}$ is an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N and O.

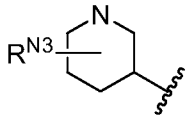
In some embodiments, $R^{1A}$ is an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 N heteroatoms.

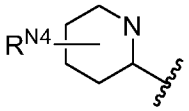
In some embodiments, $R^{1A}$ is an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 O heteroatoms.

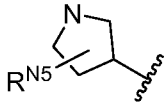
In some embodiments, $R^{1A}$ is selected from any one of the following structures:

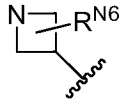

($R^{1A1}$)

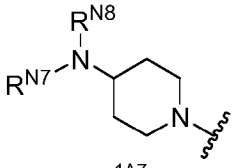

($R^{1A2}$)

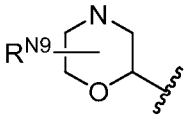

($R^{1A3}$)

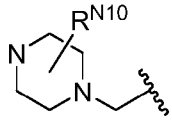

($R^{1A4}$)

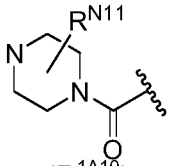

($R^{1A5}$)

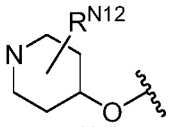

($R^{1A6}$)

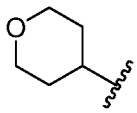

($R^{1A7}$)

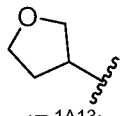

($R^{1A8}$)

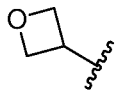

($R^{1A9}$)


($R^{1A10}$)


($R^{1A11}$)


($R^{1A12}$)

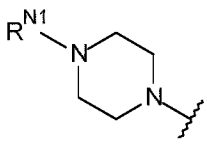

($R^{1A13}$)

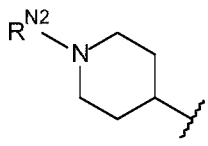

($R^{1A14}$)

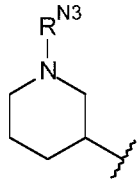
wherein:

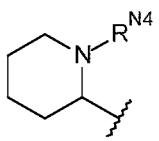
each of $R^{N1}$, $R^{N2}$, $R^{N3}$, $R^{N4}$, $R^{N5}$, $R^{N6}$, $R^{N9}$, $R^{N10}$, $R^{N11}$ and $R^{N12}$ is independently selected from $C_{1-3}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkyl(CN), $CO(C_{1-3}$ alkyl), $NH_2$, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $NHCOC_{1-3}$ alkyl, $CONH_2$, $CONHC_{1-3}$ alkyl, $CON(C_{1-3}$ alkyl)$_2$, =O and $C_{3-5}$ cycloalkyl, where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups.

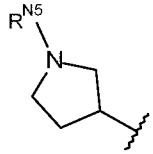
In some embodiments, $R^{1A}$ is selected from any one of the following structures:

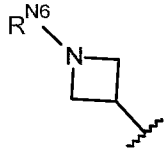

($R^{1A1}$)

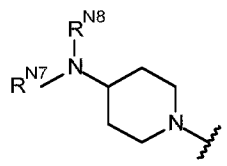

($R^{1A2}$)


($R^{1A3}$)

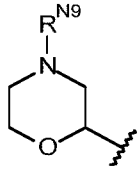

($R^{1A4}$)


($R^{1A5}$)

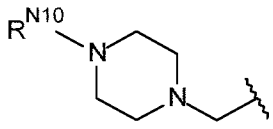

($R^{1A6}$)



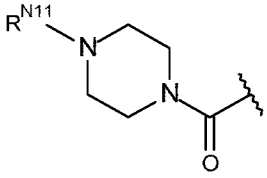
($R^{1A7}$)



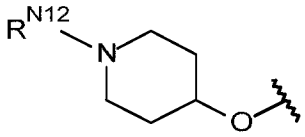
($R^{1A8}$)



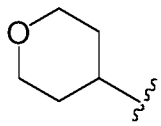
($R^{1A9}$)



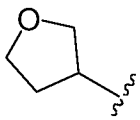
($R^{1A10}$)



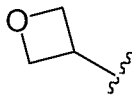
($R^{1A11}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

each of $R^{N1}$, $R^{N2}$, $R^{N3}$, $R^{N4}$, $R^{N5}$, $R^{N6}$, $R^{N9}$, $R^{N10}$, $R^{N11}$ and $R^{N12}$ is independently selected from H, $C_{1-4}$ alkyl (i.e. methyl, ethyl, prop-1-yl, prop-2-yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl), $C_{2-4}$ alkenyl (i.e. $-CH=CH_2$, $-CH_2CH=CH_2$, $-CH=CHCH_3$, $-CH=CHCH_2CH_3$, $-CH_2CH=CHCH_3$, $-CH_2CH_2CH=CH_2$), $C_{2-4}$ alkynyl (i.e. $-C\equiv CH$, $-C\equiv CCH_3$, $-CH_2C\equiv CH$, $-C\equiv CCH_2CH_3$, $-CH_2C\equiv CCH_3$, $-CH_2CH_2C\equiv CH$), $C_{1-4}$ alkyl(CN) (i.e. $-CH_2CN$, $-CH(CN)CH_3$, $-CH_2CH_2CN$, $-CH(CN)CH_2CH_3$, $-CH_2CH(CN)CH_3$, $-CH_2CH_2CH_2CN$, $-CH(CN)CH_2CH_2CH_3$, $-CH_2CH(CN)CH_2CH_3$, $-CH_2CH_2CH(CN)CH_3$, $(CH_2)_4CN$), $C_{3-4}$ cycloalkyl (i.e. cyclopropyl, methylcyclopropyl, cyclobutyl) $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups; and.

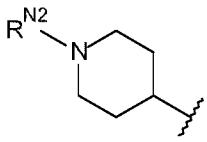
each of $R^{N7}$ and $R^{N8}$ is independently selected from either H or methyl.

In some embodiments, $R^{1A}$ is $CH(R^{C1})NHZ^1$, where $R^{C1}$ is selected from H and $C_{1-3}$ alkyl, and $Z^1$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me.

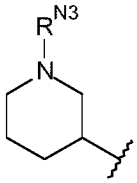
According to some embodiments, when $R^{1A}$ is $CH(R^{C1})NHZ^1$, $R^{C1}$ is selected from H, $C_{1-3}$ alkyl, $C_{3-5}$ cycloalkyl and oxetanyl, and $Z^1$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me, provided that when $R^{C1}$ is selected from H and $C_{1-3}$ alkyl, $Z^1$ is not H.

According to some embodiments, when $R^{1A}$ is $XNHZ^2$, X is selected from $CF_2$, $CMe_2$, cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidine, and $Z^2$ is selected from $C(=O)OC_{1-3}$ alkyl and C(=O)Me, provided that when X is $CF_2$ or $CMe_2$, $Z^1$ is not H.

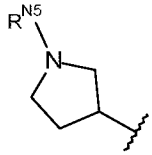
In some embodiments, $R^{1A}$ is selected from any one of the following structures:



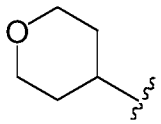
($R^{1A2}$)



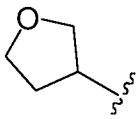
($R^{1A3}$)



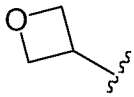
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)

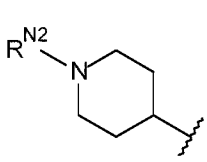


($R^{1A14}$)

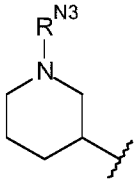
wherein:

$R^{N2}$, $R^{N3}$ and $R^{N5}$ are independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkyl(CN), $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups.

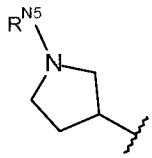
In some embodiments, $R^{1A}$ is present and is selected from any one of the following structures:



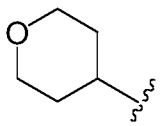
($R^{1A2}$)



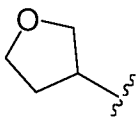
($R^{1A3}$)



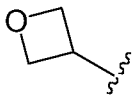
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)



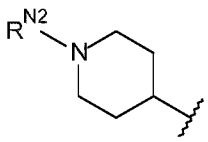
($R^{1A14}$)

wherein:

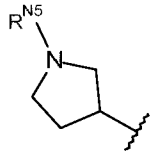
$R^{N2}$ is selected from $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkyl(CN), $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^{N3}$ and $R^{N5}$ are independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkyl(CN), $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups.

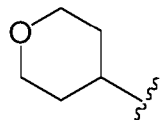
In some embodiments, $R^{1A}$ is present and is selected from any one of the following structures:



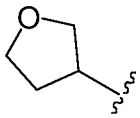
($R^{1A2}$)



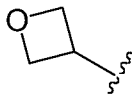
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)

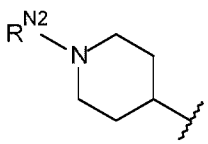


($R^{1A14}$)

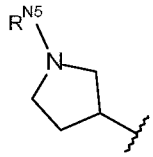
wherein:

$R^{N2}$ and $R^{N5}$ are independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups.

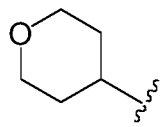
In some embodiments, $R^{1A}$ is present and is selected from any one of the following structures:



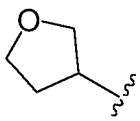
($R^{1A2}$)



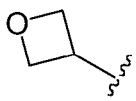
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)



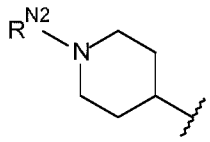
($R^{1A14}$)

wherein:

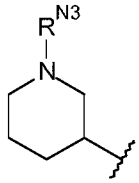
$R^{N2}$ is selected from $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups; and

$R^{N5}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups.

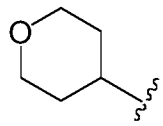
In some embodiments when A is a 5 or 6 membered heteroaryl group, $R^{1A}$ is present and is selected from any one of the following structures:



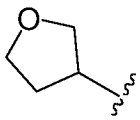
($R^{1A2}$)



($R^{1A3}$)



($R^{1A12}$)



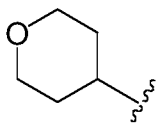
($R^{1A13}$)

wherein:

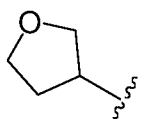
$R^{N2}$ is selected from $C_{2-3}$ alkyl, $C_3$ alkenyl, and $C(=O)C_1$ alkyl; and

$R^{N3}$ is $C_1$ alkyl.

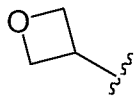
In some embodiments, $R^{1A}$ is present and is selected from any one of the following structures:



($R^{1A12}$)

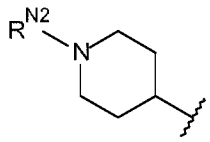


($R^{1A13}$)

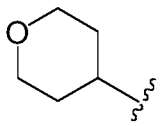


($R^{1A14}$)

In some embodiments, when A is a 5 or 6 membered heteroaryl group, $R^{1A}$ is present and is selected from any one of the following structures:



($R^{1A2}$)



($R^{1A12}$)

wherein:

$R^{N2}$ is selected from $C_3$ alkyl and $C_3$ alkynyl.

*$R^{1B}$*

When A is a 5 to 10 membered heteroaryl group, A may optionally bear one or two substituents $R^{1B}$.

Each $R^{1B}$ group may be selected from O-$C_{1-2}$ alkyl (i.e. methoxy, ethoxy), $C_{1-2}$ alkyl (i.e. methyl or ethyl), halo (i.e. F, Cl, Br, I) and CN. The $C_{1-2}$ alkyl groups may be substituted by one or more fluoro groups (e.g. $CF_3$, $CF_2CH_3$, $CFH_2$, $OCF_2H$, $OCH_2CF_3$).

In some embodiments, each $R^{1B}$ is independently selected from O-$C_{1-2}$ alkyl (i.e. methoxy, ethoxy), or $C_{1-2}$ alkyl (i.e. methyl or ethyl), where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups (e.g. $CF_3$, $CF_2CH_3$, $CFH_2$, $OCF_2H$, $OCH_2CF_3$).

The $R^{1B}$ groups are located at the ring position on A which is *alpha* to the NH group. There may be up to 2 $R^{1B}$ groups (i.e. 1 or 2) depending on the nature of A, and in particular on the number of ring atoms and ring heteroaroms, as well as whether $R^{1A}$ and/or $R^{1C}$ are present.

In some embodiments, each $R^{1B}$ group may be selected from fluoro, methoxy, methyl and $CF_3$.

In some embodiments, $R^{1B}$ is absent.

*$R^{1C}$*

According to the first aspect, A may optionally bear one or two substituents $R^{1C}$.

Each $R^{1C}$ group may be selected from O-$C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

The $R^{1C}$ groups may be located at any available ring position on A, except that which is *alpha* to the NH group. There may be up to 2 $R^{1B}$ groups (i.e. 1 or 2) depending on the nature of A, and in particular on the number of ring atoms and ring heteroaroms, as well as whether $R^{1A}$ and/or $R^{1B}$ are present.

In some embodiments, $R^{1C}$ is absent.

*$R^2$*

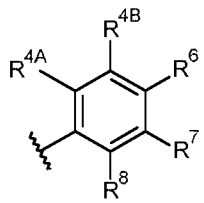
$R^2$ is selected from H, halo (i.e. F, Cl, Br, I), $C_{1-3}$ alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl), O-$C_{1-3}$ alkyl (i.e. methoxy, ethoxy, prop-1-oxy and prop-2-oxy), O-$(CH_2)$n-$C_{3-4}$ cycloalkyl, O-$C_{3-4}$ cycloalkyl (i.e. cyclopropyloxy, cyclopropylmethoxy, cyclobutyloxy), oxetanyl, $C_{3-4}$ cycloalkyl (i.e. cyclopropyl, cyclopropylmethyl and cyclobutyl), $SO_2C_{1-3}$ alkyl (i.e. methylsulfonyl, ethylsulfonyl, 1-propylsulfonyl and 2-propylsulfonyl), cyano and $OCH_2$-cyclopropyl.The $C_{1-3}$ alkyl groups may be substituted by one or more fluoro groups (e.g. $CF_3$, $CF_2CH_3$, $CFH_2$, $OCF_2H$, $OCH_2CF_3$).

In some embodiments, $R^2$ is $CF_3$.

*$R^3$*

$R^3$ is selected from substituted phenyl and a substituted 6 membered heteroaryl group, where the heteroaryl ring system contains 1 or 2 N heteroatoms. $R^3$ bears a substituent $R^4$ either *alpha* or *beta* to the $–C_2H_4$- group and may bear further substituents selected from F, $CH_3$ and $CF_3$.

When $R^3$ is substituted phenyl, it has the structure:

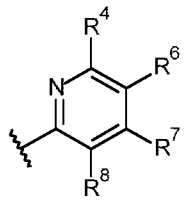



($R^{3a}$)

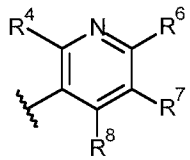
where $R^6$, $R^7$ and $R^8$ are independently selected from H, F, methyl and $CF_3$. One of $R^{4A}$ and $R^{4B}$ is $R^4$, and the other is selected from H, F, methyl and $CF_3$.

When $R^3$ is a substituted 6 membered heteroaryl group, where the heteroaryl ring system contains 1 or 2 N heteroatoms, it may be selected from the any of the groups: pyrrolyl (azole) (5-membered), pyridyl (azine) (6-membered), imidazolyl (1,3-diazole) (5-membered), pyrazolyl (1,2-diazole) (5-membered), pyridazinyl (1,2-diazine) (6-membered), pyrimidinyl (1,3-diazine) (6-membered) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (6-membered).

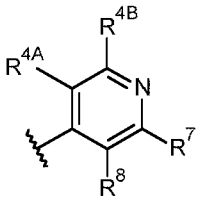
When $R^3$ is a substituted 6 membered heteroaryl group, it may have one of the following structures:



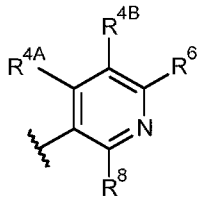
($R^{3b}$)



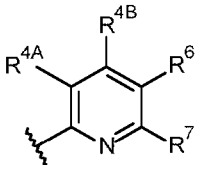
($R^{3c}$)



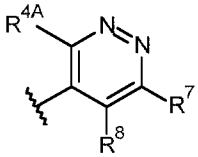
($R^{3d}$)



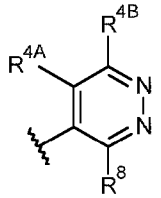
($R^{3e}$)



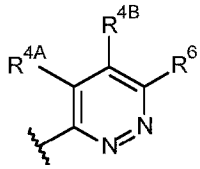
($R^{3f}$)



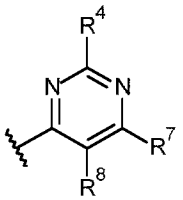
($R^{3g}$)



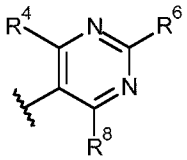
($R^{3h}$)



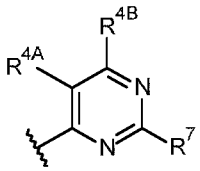
($R^{3i}$)



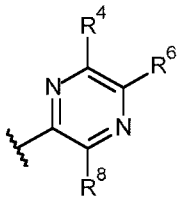
($R^{3j}$)



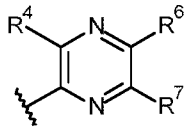
($R^{3k}$)



($R^{3l}$)



($R^{3m}$)



($R^{3n}$)

where $R^6$, $R^7$ and $R^8$ (if present) are independently selected from H, F, methyl and $CF_3$. One of $R^{4A}$ and $R^{4B}$ (if present) is $R^4$, and the other is selected from H, F, methyl and $CF_3$.

When $R^4$ is *alpha* to the -$C_2H_4$-group, it may also be described as being *ortho*. When $R^4$ is beta to the -$C_2H_4$-group, it may also be described as being *meta*.

In some embodiments, $R^4$ is *alpha* to the -$C_2H_4$-group.

The further optional substituents on $R^3$ are independently selected from F, methyl and $CF_3$. These further groups may be at any available ring position on $R^3$, except that occupied by $R^4$. There may be up to 4 further optional substituents groups (i.e. 1, 2, 3 or 4) depending on the nature of $R^3$, and in particular on the number of ring heteroaroms.

In some embodiments, $R^3$ is phenyl and $R^6$, $R^7$ and $R^8$ (if present) are H.

*$R^4$*

$R^4$ is selected from $CH_2$-C(O)N($R^{N13}$)$Z^4$, N$R^{N14}$($SO_2$)$R^{S1}$ and C(O)N($R^{N13}$)$Z^4$.

When $R^4$ is -$CH_2$-C(O)N($R^{N13}$)$Z^4$, $R^{N13}$ is selected from H and $C_{1-2}$ alkyl and $Z^4$ is selected from H, $C_{1-2}$ alkyl or $OCH_3$ Thus, $R^4$ is selected from:

(i) -$CH_2$-C(O)$NH_2$;
(ii) -$CH_2$-C(O)NHMe;
(iii) -$CH_2$-C(O)$NMe_2$;
(iv) -$CH_2$-C(O)N$HC_2H_5$;
(v) -$CH_2$-C(O)N(Me)$C_2H_5$;
(vi) -$CH_2$-C(O)N($C_2H_5$)$_2$;
(vii) -$CH_2$-C(O)N(OMe)H;
(viii) -$CH_2$-C(O)N(OMe)Me; and
(ix) -$CH_2$-C(O)N(OMe)$C_2H_5$.

When $R^4$ is -N$R^{N14}$($SO_2$)$R^{S1}$, $R^{N14}$ is selected from H and $C_{1-3}$ alkyl , and $R^{S1}$ is selected from $C_{1-3}$ alkyl. Thus, $R^4$ is selected from:

(i) -NH($SO_2$)Me;
(ii) -NH($SO_2$)$CH_2CH_3$;
(iii) -NH($SO_2$)$CH_2CH_2CH_3$;
(iv) -NH($SO_2$)CH($CH_3$)$_2$;

(v) -NMe($SO_2$)Me;

(vii) -NMe ($SO_2$)$CH_2CH_3$;

(viii) -NMe ($SO_2$)$CH_2CH_2CH_3$;

(ix) -NMe ($SO_2$)$CH(CH_3)_2$;

(x) -$NCH_2CH_3(SO_2)Me$;

(xi) -$NCH_2CH_3(SO_2)CH_2CH_3$;

(xii) -$NCH_2CH_3(SO_2)CH_2CH_2CH_3$;

(xiii) -$NCH_2CH_3(SO_2)CH(CH_3)_2$;

(xiv) -$N(CH_2)_2CH_3(SO_2)Me$;

(xv) -$N(CH_2)_2CH_3(SO_2)CH_2CH_3$;

(xvi) -$N(CH_2)_2CH_3(SO_2)CH_2CH_2CH_3$;

(xvii) -$N(CH_2)_2CH_3(SO_2)CH(CH_3)_2$;

(xviii) -$NCH(CH_3)_2(SO_2)Me$;

(xix) -$NCH(CH_3)_2(SO_2)CH_2CH_3$;

(xx) -$NCH(CH_3)_2(SO_2)CH_2CH_2CH_3$; and

(xxi) -$NCH(CH_3)_2(SO_2)CH(CH_3)_2$.

When $R^4$ is -$C(O)N(R^{N13})Z^4$, $R^{N13}$ is selected from H and $C_{1-2}$ alkyl ; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$. Thus, $R^4$ is selected from:

(i) -$CH_2$-$C(O)NH_2$;

(ii) -$CH_2$-C(O)NHMe;

(iii) -$CH_2$-$C(O)NMe_2$;

(iv) -$CH_2$-$C(O)NHC_2H_5$;

(v) -$CH_2$-$C(O)N(Me)C_2H_5$;

(vi) -$CH_2$-$C(O)N(C_2H_5)_2$;

(vii) -$CH_2$-C(O)N(OMe)H;

(viii) -$CH_2$-C(O)N(OMe)Me; and

(ix) -$CH_2$-$C(O)N(OMe)C_2H_5$.

In some embodiments, $R^4$ is selected from $CH_2$-$C(O)N(R^{N13})Z^4$ and $C(O)N(R^{N13})Z^4$.

In some embodiments, $R^4$ is -$CH_2$-$C(O)NH_2$.

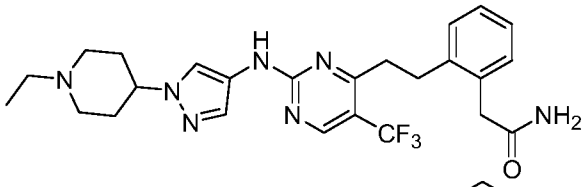
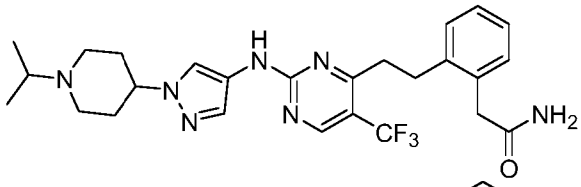
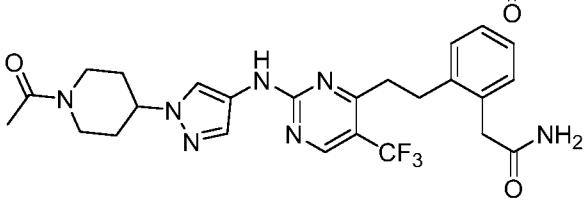
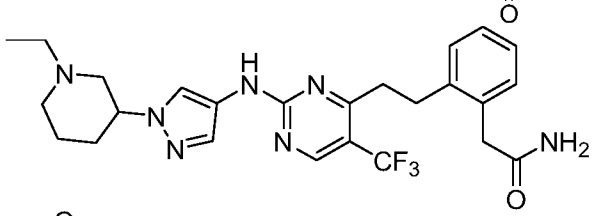
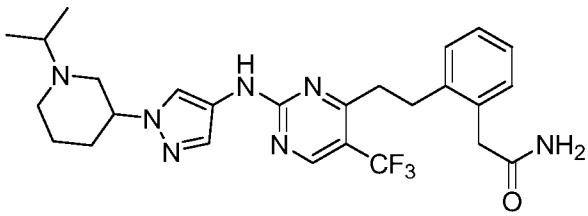
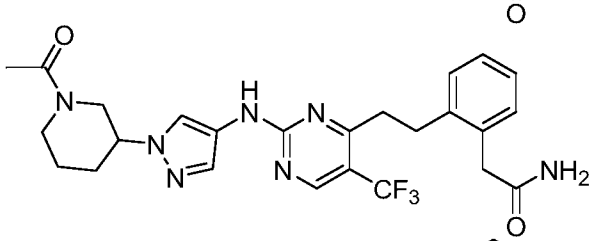
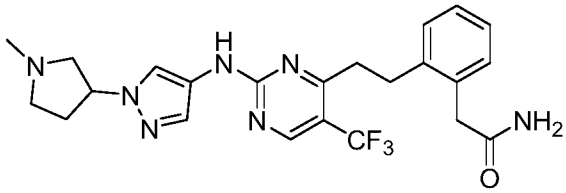
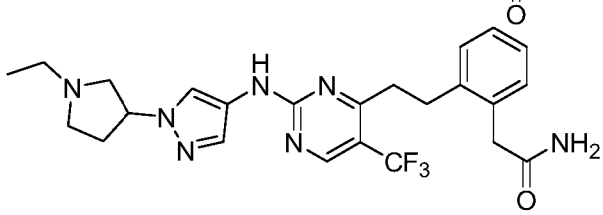
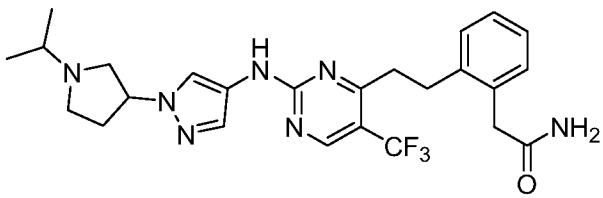
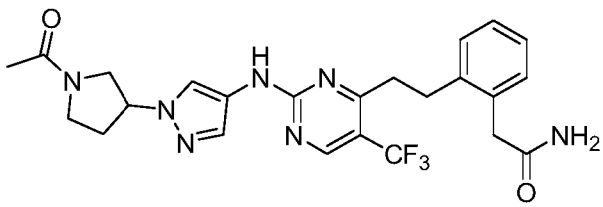
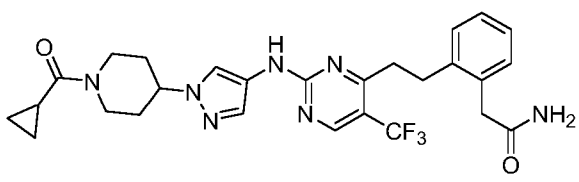
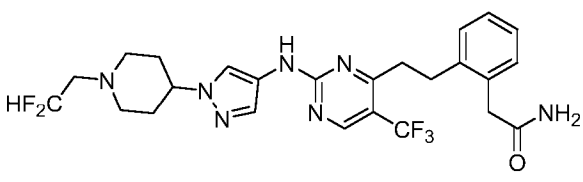
In some embodiments, $R^4$ is –NMe(SO2)Me.

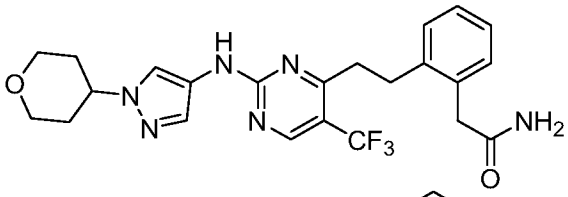
In some embodiments, $R^4$ is –C(O)NHMe.

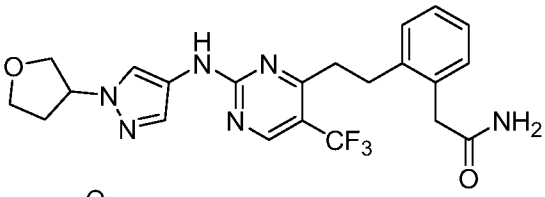
In some embodiments $R^3$ is substituted phenyl, and $R^4$ is either alpha or beta to the $-C_2H_4-$ group, and is $-CH_2-C(O)N(R^{N13})Z^4$ where $R^{N13}$ is selected from H and $CH_3$; and $Z^4$ is selected from H, $CH_3$ and $OCH_3$. Preferably, $R^4$ is alpha to the $-C_2H_4-$ group.

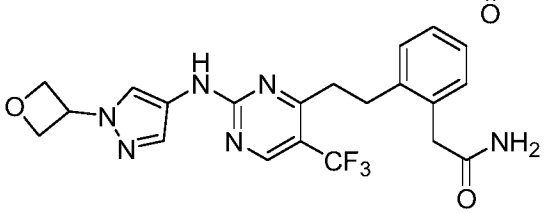
The preferences expressed in relation to compounds of formula (I) also apply to compounds of formula (IA), (IB), (IBa) and (IBb), where appropriate.

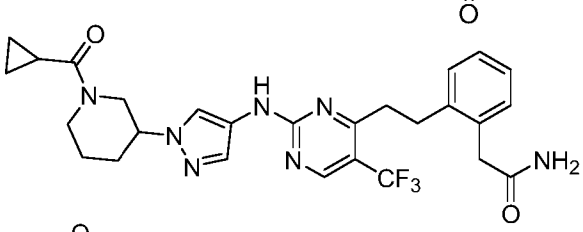
Embodiments of the invention which are of particular interest include the following compounds or isomers, salts, solvates or prodrugs thereof:

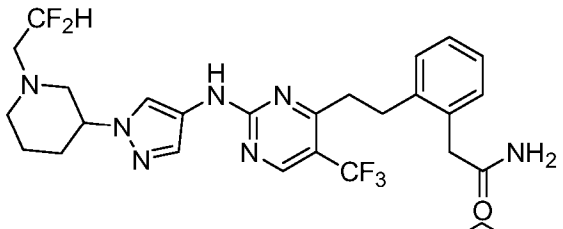













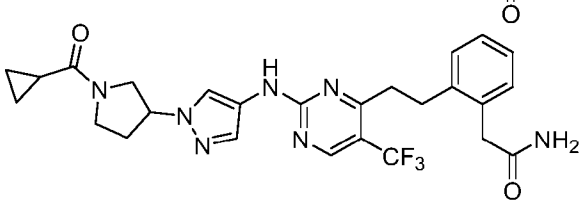


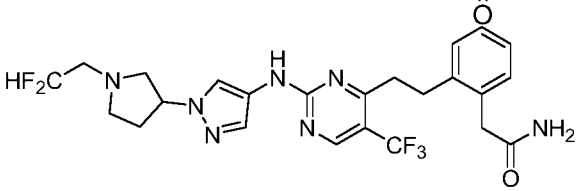


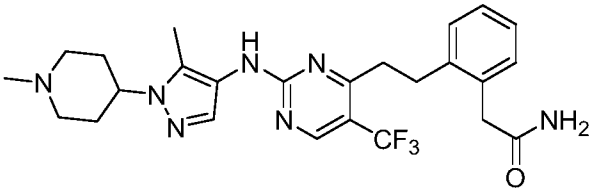


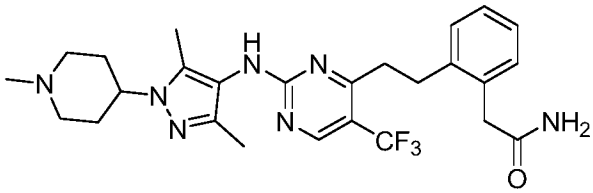


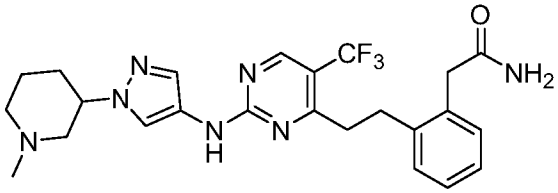


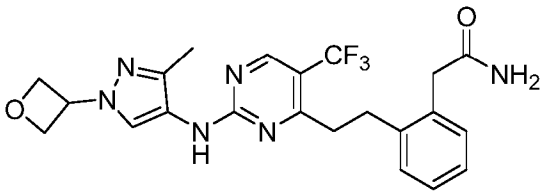


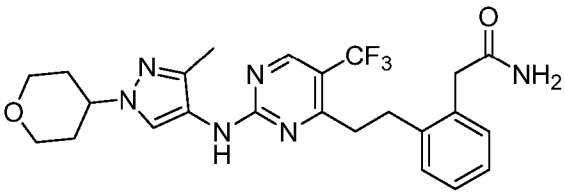


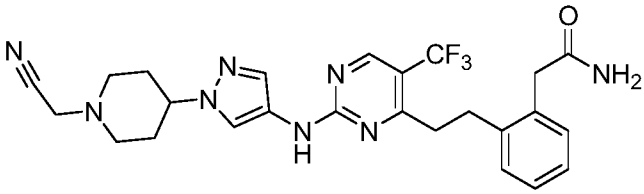


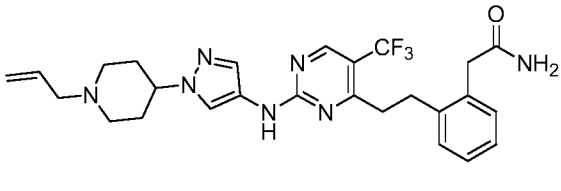


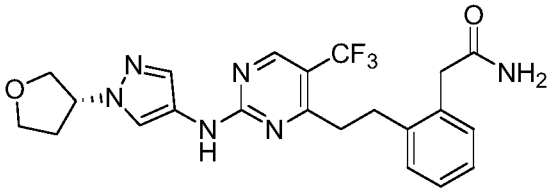






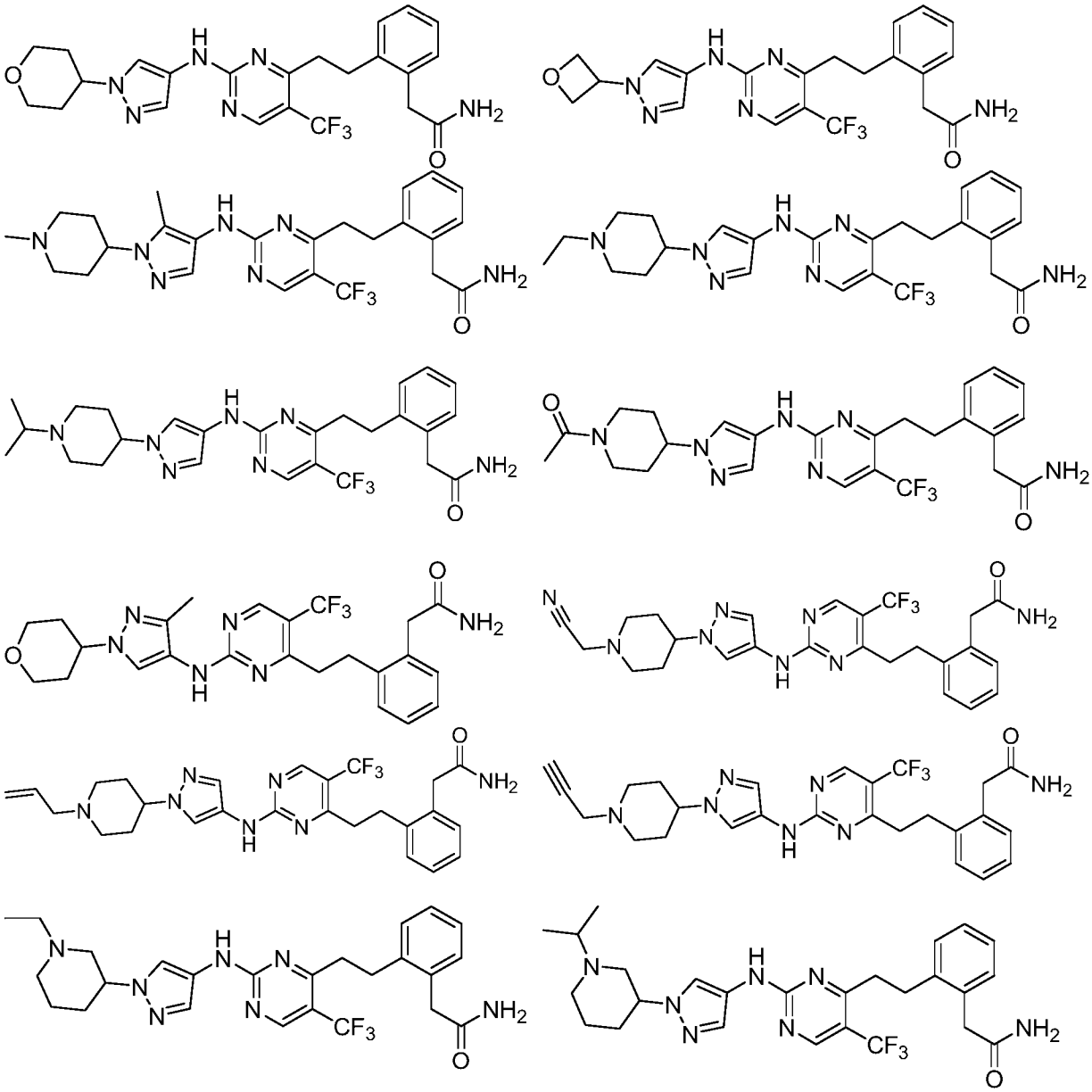


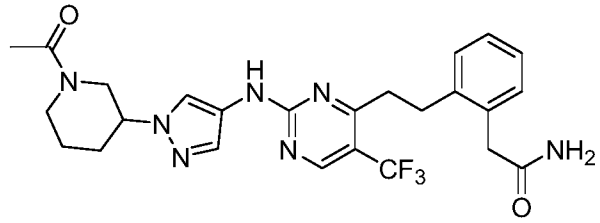


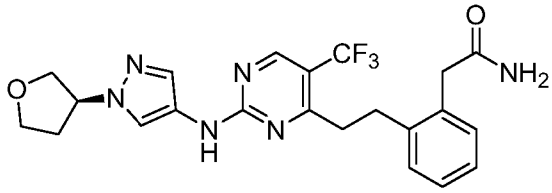


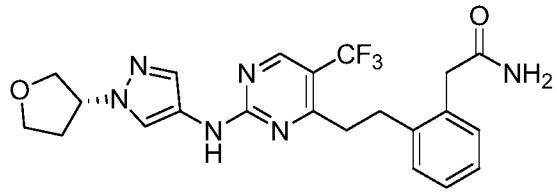
In some embodiments, the compound is selected from any one of compounds C1 to C18 of the Examples, or isomers, salts, solvates or prodrugs thereof.

In some embodiments, the compound is selected from any one of the following compounds, or isomers, salts, solvates or prodrugs thereof:

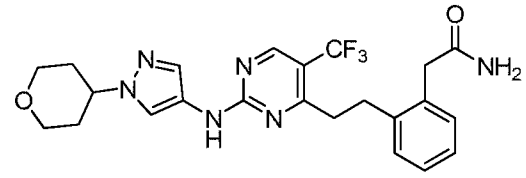


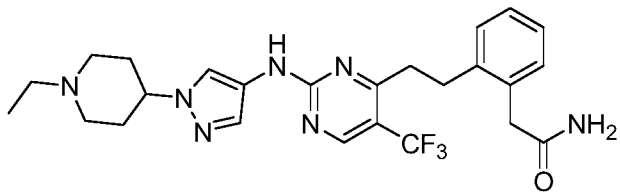


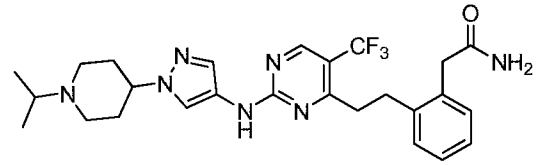


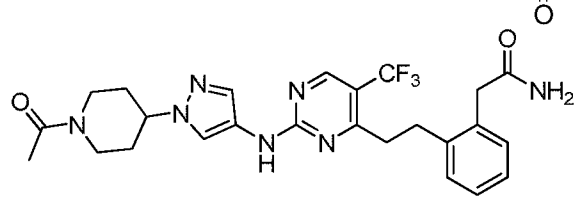


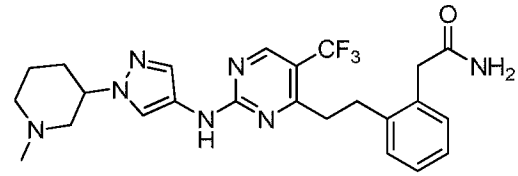
In some embodiments, the compound is selected from any one of the following compounds, or isomers, salts, solvates or prodrugs thereof:

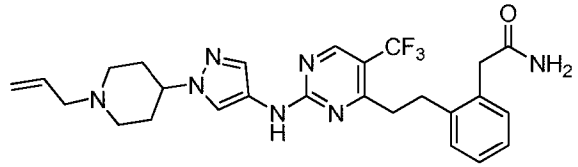


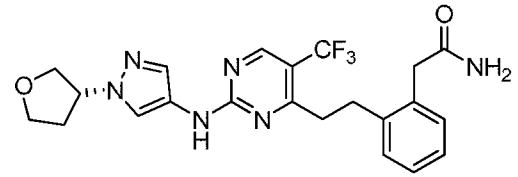


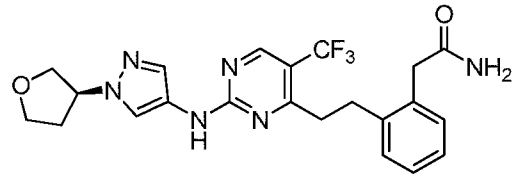




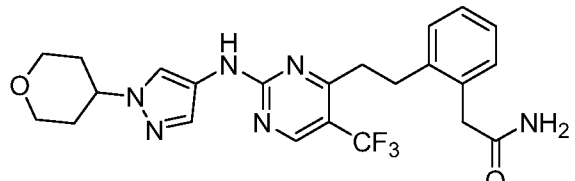


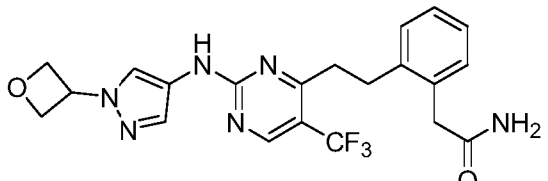


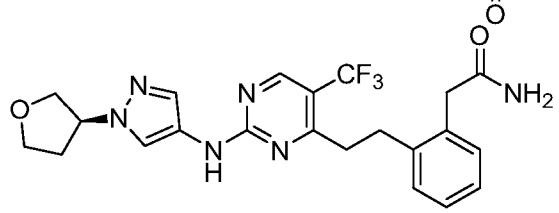


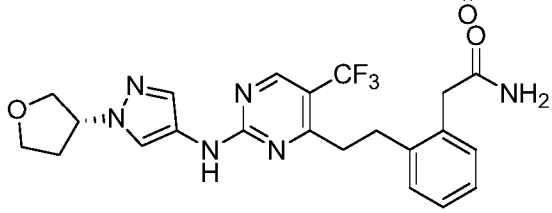


In some embodiments, the compound is selected from any one of the following compounds, or isomers, salts, solvates or prodrugs thereof:

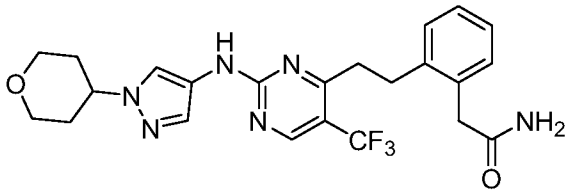


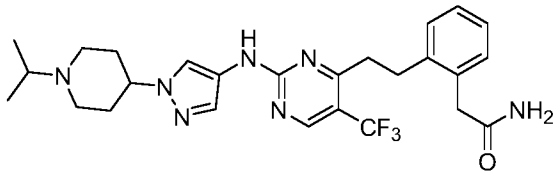


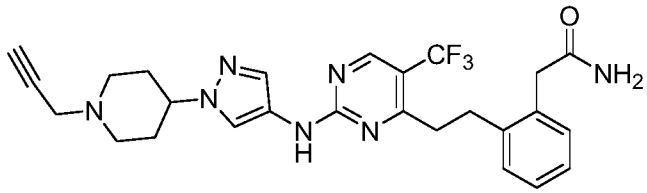




In some embodiments, the compound is selected from any one of the following compounds, or isomers, salts, solvates or prodrugs thereof:





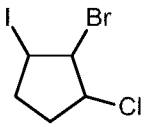


*Includes Other Forms*

Included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form ($-COO^-$), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group includes the protonated form ($-N^+HR^1R^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form ($-O^-$), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

*Alpha/Beta*

The terms *alpha* and *beta* are used herein to indicate the relative position of substituent groups on rings. For the avoidance of doubt, their meaning is illustrated with the structure below:



wherein the bromo group is *alpha* to the chloro group, and the iodo group is *beta* to the chloro group.

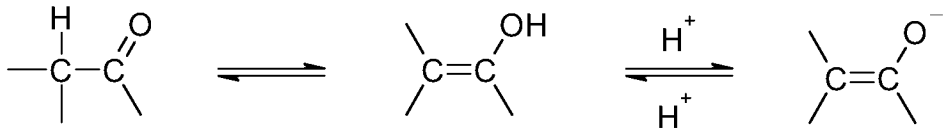
*Isomers, Salts, Solvates, Protected Forms, and Prodrugs*

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms;

keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers", as used herein, are structural (or constitutional) isomers (i.e. isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., $C_{1-7}$ alkyl includes *n*-propyl and *iso*-propyl; butyl includes *n*-, *iso*-, *sec*-, and *tert*-butyl; methoxyphenyl includes *ortho*-, *meta*-, and *para*-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hyroxyazo, and nitro/aci-nitro.




keto enol enolate

Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including $^{1}H$, $^{2}H$ (D), and $^{3}H$ (T); C may be in any isotopic form, including $^{12}C$, $^{13}C$ and $^{14}C$; O may be in any isotopic form, including $^{16}O$ and $^{18}O$; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g. asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge et al. J. Pharm. Sci., 66, 1-19 (1977).

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -$COO^-$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as $Na^+$ and $K^+$, alkaline earth cations such as $Ca^{2+}$ and $Mg^{2+}$, and other cations such as $Al^{3+}$. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., $NH_4^+$) and substituted ammonium ions (e.g., $NH_3R^+$, $NH_2R_2^+$, $NHR_3^+$, $NR_4^+$). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g., -$NH_2$ may be -$NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulphuric, sulphurous, nitric, nitrous, phosphoric, and phosphorous. Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: acetic, propionic, succinic, glycolic, stearic, palmitic, lactic, malic, pamoic, tartaric, citric, gluconic, ascorbic, maleic, hydroxymaleic, phenylacetic, glutamic, aspartic, benzoic, cinnamic, pyruvic, salicyclic, sulfanilic, 2-acetyoxybenzoic, fumaric, phenylsulfonic, toluenesulfonic, methanesulfonic, ethanesulfonic, ethane disulfonic, oxalic, pantothenic, isethionic, valeric, lactobionic, and gluconic. Examples of suitable polymeric anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term “solvate” is used herein in the conventional sense to refer to a complex of solute (e.g. active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term “chemically protected form”, as used herein, pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions, that is, are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts, Wiley, 1999).

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a *t*-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or *t*-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)$CH_3$, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal or ketal, respectively, in which the carbonyl group (>C=O) is converted to a diether (>C($OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide or a urethane, for example, as: a methyl amide (-NHCO-$CH_3$); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulphonyl)ethyloxy amide (-NH-Psec); or, in suitable cases, as an N-oxide (>NO•).

For example, a carboxylic acid group may be protected as an ester for example, as: an $C_{1-7}$ alkyl ester (e.g. a methyl ester; a t-butyl ester); a $C_{1-7}$ haloalkyl ester (e.g., a $C_{1-7}$ trihaloalkyl ester); a tri$C_{1-7}$ alkylsilyl-$C_{1-7}$ alkyl ester; or a $C_{5-20}$ aryl-$C_{1-7}$ alkyl ester (e.g. a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-$CH_2NHC(=O)CH_3$).

It may be convenient or desirable to prepare, purify, and/or handle the active compound in the form of a prodrug. The term “prodrug”, as used herein, pertains to a compound which, when metabolised (e.g. *in vivo*), yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties. For example, some prodrugs are esters of the active compound (e.g. a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required. Examples of such metabolically labile esters include those wherein R is C1-7 alkyl (e.g. -Me, -Et); $C_{1-7}$ aminoalkyl (e.g. aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and acyloxy-$C_{1-7}$ alkyl (e.g. acyloxymethyl; acyloxyethyl; e.g. pivaloyloxymethyl; acetoxymethyl; 1-acetoxyethyl; 1-(1-methoxy-1-methyl)ethyl-carbonxyloxyethyl; 1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl; 1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl; 1-cyclohexyl-carbonyloxyethyl; cyclohexyloxy-carbonyloxymethyl; 1-cyclohexyloxy-carbonyloxyethyl; (4-tetrahydropyranyloxy) carbonyloxymethyl; 1-(4-tetrahydropyranyloxy)carbonyloxyethyl; (4-tetrahydropyranyl)carbonyloxymethyl; and 1-(4-tetrahydropyranyl)carbonyloxyethyl).

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound. For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

**Selectivity**

The compounds of formula (I) may exhibit improved selectivity for VEGFR3 over other kinases such as VEGFR2. The selectivity of the compounds for inhibiting VEGFR3 over other kinases, such as VEGFR2 can be demonstrated by cellular assay results (see, for example, the VEGFR3 assay described below).

The compounds of formula (I) may exhibit improved VEGFR3 activity and accordingly improved *in vivo* efficacy for cancer.

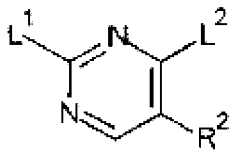
The compounds of formula (I) may exhibit improved FAK activity and accordingly improved *in vivo* efficacy for cancer.

The compounds of formula (I) may exhibit improved pharmacokinetic and safety profiles. These compounds may have diminished activity on safety targets, such as hERG and/or CYP450s.

**General synthesis methods**

The compounds of the invention can be prepared by employing the following general methods and using procedures described in detail in the experimental section. The reaction conditions referred to are illustrative and non-limiting.

The process for the preparation of a compound of formula (I) or isomers, salts, solvates or prodrug thereof comprises reacting a compound of formula F1



F1

with a compound of formula A-$NH_2$ to displace the group $L^1$ and with a compound of formula $HC\equiv R^3$ to displace the group $L^2$, or

with a compound of formula $HC\equiv R^3$ to displace the group $L^2$ and with a compound of formula A-$NH_2$ to displace the group $L^1$,

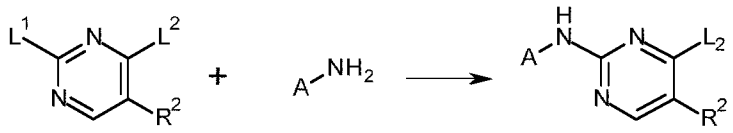
wherein A, $R^2$ and $R^3$ are as defined in formula (I) above and $L^1$ and $L^2$ are leaving groups.

It will be appreciated that the compound of formula A-$NH_2$ and the compound of formula $HC\equiv R^3$ can be reacted with the compound of formula F1 separately or sequentially in any order or simultaneously.

The leaving groups $L^1$ and $L^2$ may be any suitable leaving groups, such as a halogen atom (F, Cl, Br, I), -SR or -$S0_2$R where R is a $C_{1-4}$ straight chain or branched alkyl group. In some embodiments, $L^1$ and $L^2$ may be the same or different and may be selected from the group consisting of Cl, Br, I, SMe, $SO_2$Me.

Compounds of formula (I), as described above, can be prepared by synthetic strategies outlined below, wherein the definitions above apply:

**Scheme A**



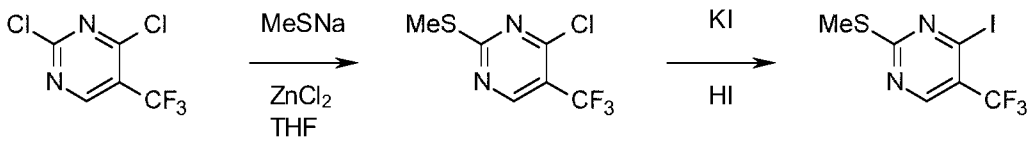
F1 F2 F3

Compounds of formula F1 may be reacted with substituted commercial or synthetic amino substituted compounds of formula F2 (as prepared in scheme C to N) to form intermediates of formula F3 where $L^1$ and $L^2$ may be the same or different and include Cl, Br, I, SMe, $SO_2Me$.

Compounds of the formula F1 may be prepared where $L^1$ and $L^2$ are different to allow regioselective substitution or when $L^1 = L^2$ suitable reaction conditions can be employed (choice of solvent, reaction temperature, addition of a Lewis acid, for example $ZnCl_2$ in $Et_2O$) to allow $L^1$ to be selectively displaced over $L^2$. Where regiochemical mixtures and di-substitution are obtained the regioisomers may be separated by chromatography.

Compounds of the formula F1 where $L^1 = L^2$ are either commercially available, for example 2,4-dichloro-5-(trifluoromethyl)pyrimidine, 2,4-dichloro-5-fluoropyrimidine, 2,4,5-trichloropyrimidine, 2,4-dichloro-5-bromopyrimidine, 2,4-dichloro-5-iodopyrimidine, 2,4-dichloro-5-methylpyrimidine, 2,4-dichloro-5-cyanopyrimidine or may be prepared readily from commercial starting materials. Where $R^2 = CF_3$ and differentiation of $L^1$ and $L^2$ is desirable, the method outlined in scheme B may be employed.

**Scheme B**



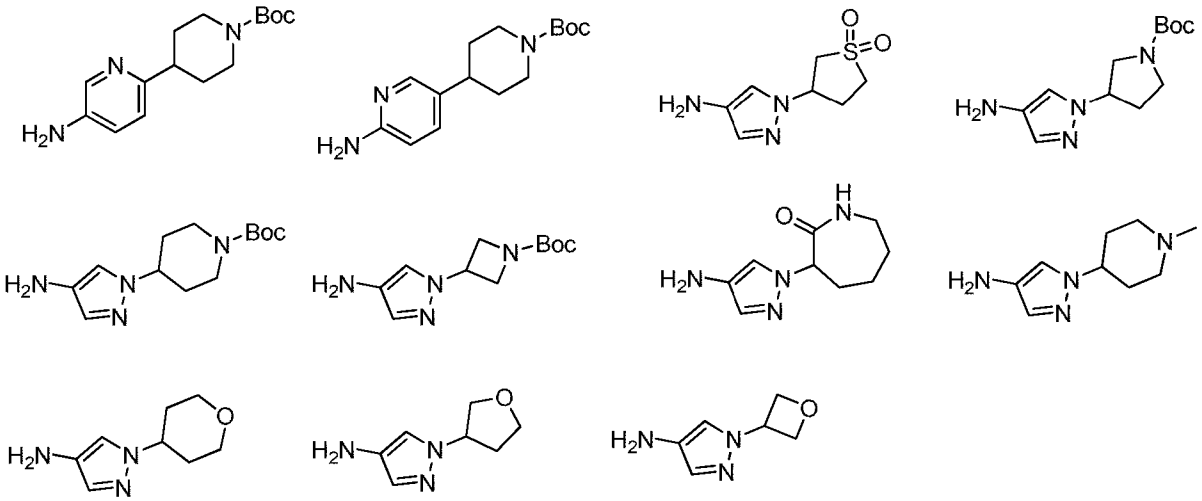

G1 G2 G3

Commercially available 2,4-dichloro-5-(trifluoromethyl)pyrimidine (G1) can be selectively reacted with sodium thiomethoxide in the presence of zinc(II) chloride to give 2-thiomethyl-4-chloro-5-(trifluoromethyl)pyrimidine (G2). 2-Thiomethyl-4-chloro-5-(trifluoromethyl)pyrimidine (G2) can be further reacted, for example by conversion to 2-thiomethyl-4-iodo-5-

(trifluoromethyl)pyrimidine (G3) under Finkelstein conditions and/or by oxidation with *m*-CPBA to give the corresponding sulfone if further differentiation of the 2 and 4-position is required or if additional activation is desirable.

Examples of commercially available amino compounds of the formula F2 include, but are not limited to those depicted in table 1.

**Table 1**

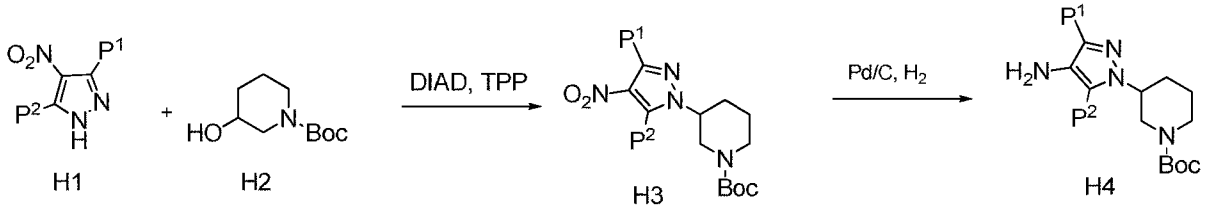


It will be appreciated that compounds of the formula F2, both commercial and synthetic, can be further modified either prior or post coupling to pyrimidines of the formula F1 *via* an extensive range of chemistries including, but not limited to hydrolysis, alkylation, acylation, electrophilic halogenation and Mitsunobu coupling.

In addition to commercially available amino compounds of the formula F2, numerous analogous nitro containing compounds are also commercially available. It will be appreciated that such compounds can be reduced under suitable conditions, for example in the presence of palladium under an atmosphere of hydrogen, to give amino compounds of the formula F2.

Synthetic amino compounds of the invention may be prepared *via* a range of procedures. It will be appreciated that heterocyclic analogues may also be prepared by analogous methods to those outlined below *via* substitution of heteroaromatic ring-containing starting materials with suitable heteroaromatic systems.

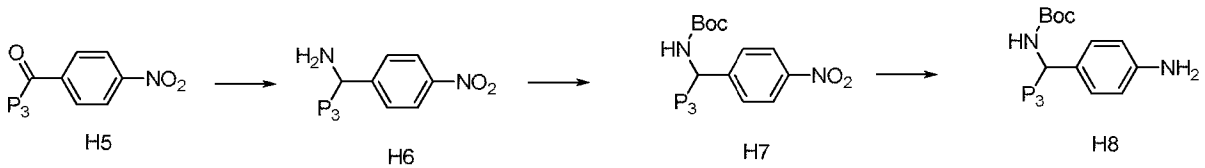
**Scheme C**




Compounds of the formula H1, where $P^1$ and $P^2$ are independently selected from hydrogen or lower alkyl, can be reacted under Mitsunobu conditions with hydroxyl piperidine H2 to form compounds of the formula H3. Subsequent reduction of the nitro group in H3 may be achieved using a variety of reducing agents, for example hydrogen gas in the presence of a metal catalyst such as palladium on carbon can provide amines H7. It will be appreciated that the regioisomeric piperidines as well as pyrrolidines and azetidine analogs of H4 can be accessed by analogous series of reactions from the appropriate analog of H2.

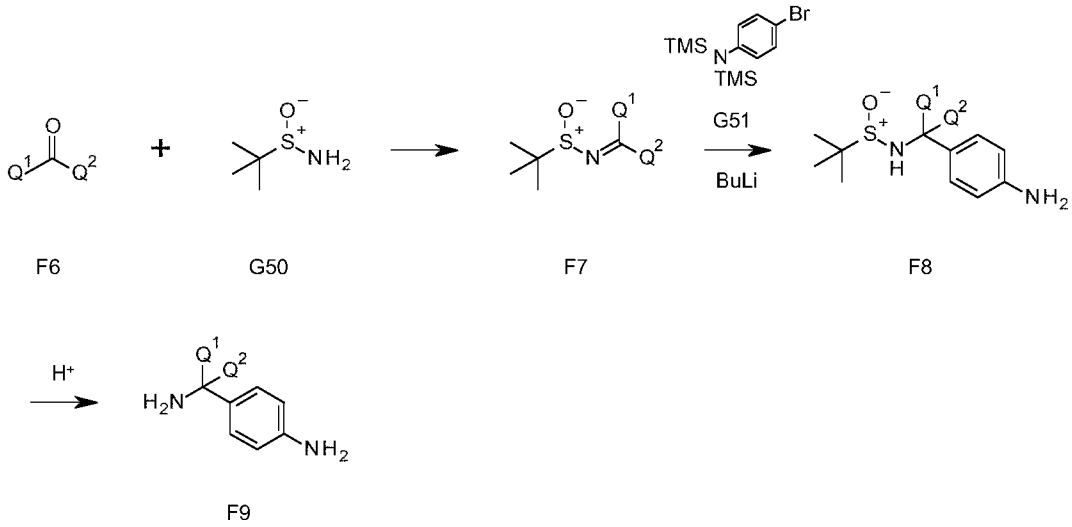
Compounds of the formula F2 containing benzylamine or substituted benzylamines may either be purchased with suitable protecting groups in place to allow selective reaction at the aniline or synthesised by a range of techniques. For example, as shown in Scheme D compounds of the formula H5 where $P^3$ may be hydrogen, lower alkyl or C3-C5 cycloalkyl, can undergo reductive amination, for example using ammonium formate and sodium acetoxyborohydride, to give benzylamines H6. Compounds of the formula H6 can be protected with an amino protecting group such as Boc to give compounds of the formula H7. Reduction of H7 using reducing agents such as hydrogen gas in the presence of palladium on carbon can provide anilines of the formula H8. It will be appreciated that the phenyl in H8 may be substituted with substituents $R^{1B}$ and/or $R^{1C}$ as described above.

**Scheme D**




Another route to compounds of the formula F2 containing benzylamine is via an Ellman type procedure as outlined in scheme N.

**Scheme N**



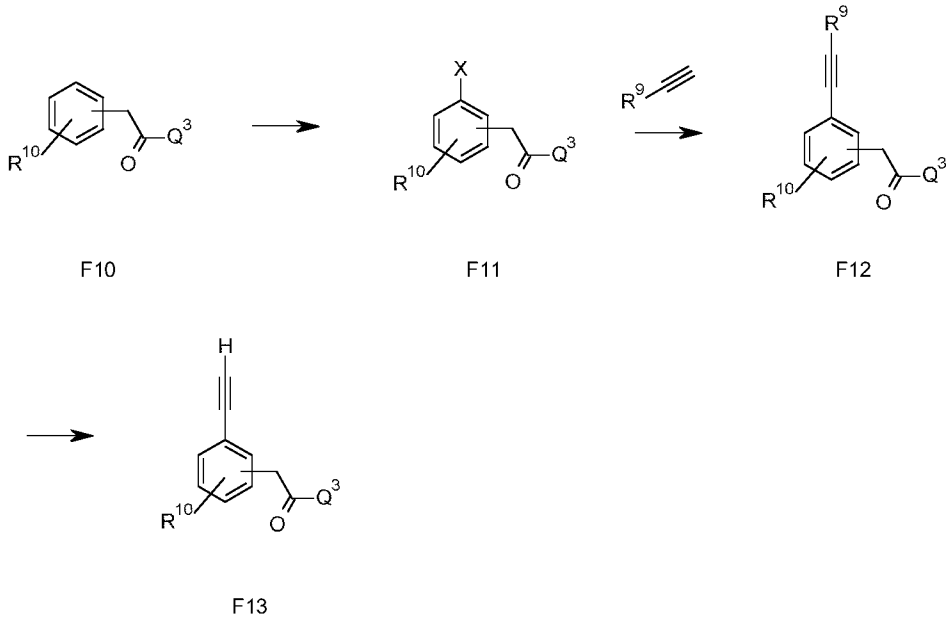

F6 G50 F7 F8

F9

Carbonyl compounds of the formula F6 can be reacted with 2-methylpropane-2-sulfinamide (G50) to give compounds of the formula F7. Compounds of the formula F7 can be reacted with anions prepared from suitably protected amino compounds, for example *N*-(4-bromophenyl)-1,1,1-trimethyl-*N*-(trimethylsilyl)silanamine (G51) treated with *n*-butyllithium, to give compounds of the formula F8. Hydrolysis of compounds of the formula F8 under acidic conditions, for example using aqueous hydrochloric acid, gives compounds of the formula F9. Where necessary, compounds of the formula F9 can be further protected to facilitate regiospecific reactivity. It will be appreciated that $Q^1$ and $Q^2$ may be the same or different and may be fused together to form a ring structure, for example as in cyclobutanone – Substituents $Q^1$ and $Q^2$ form either $R^{C1}$ or part of X in compounds of formula I. It will also be appreciated that anions of suitably protected amino heterocycles may be added to compounds of the formula F7 to give heterocyclic analogues of compounds of the formula F9. It will also be appreciated that the phenyl in F9 may be substituted with substituents $R^{1B}$ and/or $R^{1C}$ as described above.

Where compounds are required where $R^3$ is aryl or substituted aryl compounds of the formula F13 may be prepared as outlined in scheme O.

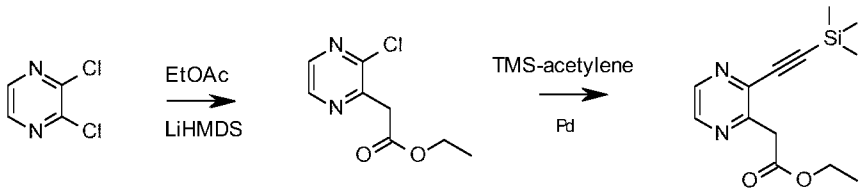
**Scheme O**



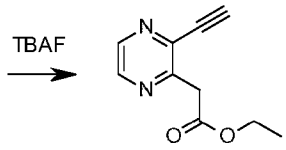

Compounds of the formulae F10 and F11 (where $R^{10}$ is selected from H, F, Me and $CF_3$; $Q^3$ may be OH, O-alkyl, $NH_2$ or substituted N and X is selected from Cl, Br and I), are either commercially available or may be prepared synthetically. It will be appreciated that for compounds of the formula F10 and F11, the nature of $Q^3$ can be readily changed. For example, a carboxylic acid may be converted to a corresponding ester or amide as required and conversely esters and amides can be hydrolysed to give carboxylic acids. Halogenation, for example using *N*-bromosuccinimide, of compounds of the formula F10 gives compounds of the formula F11, Compounds of the formula F11 may be reacted under Sonagashira type coupling conditions to give acetylenes of the formula F12 where $R^9$ is TMS, TES or $C(CH_3)_2OH$. $R^9$ may then be removed to generate compounds of the formula F13. When $R^9$ is TMS or TES, potassium carbonate or tetra-*n*-butyl ammonium fluoride may be employed to induce this transformation. When $R^9$ is $C(CH_3)_2OH$, sodium hydride in refluxing toluene may be used.

When compounds in which $R^3$ is heteroaryl are desired, heteroaryl analogues of F13 may be prepared as outlined in Schemes P, Q and R.

**Scheme P**



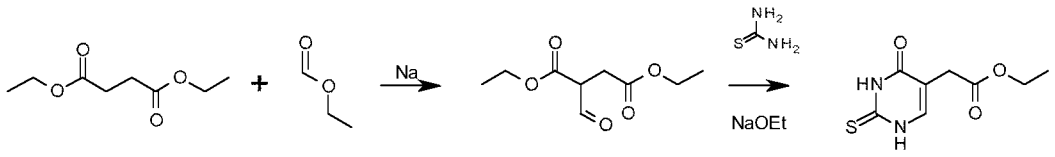

G52 G53 G54



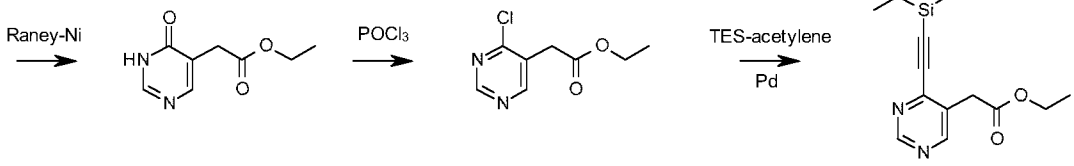

G55

For pyrazine containing analogues, 2,3-di-chloropyrazine (G52) can be reacted with ethyl acetate in the presence of LiHMDS to give ester G53. Coupling of ester G53 with TMS acetylene under Sonagashira conditions gives ethyl 2-(3-((trimethylsilyl)ethynyl)pyrazin-2-yl)acetate (G54). Removal of the trimethylsilyl group using TBAF gives ethyl 2-(3-ethynylpyrazin-2-yl)acetate (G55).

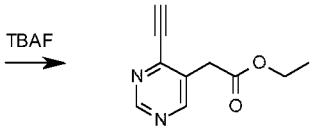
**Scheme Q**




G56 G57 G58 G59




G60 G61 G62

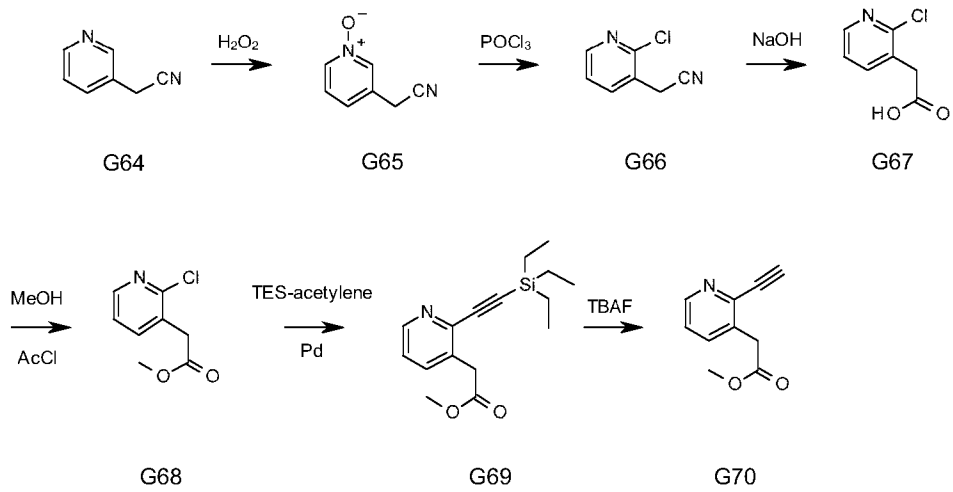



G63

For pyrimidine analogues, diethyl succinate (G56) and ethyl formate (G57) can be condensed to give aldehyde G58 in the presence of sodium metal. Cyclisation using

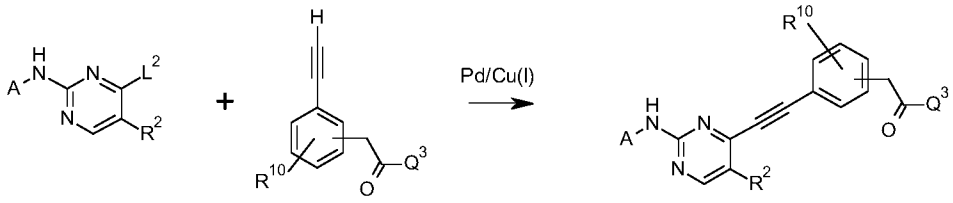
thiourea gives 4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine (G59). Desulfurisation using Raney-nickel gives pyrimidone G60, which can be converted to 4-chloro pyrimidine G61 using phosphorous oxychloride. Coupling of compound G61 with TES-acetylene under Sonagashira conditions, followed by removal of the triethylsilyl group using TBAF gives ethyl 2-(4-ethynylpyrimidin-5-yl)acetate (G63). It will be appreciated that the regioisomeric pyrimidine can be accessed by analogous series of reactions from the isomer of G59.

**Scheme R**

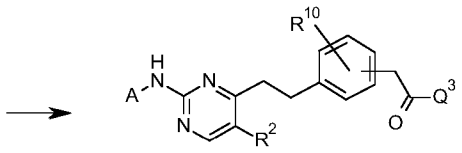



For 3-pyridyl acetates, 2-(pyridin-3-yl)acetonitrile (G64) can be oxidised to *N*-oxide G65. Chlorination with phosphorous oxychloride gives 2-chloropyridine G66 which can be hydrolysed with sodium hydroxide to acetic acid G67. Ester formation using methanol gives 2-chloropyridine ester G68. Coupling of ester G68 with TES-acetylene under Sonagashira conditions, followed by removal of the triethylsilyl group using TBAF gives methyl 2-(2-ethynylpyridin-3-yl)acetate (G70). It will be appreciated that the other regioisomeric pyridine analogues can be prepared using an analogous sequence starting from other commercially available pyridyl acetates.

**Scheme S**




F3 F13 F14



F15

Pyrimidines of the formula F3 may be reacted with terminal acetylenes of the formula F13 to give acetylenes of the formula F14 in a Sonagashira type coupling. The acetylene in compounds of the formula F14 may be reduced to an alkane of the formula F15 using hydrogen gas in the presence of a transition metal catalyst. The exact choice of catalyst and conditions employed is dependent on the nature of $R^2$. For example, where $R^2$ is selected from F, $CF_3$, methyl and methoxy, 10% Pd/C may be used, where $R^2$ is Cl, platinum oxide is employed. Functional group manipulation may be carried out on compounds of the formula F15 if necessary. For example, compounds of the formula F15 where $Q^3$ is O-alkyl (i.e. esters) may then be deprotected to give carboxylic acids of the formula F15 where $Q^3$ is OH. In esters where $Q^3$ is OMe, lithium hydroxide solutions may be employed. Where $Q^3$ is O*t*-Bu, acidic solutions, for example trifluoroacetic acid in dichloromethane may be used to facilitate hydrolysis. It will be appreciated that under acidic conditions Boc protecting groups in A will also be cleaved.

Compounds of the formula F15 where $Q^3$ is OH may then be converted to amides and substituted amides as described in formula (I) using a suitable choice of amine in the presence of a coupling agents for example EDCI.HCl or HATU.

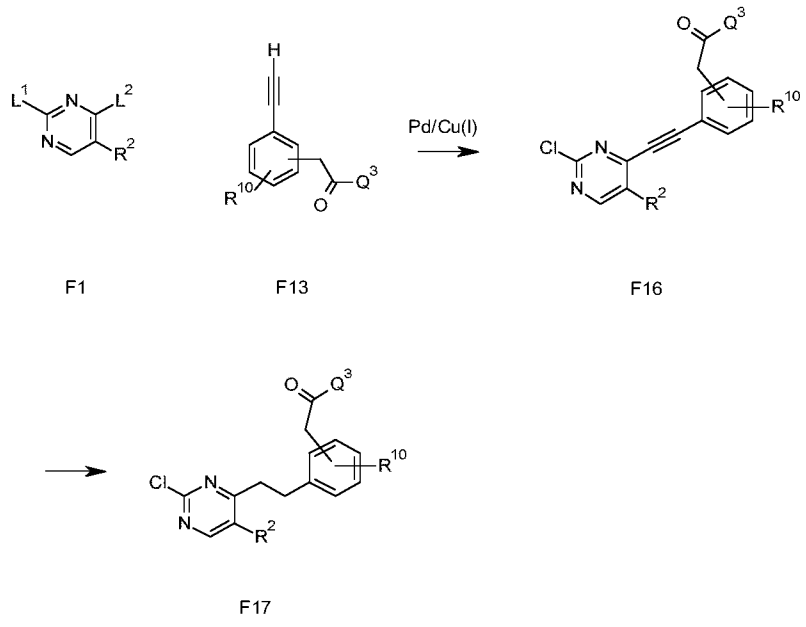
It will be appreciated that heteroaromatic analogues of compounds of the formula F13 (as described in schemes P, Q and R) may be coupled in an analogous manner to that described in scheme S and then further elaborated to amides as described above.

Compounds of the formula F15, in which $Q^3$ = an amide or substituted amide may then be further modified by derivitisation of amine functionality present in A. For example,

compounds of the formula F15 where A was prepared as described in schemes C to M, in which a *tert*-butyl carbamate is present, may be hydrolysed in the presence of mild acid, for example trifluoroacetic acid, to give the parent amine. The amine functionality maybe further derivatised by reductive alkylation with formaldehyde in the presence of sodium triacetoxyborohydride to give *N*-Me analogues; by reductive alkylation with acetaldehyde in the presence of sodium triacetoxyborohydride to give *N*-Et analogues or the *N*-acetyl analogues may be prepared by reaction with a suitable acylating agent, for example acetic anhydride.

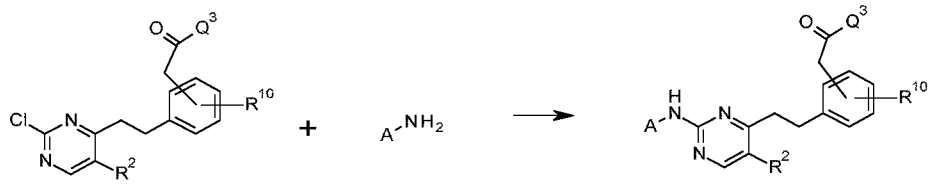
Further to the approach described in scheme S, another approach can be employed, where $R^2$ is not $CF_3$, and pyrimidines of the formula F1 are initially coupled to acetylenes of the formula F13 as detailed in scheme T.

**Scheme T**




Pyrimidines of the formula F1 may be coupled to acetylenes of the formula F13 to give acetylenes of the formula F16 in a Sonagashira type coupling. Depending on the nature of $R^2$ these couplings may either be regioselective, or where mixtures are obtained, regioisomers may be separated by chromatography. The acetylene in compounds of the formula F16 may be reduced to an alkane of the formula F17 using hydrogen gas in the presence of a transition metal catalyst. The exact choice of catalyst and conditions employed is dependent on the nature of $R^2$. For example, where $R^2$ is Me, 10% Pd/C may be used, where $R^2$ is Cl, platinum oxide is employed. The desired amide may already be present in compounds of the formula F13, or an ester may be used and subsequently derivatised as described above.

**Scheme U**

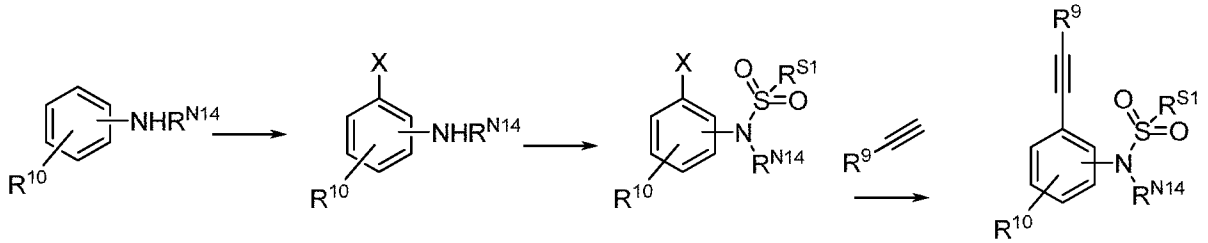


F17 F2 F15

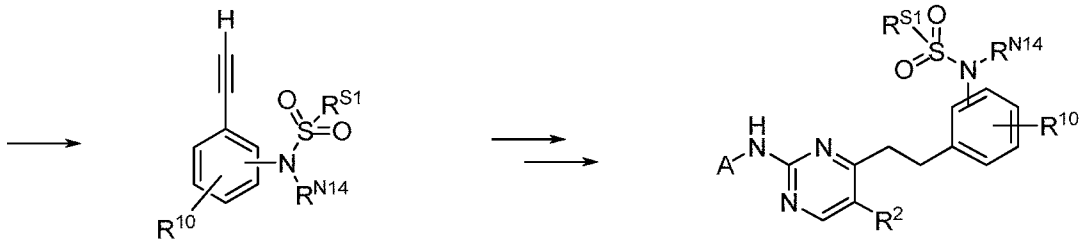
Compounds of the formula F17 may be reacted with amino compounds of the formula F2, prepared as described above, to give compounds of the formula F15. Such couplings may be mediated under acidic conditions, for example using trifluoroacetic acid in trifluoroethanol or using palladium catalysis in a Buchwald/Hartwig type coupling.

Compounds of the formula F15 may then be further elaborated as desired as described above.

**Scheme V**



F16 F17 F18 F19

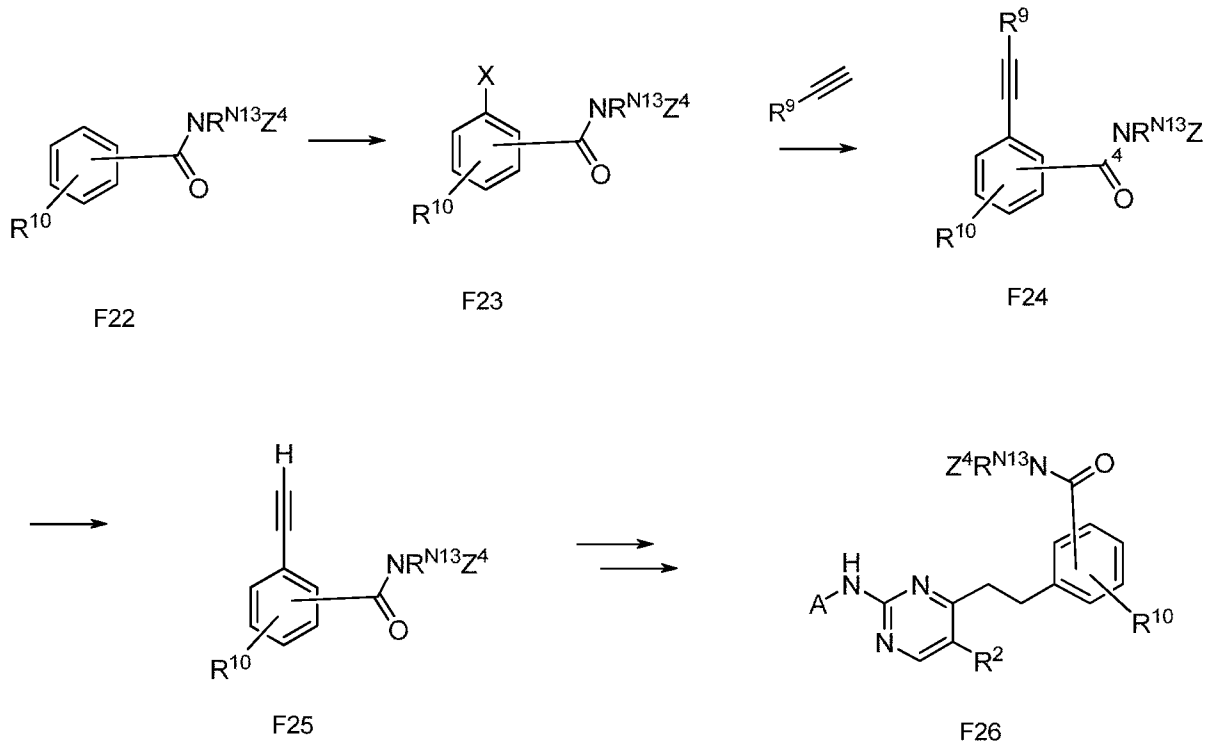


F20 F21

Compounds of the formulae F16 and F17 where $R^{10}$ is selected from H, F, Me and $CF_3$; and X is selected from Cl, Br and I, are either commercially available or may be synthesized using literature procedures. For example, compounds of formula F16 where $R^{10}$ is H or Me

may be reacted with *N*-halosuccinimide to give compounds of formula F17. Additionally, anilines of formula F16 where $R^{10}$ is $CF_3$ can be iodinated with benzyltrimethylammonium dichloroiodide or $Ag_2SO_4/I_2$. Compounds of the formula F17 may be reacted with alkyl sulfonyl chlorides to give compounds of the formula F18 where R' is H, $CH_3$ or $OCH_3$. Compounds of the formula F18 may be reacted under Sonagashira type coupling conditions to give acetylenes of the formula F19 where the alkyne protecting group, $R^9$ is TMS, TES or $C(CH_3)_2OH$. In compounds of the formula F19, $R^9$ may be removed to generate compounds of the formula F20. When $R^9$ is TMS or TES, potassium carbonate or sodium hydroxide or tetra-*n*-butyl ammonium fluoride may be employed to induce this transformation. When $R^9$ is $C(CH_3)_2OH$, sodium hydride in refluxing toluene may be used. Compounds of the formula F20 may be reacted in an analogous manner to the routes described in Schemes S, T and U to give compounds of the formula F21.

**Scheme W**




F22 F23 F24

F25 F26

Compounds of the formulae F22 and F23 are either commercially available or may be prepared synthetically. For example, compounds of the formula F22 may be halogenated using N-halsuccinimide to give compounds of the formula F23. Alternatively, optionally a substituted 2-iodobenzoic acid may be amidated to give compounds of formula F23. Compounds of the formula F23 may be reacted under Sonagashira type coupling conditions to give acetylenes of the formula F24 where the protecting group, $R^9$ is TMS, TES or $C(CH_3)_2OH$. In compounds of the formula F24, $R^9$ may then be removed to generate

compounds of the formula F25. Potassium carbonate or tetra-*n*-butyl ammonium fluoride can be used to remove the protecting group, when $R^9$ is TMS or TES. When $R^9$ is $C(CH_3)_2OH$, sodium hydride in refluxing toluene may be used. Compounds of the formula F20 may be reacted in an analogous manner to the routes described in Schemes S and T to give compounds of the formula F21.

**Use of Compounds of the Invention**

The present invention provides active compounds, specifically, active 2,4,5-substituted pyrimidines .

The term “active”, as used herein, pertains to compounds which are capable of inhibiting VEGFR3 activity, and specifically includes both compounds with intrinsic activity (drugs) as well as prodrugs of such compounds, which prodrugs may themselves exhibit little or no intrinsic activity.

Assays which may be used in order to assess the VEGFR3 inhibition offered by a particular compound are described in the examples below.

The present invention further provides a method of inhibiting VEGFR3 activity in a cell, comprising contacting said cell with an effective amount of an active compound, preferably in the form of a pharmaceutically acceptable composition. Such a method may be practised *in vitro* or *in vivo*.

The present invention further provides active compounds which inhibit VEGFR3 activity, as well as methods of inhibiting VEGFR3, comprising contacting a cell with an effective amount of an active compound, whether *in vitro* or *in vivo*.

Active compounds may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

The invention further provides active compounds for use in a method of treatment of the human or animal body. Such a method may comprise administering to such a subject a therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

The term “treatment”, as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g. in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e. prophylaxis) is also included.

The term “therapeutically-effective amount” as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio.

**Cancer**

In an embodiment, there is provided active compounds which are anticancer agents. One of ordinary skill in the art is readily able to determine whether or not a candidate compound treats a cancerous condition for any particular cell type, either alone or in combination.

In an embodiment, there is provided the use of the active compounds for the treatment of cancer in the human or animal body. There is further provided active compounds for use in a method of treatment of cancer in the human or animal body. Such a use or method may comprise administering to such a subject a therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

Examples of cancers include, but are not limited to, bone cancer, brain stem glioma, breast cancer, cancer of the adrenal gland, cancer of the anal region, cancer of the bladder, cancer of the endocrine system, cancer of the oesophagus, cancer of the brain, cancer of the head or neck, cancer of the kidney or ureter, cancer of the liver, cancer of the parathyroid gland, cancer of the penis, cancer of the small intestine, cancer of the thyroid gland, cancer of the urethra, carcinoma of the cervix, carcinoma of the endometrium, carcinoma of the fallopian tubes, carcinoma of the renal pelvis, carcinoma of the vagina, carcinoma of the vulva, chronic or acute leukemia, acute myelogenous leukemia, colon cancer, melanoma such as cutaneous or intraocular melanoma, haemetological malignancies, Hodgkin's disease, lung cancer, non-small cell lung cancer (NSCLC), mesothelioma, lymphocytic lymphomas, neoplasms of the central nervous system (CNS), ovarian cancer, pancreatic cancer, pituitary adenoma, primary CNS lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, sarcoma of soft tissue, skin cancer, spinal axis tumors, stomach cancer and uterine cancer.

In some embodiments, the cancer includes types and/or subtypes that display amplification of FAK expression. These include: hepatocellular carcinoma, non-small cell lung cancer, small cell lung carcinoma, breast cancer, pancreatic cancer, brain cancer, sarcoma, osteosarcoma, ovarian cancer, cervical cancer, colon cancer, neuroblastoma, thyroid cancer, prostate cancer, head and neck cancer, hematopoietic cancer and mesothelioma.

In a further embodiment FAK inhibitor compounds will be used for the treatment of tumor types or subtypes that have inactivated NF2 gene, or mutated KRAS and CDKN2A genes or inactivated p53 gene.

Any type of cell may be treated, including but not limited to, lung, gastrointestinal (including, e.g., bowel, colon), breast (mammary), ovarian, prostate, liver (hepatic), kidney (renal), bladder, pancreas, brain, skin, blood, endothelial or epithelial.

Compounds of the present invention may also be useful in inhibiting lymphangiogenesis and/or suppressing lymph node metastasis. Compounds of the present invention may also be useful in inhibiting tumor angiogenesis, tumor cell invasion and/or suppressing metastasis. Compounds of the present invention may also be useful in preventing the spread of cancer and in the prevention of metastasis.
Compounds of the present invention may also be useful in inhibiting several cancer properties, processes and cell configurations, including but not limited to, growth, survival, de-differentiation (epithelial-to-mesenchymal transition), invasion, metastasis, angiogenesis, lymphangiogenesis, cancer stem cells.

In one embodiment there is provided the use of a compound of formula (I) or an isomer, salt, solvate, protected form or prodrug thereof to prevent the spread of cancer or prevent metastasis. There is also provided a compound of formula (I) or an isomer, salt, solvate or prodrug thereof for use in a method for preventing the spread of cancer or preventing of metastasis.

In another embodiment there is provided an anti-cancer treatment comprising a compound of formula (I) or an isomer, salt, solvate or prodrug thereof and an anti-tumour agent.

The anti-cancer treatment defined herein may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or

chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

(i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cisplatin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5 fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); 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 taxol and docetaxel (Taxotere) and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), 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 5*-reductase such as finasteride;

(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661 and 4-((2,4-dichloro-5-methoxyphenyl)amino)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinoline-3-carbonitrile (bosutinib, SKI-606; Cancer research (2003), 63(2), 375-81), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase);

(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 [HerceptinT], the anti-EGFR antibody panitumumab, the anti erbB1 antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern et al. Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine

(gefitinib, ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI 774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), 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)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic and antilymphangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor A (VEGFA) antibody bevacizumab (AvastinT), the anti-vascular endothelial cell growth factor A (VEGFA) antibody ranibizumab, the anti-VEGF aptamer pegaptanib, the anti-vascular endothelial growth factor receptor 3 (VEGFR3) antibody IMC-3C5, the anti-vascular endothelial cell growth factor C (VEGFC) antibody VGX-100, the anti-vascular endothelial cell growth factor D (VEGFD) antibody VGX-200, the soluble form of the vascular endothelial growth factor receptor 3 (VEGFR3) VGX-300 and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (vandetanib; ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (cediranib; AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985), pazopanib (GW786034), axitinib (AG013736), sorafenib and sunitinib (SU11248; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin avb3 function and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene directed enzyme pro drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or

a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example 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

A combination of particular interest is with docetaxel. Other possible combinations of interest include with paclitaxel, gemcitabine, cisplatin, carboplatin, oxaliplatin, 5-fluorouracil, doxorubicin, temozolomide, sunitinib, axitinib, sorafenib, pazopanib, cabozantinib, the camptothecin prodrug irinotecan and radiotherapy.

**Diseases ameliorated by the control and/or inhibition of lymphangiogenesis**

The present invention provides active compounds which are useful in preventing and/or treating diseases or conditions ameliorated by the control and/or inhibition of lymphangiogenesis.

In one embodiment there is provided the use of a compound of formula (I) or an isomer, salt, solvate, protected form or prodrug thereof to inhibit, suppress or reduce lymphangiogenesis. There is also provided a compound of formula (I) or an isomer, salt, solvate, protected form or prodrug thereof for use in the method of inhibiting, suppressing or reducing lymphangiogenesis.

As discussed above, these diseases or conditions may include:

(a) eye diseases, for example corneal graft rejection and age related macular degeneration;

(b) skin inflammations, such as skin lesions in patients with psoriasis;

(c) rejection in renal transplantation.

**Diseases ameliorated by the control and/or inhibition of angiogenesis or inflammation**

The active compounds of formula (I) are useful in preventing and/or treating diseases or conditions ameliorated by the control and/or inhibition of angiogenesis or inflammation.

In one embodiment there is provided the use of a compound of formula (I) or formula (II) or an isomer, salt, solvate, protected form or prodrug thereof to inhibit, suppress or reduce angiogenesis. There is also provided a compound of formula (I) or formula (II) or an isomer, salt, solvate, protected form or prodrug thereof for use in the method of inhibiting, suppressing or reducing angiogenesis.

These diseases or conditions may include:

(a) eye diseases, for example corneal graft rejection and age related macular degeneration;

(b) skin inflammations, such as skin lesions in patients with psoriasis;

(c) rejection in renal transplantation

(d) rheumatoid arthritis

(e) diabetic retinopathy,

(f) cardiovascular diseases, such as atherosclerosis

(g) autoimmune disease

(h) fibrosis

(i) restenosis

(j) diabetes mellitus

(j) thrombosis

(k) glomerulonephritis

(l) neurodegeneration

**Administration**

The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or at the site of desired action, including but not limited to, oral (e.g. by ingestion); topical (including e.g. transdermal, intranasal, ocular, buccal, and sublingual); pulmonary (e.g. by inhalation or insufflation therapy using, e.g. an aerosol, e.g. through mouth or nose); rectal; vaginal; parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, intravitreal and intrasternal; by implant of a depot, for example, subcutaneously, intravitreal or intramuscularly. The subject may be a eukaryote, an animal, a vertebrate animal, a mammal, a rodent (e.g. a guinea pig, a hamster, a rat, a mouse), murine (e.g. a mouse), canine (e.g. a dog), feline (e.g. a cat),

equine (e.g. a horse), a primate, simian (e.g. a monkey or ape), a monkey (e.g. marmoset, baboon), an ape (e.g. gorilla, chimpanzee, orang-utan, gibbon), or a human.

**Formulations**

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation) comprising at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilisers, or other materials, as described herein.

The term “pharmaceutically acceptable” as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be “acceptable” in the sense of being compatible with the other ingredients of the formulation.

Suitable carriers, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington’s Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active compound with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Formulations may be in the form of liquids, solutions, suspensions, emulsions, elixirs, syrups, tablets, losenges, granules, powders, capsules, cachets, pills, ampoules,

suppositories, pessaries, ointments, gels, pastes, creams, sprays, mists, foams, lotions, oils, boluses, electuaries, or aerosols.

Formulations suitable for oral administration (e.g. by ingestion) may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion; as a bolus; as an electuary; or as a paste.

A tablet may be made by conventional means, e.g., compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g. povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g. lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc, silica); disintegrants (e.g. sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g. sodium lauryl sulfate); and preservatives (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid). Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration (e.g. transdermal, intranasal, ocular, buccal, and sublingual) may be formulated as an ointment, cream, suspension, lotion, powder, solution, past, gel, spray, aerosol, or oil. Alternatively, a formulation may comprise a patch or a dressing such as a bandage or adhesive plaster impregnated with active compounds and optionally one or more excipients or diluents.

Formulations suitable for topical administration in the mouth include losenges comprising the active compound in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active compound in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active compound in a suitable liquid carrier.

Formulations suitable for topical administration to the eye also include eye drops wherein the active compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active compound.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid for administration as, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active compound.

Formulations suitable for administration by inhalation include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichoro-tetrafluoroethane, carbon dioxide, or other suitable gases.

Formulations suitable for topical administration via the skin include ointments, creams, and emulsions. When formulated in an ointment, the active compound may optionally be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active compounds may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

When formulated as a topical emulsion, the oily phase may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the

so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required.

Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active compound, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g. by injection, including cutaneous, subcutaneous, intramuscular, intravenous and intradermal), include aqueous and non-aqueous isotonic, pyrogen-free, sterile injection solutions which may contain anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. Examples of suitable isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active compound in the solution is from about 1

ng/mL to about 10 µg/mL, for example from about 10 ng/ml to about 1 µg/mL. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets. Formulations may be in the form of liposomes or other microparticulate systems which are designed to target the active compound to blood components or one or more organs.

**Dosage**

It will be appreciated that appropriate dosages of the active compounds, and compositions comprising the active compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the treatments of the present invention. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, and the age, sex, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration *in vivo* can be effected in one dose, continuously or intermittently (e.g. in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician.

In general, a suitable dose of the active compound is in the range of about 100 µg to about 250 mg per kilogram body weight of the subject per day. Where the active compound is a salt, an ester, prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

## EXAMPLES

The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

### Acronyms

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), *n*-propyl (nPr), *iso*-propyl (iPr), *n*-butyl (nBu), *tert*-butyl (tBu), *n*-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), methoxy (MeO), ethoxy (EtO), trimethylsilyl (TMS), *tert*-butyloxycarbonyl (Boc), and acetyl (Ac).

For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), , ether or diethyl ether ($Et_2O$), ethyl acetate (EtOAc), triethylamine ($Et_3N$), dichloromethane (methylene chloride, DCM), trifluoroacetic acid (TFA), trifluoroethanol (TFE), dimethylformamide (DMF), sodium sulphate ($Na_2SO_4$), tetrahydrofuran (THF), *meta*-chloroperbenzoic acid (*m*CPBA), hexamethyldisilazane sodium salt (NaHMDS), *O*-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU), dimethylsulfoxide (DMSO), magnesium sulphate ($MgSO_4$), sodium hydrogen carbonate ($NaHCO_3$), *tert*-butanol (*t*-BuOH), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride salt (EDCI.HCl), tetra-*n*-butylammonium fluoride (TBAF), *N*,*N*-diisopropylethylamine (DIPEA), 1-hydroxybenzotriazole (HOBt), *trans*-dichlorobis(triphenylphosphine)palladium(II) ($PdCl_2(PPh_3)_2$), tris(dibenzylideneacetone) dipalladium(0) ($Pd_2(dba)_3$), tri-*t*-butyl phosphonium tetrafluoroborate (*t*-$Bu_3PH.BF_4$), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), triphenylphosphine ($PPh_3$) and 1,2-dichloroethane (DCE).

*General Experimental Details*

Unless otherwise stated the following generalisations apply.

In the examples below, in case the structures contain one or more stereogenic centres and the stereochemistry is depicted in the diagram, the respective stereochemistry is assigned in an arbitrary absolute configuration. These structures depict single enantiomers as well as mixtures of enantiomers in all ratios, and/or mixtures of diastereoisomers in all ratios.

The compounds of formula (I) have been named according to the standards used in the program ACD/Name Batch from Advanced Chemistry Development Inc., ACD/Labs (7.00 Release). Product version: 7.10, build: 15 Sep 2003.

NMR, HPLC and MS data provided in the examples described below are registered on:

NMR: Agilent DD2 (500 MHz), Aglient DD2 (600 MHz) or Varian DD2 (300 MHz) using residual signal of deuterated solvent as internal reference .

LCMS: Agilent 1100 Series LC/MSD, column Luna 5 µm C8, 150 x 4.6 mm, with mobile phase 80% ACN, 15% H2O, 5% buffer (3:1 MeOH/H2O, 315 mg HCO2NH4, 1 mL AcOH) and MS detection (ESI method).

Analytical thin-layer chromatography was performed on Merck silica gel 60F254 aluminium-backed plates which were visualised using fluorescence quenching under UV light or using an acidic anisaldehyde or a basic potassium permanganate dip. Flash chromatography was performed using either a Teledyne Isco CombiFlash Rf purification system using standard RediSep® cartridges. Microwave irradiation was achieved using a CEM Explorer 48 Microwave Reactor. All reactions carried out using microwave irradiation were stirred..

Where necessary, anhydrous solvents were prepared using a Glascontour purification system or purchased from Sigma-Aldrich.

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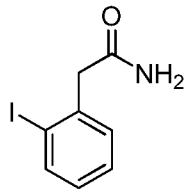
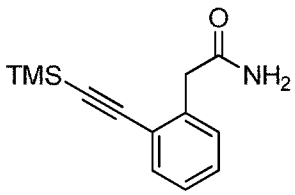
***Synthesis of Key Intermediates***

**Intermediate A1: 2-(2-iodophenyl)acetamide**



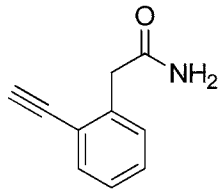
1-Hydroxybenzotriazole (2.58 g, 19.1 mmol), EDCI (2.96 g, 19.1 mmol) and diisopropylethylamine (12.1 mL, 69.3 mmol) were added sequentially to a solution of 2-(2-iodophenyl)acetic acid (4.54 g, 17.3 mmol) in DMF (22 mL) and THF (151 mL) under a $N_2$ atmosphere. The reaction mixture was allowed to stir at rt for 10 min. Ammonium carbonate (6.66 g, 69.3 mmol) was then added in one portion to the reaction mixture, which was then left to stir at rt overnight. The mixture was conc. *in vacuo* and water was added. The mixture was extracted with EtOAc, washed with $H_2O$, sat. aq. $NaHCO_3$ sol. and brine before drying over $MgSO_4$ and conc. *in vacuo*. The solid was suspended in EtOAc before being collected by vacuum filtration to give the title compound as an off-white solid (2.73 g, 60 %). LCMS (Method 1) Rt 1.859 min.

**Intermediate A2: 2-(2-((trimethylsilyl)ethynyl)phenyl)acetamide**



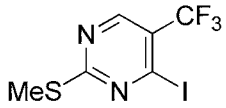
Intermediate **A1** (3.66 g, 14.0 mmol) was dissolved in DMF (25mL) and THF (100mL) was added before the solution was degassed by evacuation and back-filling with $N_2$ (x5). Copper iodide (0.133 g, 0.700 mmol), triethylamine (6.8 mL, 49.0 mmol) and $Pd(PPh_3)_4$ (0.404 g, 0.35 mmol) were added and the mixture was allowed to stir at rt for 10 min before trimethylsilylacetylene (3.2 mL, 22.4 mmol) was added. The mixture was left to stir at rt for 19 h. The mixture was diluted with EtOAc, washed with $H_2O$ and brine, dried over $MgSO_4$ and conc. *in vacuo*. The crude material was taken up in EtOAc and filtered to remove the insoluble impurities. Further purification by flash chromatography on silica, washing with DCM and 60% EtOAc/*n*-Hexane allowed for the major impurities to be removed and the product was then eluted with EtOAc, to give the title compound as a white solid (2.13 g, 66 %). LCMS (Method 1) Rt 2.328 min.

**Intermediate A3: 2-(2-ethynylphenyl)acetamide**



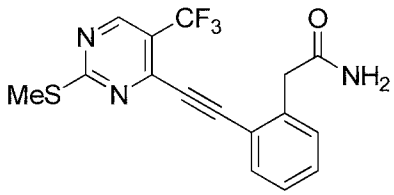
TBAF (1.0M in THF) (2.9 mL, 2.85 mmol) was added dropwise to a stirred solution of intermediate **A2** (0.440 g, 1.90 mmol) in THF (15 mL) at 0 °C under nitrogen. The resulting solution was stirred 0°C for 1h before being conc. *in vacuo*. Sat. aq. $NaHCO_3$ sol. was added to the residue which was extracted with EtOAc, washed with $H_2O$ and brine and dried over $MgSO_4$ before conc. *in vacuo* to afford the title compound (297mg, 98%) as off white solid. LCMS (Method 1) Rt 1.793 min. ESIMS *m/z* $[M+H]^+$ 160.2.

**Intermediate A4: 4-iodo-2-(methylthio)-5-(trifluoromethyl)pyrimidine**



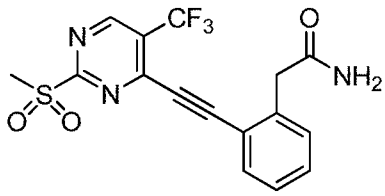
To a reaction vessel charged with 4-chloro-2-(methylthio)-5-(trifluoromethyl)pyrimidine (1.98 g, 8.66 mmol) and sodium iodide (3.89 g, 26.0 mmol) was added hydriodic acid (28 mL, 57 %). The vessel was sealed and the mixture allowed to stir for 48h at rt before being poured into water. The resulting precipitate was collected by vacuum filtration, washed with sat. aq. $NaHCO_3$ sol. and dried under vacuum to give the title compound as a pale yellow solid (1.46 g, 53 %). LCMS (Method 1) Rt 3.003 min.

**Intermediate A5: 2-(2-{[2-(methylthio)-5-(trifluoromethyl)pyrimidin-4-yl]ethynyl}phenyl)acetamide**



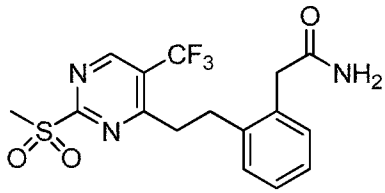
To a microwave reaction vessel charged with intermediate **A3** (0.958 g, 6.02 mmol), intermediate **A4** (1.60 g, 5.02 mmol), CuI (0.096 g, 0.502 mmol), $PdCl_2(PPh_3)_2$ (0.352g, 0.502 mmol) and triphenylphosphine (0.132 g, 0.502 mmol) was added triethylamine (17 mL) and THF (33 mL). The mixture was irradiated at 100°C in a microwave reactor for 10 min. The reaction mixture was conc. *in vacuo* before being diluted with EtOAc and filtered through Celite®. Purification by flash chromatography on silica, eluting with DCM then gradient elution with 20%-100% EtOAc/DCM mixtures, gave the title compound as a pale yellow solid (1.05 g, 60 %).

**Intermediate A6: 2-(2-{[2-(methylsulfonyl)-5-(trifluoromethyl)pyrimidin-4-yl]ethynyl}phenyl)acetamide**



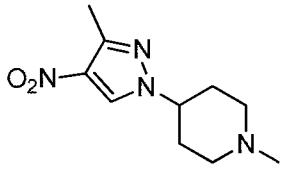
To a stirred solution of intermediate **A5** (1.04 g, 2.96 mmol) in DCM (100 mL) at 0 °C was added mCPBA (1.61 g, 6.51 mmol, 77 %) in one portion. The mixture was allowed to stir at 0°C for 10 min before warming to rt for 17h. Sat. aq. $NaHCO_3$ sol. was added and the layers separated. The aqueous layer was extracted further with DCM before the organics were combined and washed with brine, dried over $MgSO_4$ and conc. *in vacuo*. The crude product thus obtained was triturated with diethyl ether to give the title compound as pale brown solid (679 mg, 60 %). LCMS (Method 1) Rt 1.851 min. ESIMS *m/z* $[M+H]^+$ 384.0.

**Intermediate A7: 2-(2-{2-[2-(methylsulfonyl)-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl)acetamide**



To a solution of intermediate **A6** (0.676 g, 1.76 mmol) in DMF was added 10 % palladium on activated carbon (0.340 g, 50 % w/w). The mixture was evacuated and back-filled with $H_2$ (x3) and was left under an atmosphere of $H_2$, stirring at rt for 20 h. The reaction mixture was filtered through Celite, rinsing with EtOAc before conc. *in vacuo*. The crude product thus obtained was triturated with $Et_2O$ to give the title compound as a pale yellow solid (538 mg, 79%). LCMS (Method 1) Rt 1.931 min. ESIMS *m/z* $[M+H]^+$ 388.3.

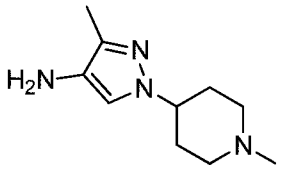
**Intermediate B1: 1-methyl-4-(3-methyl-4-nitro-1*H*-pyrazol-1-yl)piperidine**



DIAD (930 µL, 4.7 mmol) was added to a solution of 3-methyl-4-nitro-1H-pyrazole (500 mg, 3.93 mmol), *N*-methyl-4-piperidinol (453 mg, 3.93 mmol) and triphenylphosphine (1238 mg, 4.7 mmol) in THF (25mL). The reaction mixture was stirred at rt for 5 days. The mixture was

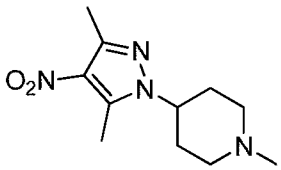
*conc. in vacuo* before purification by flash chromatography on silica, washing with 50% EtOAc/DCM, followed by 5/45/50 MeOH/EtOAc/DCM mixture. The product was eluted with 2/5/43/50 NEt3/MeOH/EtOAc/DCM mixture to give the title compound as an off-white low melting solid (202 mg, 23%). LCMS (Method 1) Rt 2.7 min, ESIMS *m/z* $[M+H]^+$ 225.3.

**Intermediate B2: 3-methyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazol-4-amine**



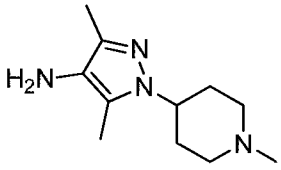
10% Palladium on activated carbon (100 mg) was added to a solution of the **B1** (200 mg, 0.893mmol) in EtOH (20mL) under a $N_2$ atmosphere. The mixture was evacuated and back-filled with $H_2$ (x3) and was left under an atmosphere of $H_2$, stirring at rt for 3h. The reaction mixture was filtered through Celite, rinsing with EtOAc before *conc. in vacuo* gave the title compound as a pink solid (160 mg, 92%) with no further purification required. LCMS (Method 1) Rt 4.0 min, ESIMS *m/z* $[M+H]^+$ 195.3.

**Intermediate B3: 4-(3,5-dimethyl-4-nitro-1H-pyrazol-1-yl)-1-methylpiperidine**



DIAD (837µL, 4.25mmol) was added to a solution of 3-methyl-4-nitro-1H-pyrazole (500mg, 3.54mmol), *N*-methyl-4-piperidinol (408mg, 3.54mmol) and triphenylphosphine (860mg, 4.25mmol) in THF (25mL). The reaction mixture was stirred at rt for 5 days. The mixture was conc. *in vacuo* before purification by flash chromatography on silica, washing with DCM, then 30%, 70%, 100% EtOAc/DCM mixtures. The product was eluted with 5%, 10% then 20% MeOH/DCM to give the title compound as an off-white crystalline solid (289mg, 34%). LCMS (Method 1) Rt 2.721min, ESIMS *m/z* $[M+H]^+$ 239.3.

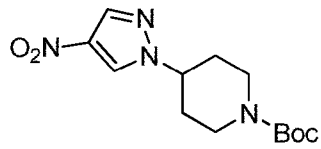
**Intermediate B4: 3,5-dimethyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazol-4-amine**



10% Palladium on activated carbon (28mg) was added to a solution of the **B3** (277mg, 1.16mmol) in EtOH (40mL) under a $N_2$ atmosphere. The mixture was evacuated and back-

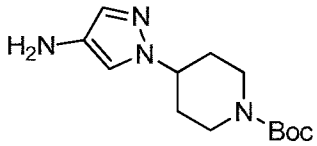
filled with $H_2$ (x3) and was left under an atmosphere of $H_2$, stirring at rt for 16h. A further portion of 10% palladium on carbon (100mg) was added and the reaction was allowed to stir for a further 4h at rt under an atmosphere of $H_2$. The reaction mixture was then filtered through Celite, rinsing with EtOAc before conc. *in vacuo* gave the title compound as a yellow, viscous oil (218mg, 90%) and no further purification was required. ESIMS *m/z* $[M+H]^+$ 209.3

**Intermediate B5: *tert*-butyl 4-(4-nitro-1*H*-pyrazol-1-yl)piperidine-1-carboxylate**



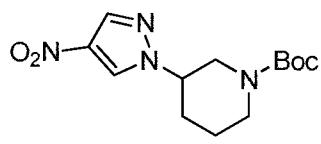
Added DIAD (1045 ul, 5.306 mmol) to a mixture of 4-nitro-1H-pyrazole (500 mg, 4.422 mmol), 1-BOC-4-hydroxypiperidine (890 mg, 4.422 mmol) and triphenylphosphine (1.392 g, 5.306 mmol) in THF (25 mL) and stirred at room temperature for 6 days. Added ethyl acetate (100mL) and washed with saturated sodium bicarbonate (50 mL), water (50 mL) and brine (50 mL). Dried the organic phase with magnesium sulfate, filtered and removed the solvent. Purified by flash chromatography on neutral alumni using dichloromethane/hexane (4/6) to give the titled compound (1.30 g, 99%). LCMS (Method 1) Rt 2.374 min.

**Intermediate B6: *tert*-butyl 4-(4-amino-1*H*-pyrazol-1-yl)piperidine-1-carboxylate**



Added 10% palladium on carbon (130 mg) to a solution of **B5** (1.31 g, 4.422) in ethanol (60 mL) and left under an atmosphere of hydrogen for 24 h. Filtered the reaction mixture through Celite washing with ethyl acetate and remove the solvent from the filtrate. Purified by flash chromatography using methanol/chloroform (4/96) to give the titled compound JAR-506-019-01 (843 mg, 72%). LCMS (Method 1) Rt 1.907 min, ESIMS *m/z* $[M+H]^+$ 267.3.

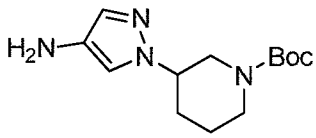
**Intermediate B7: *tert*-butyl 3-(4-nitro-1*H*-pyrazol-1-yl)piperidine-1-carboxylate**



Added DIAD (2090 ul, 10.613 mmol) to a mixture of 4-nitro-1H-pyrazole (1.000 g, 8.844 mmol), 1-BOC-3-hydroxypiperidine (1780 mg, 8.844 mmol) and triphenylphosphine (2.784 g,

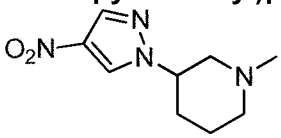
10.613 mmol) in THF (50 mL) and stirred at room temperature for 2 d. Added ethyl acetate (100mL) and washed with saturated sodium bicarbonate (50 mL), water (50 mL) and brine (50 mL). Dried the organic phase with magnesium sulfate, filtered and removed the solvent. Purified by flash chromatography on neutral alumni using dichloromethane/hexane (1/9) to give the titled compound (565 g, 22%). LCMS (Method 1) Rt 2.464 min.

**Intermediate B8: *tert*-butyl 3-(4-amino-1*H*-pyrazol-1-yl)piperidine-1-carboxylate**



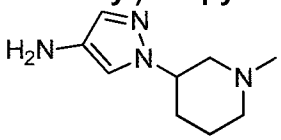
To a solution of **B7** (440 mg, 1.485) in ethanol (20 mL) was added 10% palladium on carbon (44 mg) and the reaction mixture was stirred under an atmosphere of hydrogen for 24 h. The reaction mixture was filtered washing with ethyl acetate and solvent was evaporated *in vacuo* from the filtrate to give the titled product (395 mg, quant.). LCMS (Method 1) Rt 1.875 min, ESIMS *m/z* $[M+H]^+$ 267.3.

**Intermediate B9: 1-methyl-3-(4-nitro-1*H*-pyrazol-1-yl)piperidine**



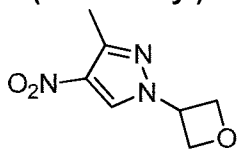
Added DIAD (1045 ul, 5.306 mmol) to a mixture of 4-nitro-1H-pyrazole (500 mg, 4.422 mmol), *N*-methyl-3-piperidinol (509 mg, 4.22 mmol) and triphenylphosphine (1.392 g, 5.306 mmol) in THF (25 mL) and stirred at room temperature for 5 d. Added ethyl acetate (100mL) and removed the solvent *in vacuo*. Purified by flash chromatography on neutral alumni using ethyl acetate/dichloromethane (2/8) to give the titled compound (502 mg, 54%). LCMS (Method 1) Rt 2.407 min.

**Intermediate B10: 1-(1-methylpiperidin-3-yl)-1*H*-pyrazol-4-amine**



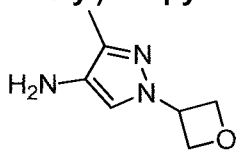
To a solution of **B9** (374 mg, 1.485) in ethanol (10 mL) was added 10% palladium on carbon (40 mg) and the reaction mixture was stirred under an atmosphere of hydrogen for 24 h. The reaction mixture was filtered washing with ethyl acetate and solvent was evaporated *in vacuo* from the filtrate to give the titled product (289 mg, 90%). LCMS (Method 1) Rt 4.144 min, ESIMS *m/z* $[M+H]^+$ 181.2.

**Intermediate B11: 3-methyl-4-nitro-1-(oxetan-3-yl)-1*H*-pyrazole**



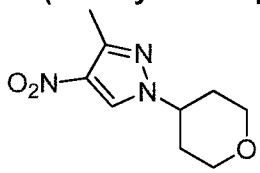
Added 3-bromooxetane (451 ul, 5.901 mmol) to a mixture of 3-methyl-4-nitro-1H-pyrazole (500 mg, 3.934 mmol) and cesium carbonate (2.564 g, 7.868 mmol) in DMF (5 mL) and stirred at 70 C for 6 d. Added ether (50mL) and filtered off the residues. Removed the solvent from the filtrate *in vacuo* and purified the residue by flash chromatography using dichloromethane/ethyl acetate (3/7) to give the titled compound (589 mg, 82%). LCMS (Method 1) Rt 1.865 min.

**Intermediate B12: 3-methyl-1-(oxetan-3-yl)-1*H*-pyrazol-4-amine**



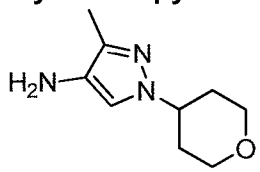
To a solution of **B11** (384 mg, 2.097) in ethanol (10 mL) was added 10% palladium on carbon (40 mg) and the reaction mixture was stirred under an atmosphere of hydrogen for 24 h. The reaction mixture was filtered washing with ethyl acetate and the solvent was evaporated *in vacuo* from the filtrate to give the titled product (298 mg, 90%). LCMS (Method 1) Rt 1.629 min.

**Intermediate B13: 3-methyl-4-nitro-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazole**



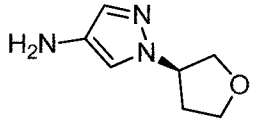
Added 3-bromotetrahydropuran (651 ul, 5.901 mmol) to a mixture of 3-methyl-4-nitro-1H-pyrazole (500 mg, 3.934 mmol) and cesium carbonate (2.564 g, 7.868 mmol) in DMF (5 mL) and stirred at 70 C for 6 d. Added ether (50mL) and filtered off the residues. Removed the solvent from the filtrate *in vacuo* and purified the residue by flash chromatography on neutral alumina using methanol/dichloromethane (1/99) to give the titled compound (334 mg, 40%). LCMS (Method 1) Rt 2.042 min.

**Intermediate B14: 3-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-amine**



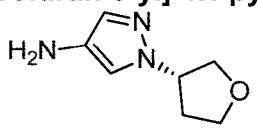
To a solution of **B13** (274 mg, 1.534) in ethanol (10 mL) was added 10% palladium on carbon (32 mg) and the reaction mixture was stirred under an atmosphere of hydrogen for 2 d. The reaction mixture was filtered washing with ethanol and the solvent was evaporated *in vacuo* from the filtrate to give the titled product (274 mg, 99%). LCMS (Method 1) Rt 1.648 min.

**Intermediate B15: 1-[(3*R*)-tetrahydrofuran-3-yl]-1*H*-pyrazol-4-amine**



A mixture of (S)-(+)-3-hydroxytetrahydrofuran (390 mg, 4.422 mmol), of 4-nitro-1H-pyrazole (500 mg, 4.422 mmol), triphenylphosphine (1.073 g, 5.306 mmol) and diisopropylcarbodimide (1.073 mg, 5.306 mmol) in THF (25 mL) was stirred for 5 d. Removed the solvent from the reaction mixture *in vacuo* and partially purified the residue by flash chromatography using ethyl acetate/dichloromethane (3/7) to give the nitro intermediate which was then stirred under an atmosphere of hydrogen in the presence of 10% palladium on carbon (100 mg) in ethanol (50 mL) for 24 h. The catalyst was removed by filtration and the solvent removed *in* vacuo. The residue was purified by flash chromatography using methanol/dichloromethane (4/96) to give the titled compound (580 mg, 86%). LCMS (Method 1) Rt 1.290 min, ESIMS *m/z* $[M+H]^+$ 154.1.

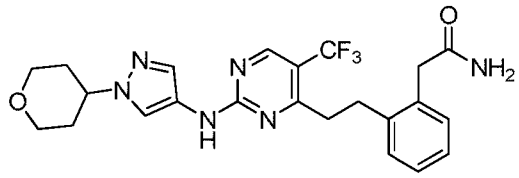
**Intermediate B16: 1-[(3*S*)-tetrahydrofuran-3-yl]-1*H*-pyrazol-4-amine**



A mixture of (R)-(-)-3-hydroxytetrahydrofuran (390 mg, 4.422 mmol), of 4-nitro-1H-pyrazole (500 mg, 4.422 mmol), triphenylphosphine (1.073 g, 5.306 mmol) and diisopropylcarbodimide (1.073 mg, 5.306 mmol) in THF (25 mL) was stirred for 5 d. Removed the solvent from the reaction mixture *in vacuo* and partially purified the residue by flash chromatography using ethyl acetate/dichloromethane (3/7) to give the nitro intermediate which was then stirred under an atmosphere of hydrogen in the presence of 10% palladium on carbon (100 mg) in ethanol (50 mL) for 24 h. The catalyst was removed by filtration and the solvent removed *in* vacuo. The residue was purified by flash chromatography using methanol/dichloromethane (4/96) to give the titled compound (540 mg, 80%). LCMS (Method 1) Rt 1.304 min, ESIMS *m/z* $[M+H]^+$ 154.1.

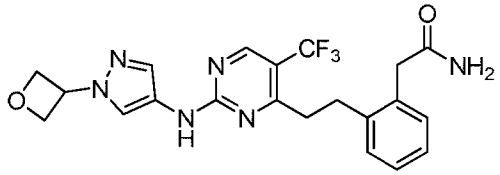
***Synthesis of Compounds of Formula (I)***

**Example C1: 2-(2-{2-[2-{[1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl)acetamide**



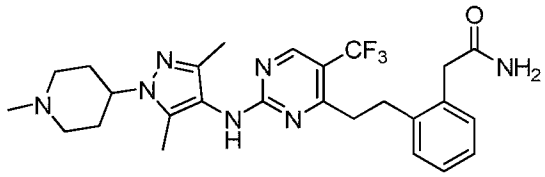
1-(Oxan-4-yl)-1H-pyrazol-4-amine (51mg, 0.303mmol) was added to a solution of **A7** (59mg, 0.151mmol) in dioxane (2mL). The reaction mixture was stirred at 70°C for 17h. The mixture was diluted with EtOAc (30mL) and was washed with sat aq $NaHCO_3$ (2 x 10mL) and brine (2 x 10mL) before drying over $MgSO_4$ and conc. *in vacuo*. The crude reaction mixture was purified by preparative TLC on silica, eluting with 5% MeOH/10% $iPr_2O/CH_2Cl_2$ to give the title compound as a white solid (19mg, 26%). $^1$H NMR (500MHz, $CDCl_3$ + 1 drop DMSO-$d_6$) 8.52-8.50 (1H, m), 8.31-8.11 (1H, m), 7.97-7.92 (1H, m), 7.62 (1H, s), 7.27-7.20 (4H, m), 5.83-5.65 (2H, m), 4.40-4-27 (1H, m), 4.18-4.08 (2H, m), 3.76-3.62 (2H, m), 3.61-3.48 (2H, m), 3.18-3.04 (3H, m), 2.15-2.03 (5H, m). LCMS (Method 1) Rt 1.883min. ESIMS *m/z* $[M+H]^+$ 475.2.

**Example C2: 2-(2-{2-[2-{[1-(oxetan-3-yl)-1*H*-pyrazol-4-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl)acetamide**



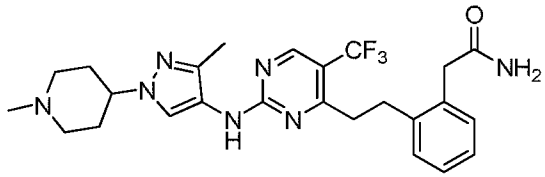
1-(Oxetan-3-yl)-1H-pyrazol-4-amine (60mg, 0.433mmol) was added to a solution of **A7** (84mg, 0.217mmol) in dioxane (2mL). The reaction mixture was stirred at 70°C for 20h. The reaction mixture was cooled to rt, with DCM and was dry-loaded onto silica before purification by flash chromatography on silica, eluting with 50% EtOAc/DCM, EtOAc, 5% MeOH/5% $iPr_2O$/DCM then 10% MeOH/10% $iPr_2O$/DCM to give the title compound as a white solid (65mg, 67%). $^1$NMR (500MHz, $CDCl_3$ + 1 drop DMSO-$d_6$) 8.54-8.50 (1H, m), 8.14 (1H, s), 7.79-7.72 (1H, m), 7.65 (1H, br s), 7.29-7.20 (4H, m), 5.70-5.42 (3H, m), 5.12-5.02 (4H, m), 3.74-3.71 (2H, m), 3.11-3.08 (4H, m). LCMS (Method 1) Rt 1.833min. ESIMS *m/z* $[M+H]^+$ 447.3.

**Example C3: 2-(2-{2-[2-{[3,5-Dimethyl-1-(1-methylpiperidin-4-yl)-1*H*-pyrazol-4-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl)acetamide**



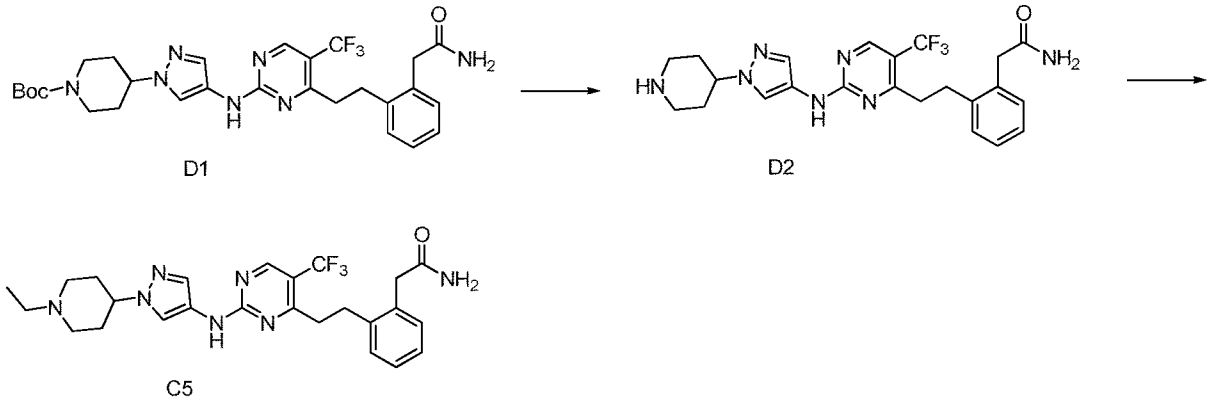
Intermediate **B4** (61mg, 0.293mmol) was added to a solution of **A7** (57mg, 0.146mmol) in dioxane (2mL). The reaction mixture was stirred at 70°C for 3 days. The reaction mixture was cooled to rt, diluted with DCM and was dry-loaded onto silica before purification by flash chromatography on silica, eluting with 50% EtOAc/DCM, then 10% MeOH/DCM then 10%MeOH/DCM + 1% $NEt_3$. The product was further purified by preparative TLC on deactivated silica, eluting with 4% MeOH/DCM to give the title compound as a colourless oil (2mg, 3%).

**Example C4: 2-(2-{2-[2-{[3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl)acetamide**



**B2** (100 mg, 0.52 mmol) was added to a solution of **A7** (100 mg, 0.260 mmol) in dioxane (5mL). The reaction mixture was stirred at 70°C for 5h. The reaction mixture was cooled to rt and was diluted with DCM and washed with sodium bicarbonate solution (aq.), dried over MgSO4 and filtered. The crude was purified by silica gel column, eluting with 2/8/40/50 NEt3/MeOH/EtOAC/DCM mixture to give the title compound as off-white solid (32mg, 14%). $^1$H NMR (500MHz, $CDCl_3$) 8.44-8.42 (m, 1H), 7.90 (s, 1H), 7.61 (bs, 1H), 7.32-6.98 (m, 4H), 5.67-5.44 (bm, 2H), 4.05-3.94 (m, 1H), 3.75-3.56 (m, 2H), 3.09-2.93 (m, 5H), 2.37-1.88 (m, 13H) . LCMS (Method 1) Rt 2.8 min. ESIMS *m/z* $[M+H]^+$ 502.3.

**Example C5: 2-(2-{2-[2-{[1-(1-ethylpiperidin-4-yl)-1*H*-pyrazol-4-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl)acetamide**



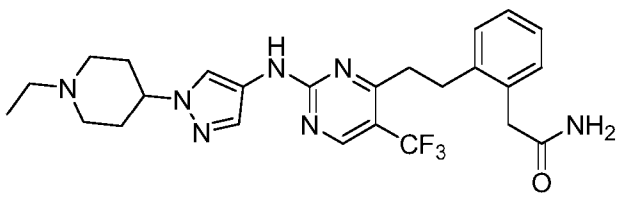

**D1: *tert*-butyl 4-(4-{[4-{2-[2-(2-amino-2-oxoethyl)phenyl]ethyl}-5-(trifluoromethyl)pyrimidin-2-yl]amino}-1*H*-pyrazol-1-yl)piperidine-1-carboxylate**

A solution of **A7** (250 mg, 0.645 mmol) and **B6** (258 mg, 0.968 mmol) in dioxane (5 mL) was heated at 50°C for 5 d. Added ethyl acetate and removed the solvent from the reaction mixture. Purification by flash chromatography using tetrahydrofuran/dichloromethane (3/7) gave the title compound (323 mg, 87%). $^1$H NMR (500MHz, $CDCl_3$) 8.51 (s, 1H), 7.90 (s, 1H), 7.75 (bs, 1H), 7.57 (s, 1H), 7.26 (m, 4H), 5.57-5.51 (bm, 2H), 4.27-4.24 (m, 3H), 3.71 (m, 2H), 3.09 (m, 4H), 2.89 (m, 2H), 2.14-1.90 (m, 4H), 1.47 (s, 9H). LCMS (Method 1) Rt 2.283 min, ESIMS *mz* [M+H]+ 574.2.

**D2: 2-(2-{2-[2-{[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl)acetamide**

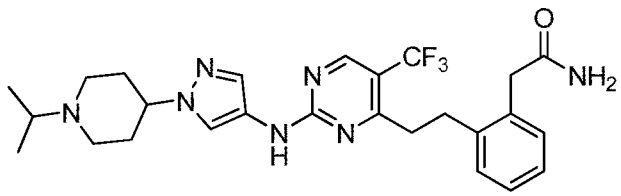
To a solution of **D1** (260 mg, 0.453 mmol) in dioxane (5 mL) was added 4M hydrogen chloride in dioxane (4 mL, 16 mmol) and the resulting solution was stirred at room temperature for 1 h. The solvent was removed and the residue filtered through a short plug of amino bonded silica eluting with methanol/chloroform (1/9) to give the title compound (204 mg, 95%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.17 (s, 1H), 8.62 (m, 1H), 7.98 (m, 1H), 7.58-7.46 (m, 2H), 7.27-6.93 (m, 5H), 4.15 (m, 1H), 3.72 (m, 1H), 3.48(m, 2H), 3.12 (m, 5H), 2.64 (m, 2H), 1.79 (m, 5H). LCMS (Method 1) Rt 2.741 min, ESIMS *m/z* [M+H]+ 474.2.

**Example C5: 2-(2-{2-[2-{[1-(1-ethylpiperidin-4-yl)-1*H*-pyrazol-4-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl)acetamide**



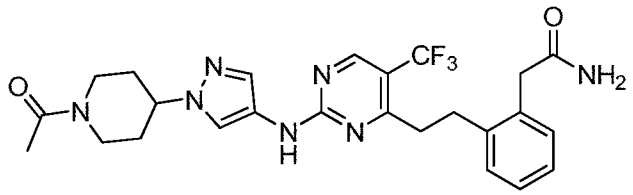
To a solution of **D2** (40 mg, 0.085 mmol) and acetaldehyde (24 uL, 0.422 mmol) in methanol (2 mL) was added sodium triacetoxyborohydride (89 mg, 0.422 mmol) and the resulting solution was stirred for 18 h. The solvent was removed and the residue filtered through a plug of amino bonded silica eluting with methanol/chloroform (1/9). The solvent was removed from the filtrate and the residue purified by PTLC using methanol/chloroform (1/9) to give the title compound (13 mg, 30%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.11 (s, 1H), 8.59 (m, 1H), 7.98 (m, 1H), 7.55 (m, 1H), 7.41 (s, 1H), 7.24-7.15 (bm, 4H), 6.92 (m, 1H), 4.09 (m, 1H), 3.48 (m, 2H), 3.12-2.94 (m, 6H), 2.36 (m, 2H), 2.05-1.89 (m, 6H), 1.00 (m, 3H). LCMS (Method 1) Rt 2.903 min, ESIMS *m/z* [M+H]+ 502.2.

**Example C6: 2-(2-{2-[2-({1-[1-(propan-2-yl)piperidin-4-yl]-1*H*-pyrazol-4-yl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl)acetamide**



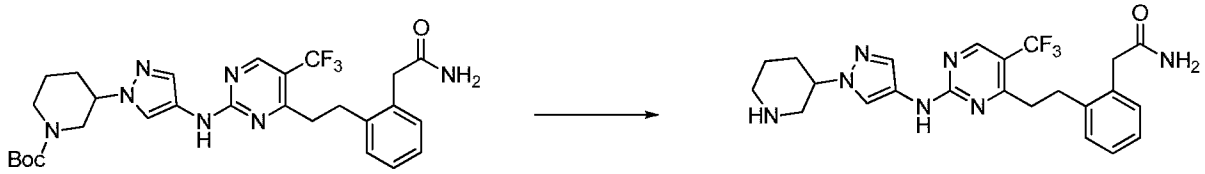
To a solution of **D2** (40 mg, 0.085 mmol) and cesium carbonate (137 mg, 0.422 mmol) in DMF (2 mL) was added 2-iodopropane (42 uL, 0.422 mmol) and the reaction mixture stirred at room temperature for 24 h. The solvent was removed and the crude passed through a short plug of amino bonded silica eluting with methanol/chloroform (1/9). The residue was purified by PTLC with methanol/chloroform (1/9) to give the titled product (14 mg, 33%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.12 (s, 1H), 8.59 (m, 1H), 7.98 (s, 1H), 7.55 (m, 1H), 7.42 (m, 1H), 7.24-7.15 (bm, 4H), 6.88 (m, 1H), 4.04 (m, 2H), 3.48 (m, 2H), 3.14-2.95 (m, 6H), 2.36 (m, 2H), 2.00-1.71 (m, 4H), 1.76 (m, 6H). LCMS (Method 1) Rt 2.805 min, ESIMS *m/z* [M+H]+ 516.3.

**Example C7: 2-(2-{2-[2-{[1-(1-acetylpiperidin-4-yl)-1*H*-pyrazol-4-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl)acetamide**



Acetyl chloride (6 uL, 0.084 mmol) was added to a solution of **D2** (20 mg, 0.042 mmol) and triethylamine (23 uL, 0.168 mmol) in DCM (2 mL) and the resulting reaction mixture was stirred at room temperature for 2 h. The solvent was removed and the residue filtered through a short plug of amino bonded silica eluting with methanol/chloroform (1/9). The

solvent was removed from the filtrate and the residue purified by PTLC using methanol/chloroform (1/9) to give the titled product (16mg, 74%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.13 (s, 1H), 8.59 (m, 1H), 7.99 (s, 1H), 7.55 (m, 1H), 7.42 (brm, 1H), 7.25-7.15 (bm, 4H), 6.88 (m, 1H), 4.45-4.36 (m, 2H), 3.88 (m, 1H), 3.48 (m, 2H), 3.20-2.68 (m, 6H), 2.02-1.67 (m, 7H). LCMS (Method 1) Rt 1.955 min, ESIMS *m/z* [M+H]+ 516.1.



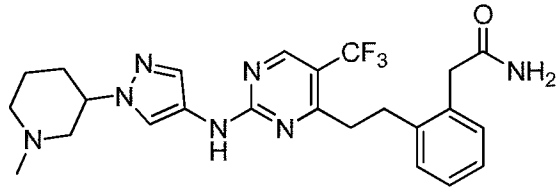

**D3: *tert*-butyl 3-(4-{[4-{2-[2-(2-amino-2-oxoethyl)phenyl]ethyl}-5-(trifluoromethyl)pyrimidin-2-yl]amino}-1*H*-pyrazol-1-yl)piperidine-1-carboxylate**

A solution of **A7** (385 mg, 0.990 mmol) and **B8** (395 mg, 1.485 mmol) in dioxane (5 mL) was heated at 70°C for 24 h. Ethyl acetate was added and the solvent removed from the reaction mixture. Purified by flash chromatography using tetrahydrofuran/dichloromethane (3/7) gave the titled product (460 mg, 81%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.14 (s, 1H), 8.59 (m, 1H), 7.99 (m, 1H), 7.60 (s, 1H), 7.40 (s, 1H), 7.23-7.15 (m, 4H), 6.89-6.83 (m, 1H), 4.15 (m, 1H), 3.77 (m, 2H), 3.46 (m, 2H), 3.12-2.84 (m, 5H), 2.07-1.65 (m, 5H), 1.38 (s, 9H). LCMS (Method 1) Rt 2.391 min, ESIMS *mz* [M+H]+ 574.2.

**D4: 2-(2-{2-[2-{[1-(piperidin-3-yl)-1*H*-pyrazol-4-yl]amino}-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl)acetamide**

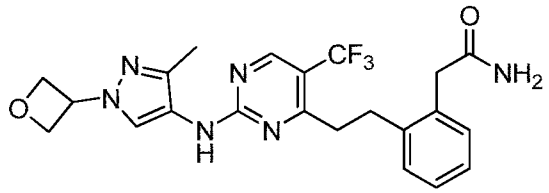
A solution of **D3** (13 mg, 0.024 mmol) and 4M hydrogen chloride in dioxane (1 mL, 4 mmol) was stirred at room temperature for 1 h. The solvent was removed and the residue filtered through an SPE-amino cartridge eluting with methanol. The solvent was removed from the filtrate to give the titled product (11 mg, 97%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.15 (s, 1H), 8.61 (m, 1H), 8.01 (m, 1H), 7.56 (s, 1H), 7.47 (m, 1H), 7.25-7.18 (bm, 4H), 6.93 (m, 1H), 4.11 (m, 1H), 3.71 (br m, 1H), 3.46 (m, 2H), 3.17-2.68 (m, 6H), 2.44 (m, 1H), 2.08-1.43 (m, 6H). LCMS (Method 1) Rt 2.871 min, ESIMS *m/z* [M+H]+ 474.2.

**Example C8: 2-(2-(2-(2-(1-(1-methylpiperidin-3-yl)-1H-pyrazol-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide**



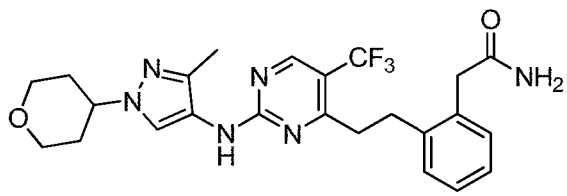
**B10** (38 mg, 0.208 mmol) was added to a solution of **A7** (50 mg, 0.104 mmol) in dioxane (5mL). The reaction mixture was stirred at 70°C for 4 d. The reaction mixture was cooled to rt and the solvent removed *in* vacuo. The crude was purified by PTLC, eluting with methanol/chloroform (1/9) to give the title compound (18 mg, 36%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.13 (s, 1H), 8.60 (m, 1H), 8.01 (m, 1H), 7.56-6.90 (bm, 7H), 4.12 (m, 2H), 3.47 (s, 2H), 3.03 (m, 5H), 2.18-1.53 (m, 9H). LCMS (Method 1) Rt 3.091 min, ESIMS *m/z* [M+H]+ 488.3.

**Example C9: 2-(2-(2-(2-(3-methyl-1-(oxetan-3-yl)-1H-pyrazol-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide**



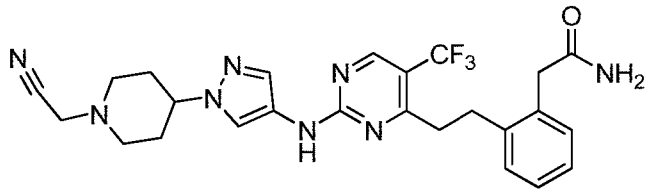
**B12** (32 mg, 0.208 mmol) was added to a solution of **A7** (50 mg, 0.104 mmol) in dioxane (2mL). The reaction mixture was stirred at 45 °C for 5 d. The reaction mixture was cooled, the solvent removed *in vacuo* and the residue purified by flash chromatography eluting with methanol/chloroform (4/96) to give the title compound (42 mg, 88%). $^1$H NMR (500MHz, DMSO-$d_6$) 9.55 (m, 1H), 8.57 (m, 1H), 7.98 (m, 1H), 7.40-6.91 (bm, 6H), 5.47 (m, 1H), 4.83 (m, 4H), 3.46 (s, 2H), 3.07-2.96 (m, 4H), 2.23 (s, 3H). LCMS (Method 1) Rt 1.927 min, ESIMS *m/z* [M+H]+ 461.1.

**Example C10: 2-(2-(2-(2-(3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide**



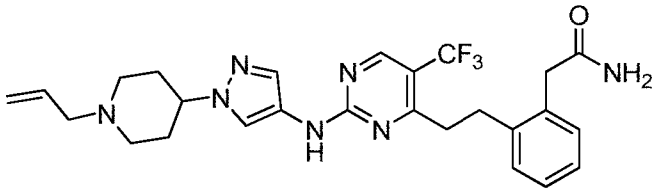
**B14** (38 mg, 0.208 mmol) was added to a solution of **A7** (50 mg, 0.104 mmol) in dioxane (2mL). The reaction mixture was heated in a microwave at 100 °C for 1 h. The reaction mixture was cooled, the solvent removed *in vacuo* and the residue purified by PTLC eluting with THF/DCM (4/6) to give the title compound (26 mg, 51%). $^1$H NMR (500MHz, DMSO-$d_6$) 9.45 (m, 1H), 8.55 (m, 1H), 7.90 (m, 1H), 7.41-6.90 (m, 6H), 4.25 (m, 1H), 3.92 (m, 2H), 3.43 (m, 4H), 3.07-2.96 (m, 4H), 2.22-1.77 (s, 7H). LCMS (Method 1) Rt 1.880 min, ESIMS *m/z* [M+H]+ 489.2.

**Example C11: 2-(2-(2-(2-(1-(1-(cyanomethyl)piperidin-4-yl)-1H-pyrazol-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide**



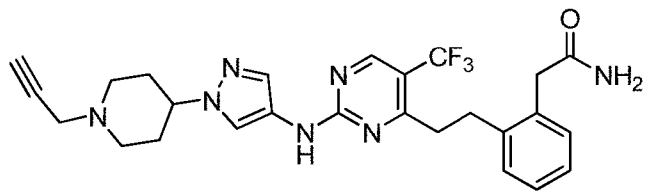
Bromoacetonitrile (3.2 uL, 0.047 mmol), **D2** (20 mg, 0.042 mmol) and potassium carbonate (12 mg, 0.084 mmol) in DMF (2mL) were stirred at 40°C for 24 h. Ethyl acetate was added to the reaction mixture and the solids filtered off. The solvent was removed from the filtrate *in vacuo* and the residue purified by PTLC using methanol/chloroform (4/96) to give the titled compound (11 mg, 51%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.12 (s, 1H), 8.59 (m, 1H), 7.97 (s, 1H), 7.58 (s, 1H), 7.41 (s, 1H), 7.20 (m, 4H), 6.87 (m, 1H), 4.13 (m, 1H), 3.74 (s, 2H), 3.47 (s, 2H), 3.12-2.86 (m, 6H), 2.33 (m, 2H), 1.97 (m, 4H). LCMS (Method 1) Rt 1.845 min, ESIMS *m/z* [M+H]+ 513.2.

**Example C12: 2-(2-(2-(2-(1-(1-allylpiperidin-4-yl)-1H-pyrazol-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide**



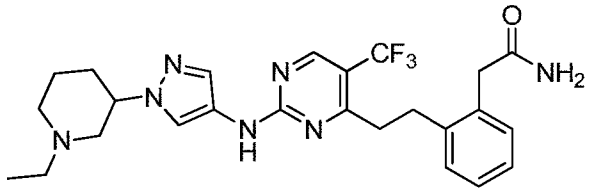
Allylbromide (4.1 uL, 0.047 mmol), **D2** (20 mg, 0.042 mmol) and potassium carbonate (12 mg, 0.084 mmol) in DMF (2mL) was stirred at 40°C for 24 h. Ethyl acetate was added to the reaction mixture and the solids filtered off. The solvent was removed from the filtrate *in vacuo* and the residue purified by PTLC using methanol/chloroform (1/9) to give the titled compound (6 mg, 28%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.12 (s, 1H), 8.59 (m, 1H), 7.97 (s, 1H), 7.55 (s, 1H), 7.41 (s, 1H), 7.20 (m, 4H), 6.91 (m, 1H), 5.81 (m, 1H), 5.14 (m, 2H), 4.09 (m, 1H), 3.47-2.87 (m, 10H), 2.07 (m, 2H), 1.94 (m, 4H). LCMS (Method 1) Rt 2.920 min, ESIMS *m/z* [M+H]+ 514.2.

**Example C13: 2-(2-(2-(2-(1-(1-(prop-2-ynyl)piperidin-4-yl)-1H-pyrazol-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide**



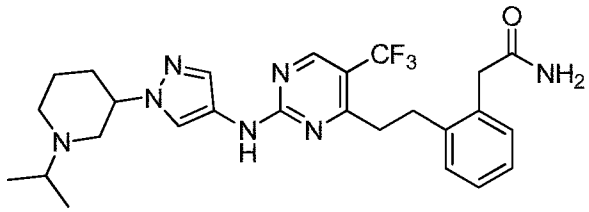
Propargylbromide (4.5 uL, 0.047 mmol), **D2** (20 mg, 0.042 mmol) and potassium carbonate (12 mg, 0.084 mmol) in DMF (2mL) were stirred at 40°C for 24 h. Ethyl acetate was added to the reaction mixture and the solids filtered off. The solvent was removed from the filtrate *in vacuo* and the residue purified by PTLC using methanol/chloroform (1/9) to give the titled compound (6 mg, 28%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.11 (s, 1H), 8.59 (m, 1H), 7.98 (s, 1H), 7.56 (s, 1H), 7.40 (s, 1H), 7.20 (m, 4H), 6.88 (m, 1H), 4.07 (m, 1H), 3.47 (s, 2H), 3.29 (s, 2H), 3.15-2.85 (m, 7H), 2.27 (m, 2H), 1.92 (m, 4H). LCMS (Method 1) Rt 1.966 min, ESIMS *m/z* [M+H]+ 512.2.

**Example C14: 2-(2-(2-(2-(1-(1-ethylpiperidin-3-yl)-1H-pyrazol-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide**



To a solution of **D4** (40 mg, 0.085 mmol) and acetaldehyde (24 uL, 0.422 mmol) in methanol (2 mL) was added sodium triacetoxyborohydride (89 mg, 0.422 mmol) and the resulting solution was stirred for 24 h. The solvent was removed and the residue filtered through a plug of amino bonded silica eluting with methanol/chloroform (1/9). The solvent was removed from the filtrate and the residue purified by PTLC using methanol/chloroform (1/9) to give the title compound (20 mg, 47%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.11 (s, 1H), 8.59 (m, 1H), 8.03 (m, 1H), 7.56 (s, 1H), 7.40 (s, 1H), 7.24-7.16 (bm, 4H), 6.86 (m, 1H), 4.23 (br s, 1H), 3.47 (m, 2H), 3.13-2.76 (m, 6H), 2.35-2.24 (m, 3H), 1.97 (m, 2H), 1.72 (m, 2H), 1.56 (m, 1H), 0.97 (m, 3H). LCMS (Method 1) Rt 2.018 min, ESIMS *m/z* [M+H]+ 502.2.

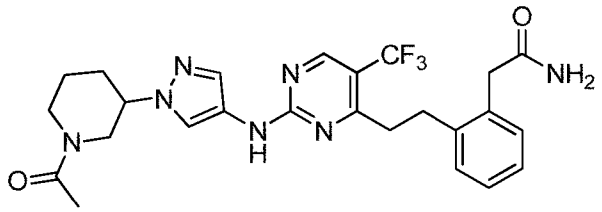
**Example C15: 2-(2-(2-(2-(1-(1-isopropylpiperidin-3-yl)-1H-pyrazol-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide**



To a solution of **D4** (40 mg, 0.085 mmol) and potassium carbonate (12 mg, 0.085 mmol) in DMF (2 mL) was added 2-iodopropane (14 uL, 0.140 mmol) and the reaction mixture stirred at room temperature for 24 h. The solvent was removed and the crude passed through a short plug of amino bonded silica eluting with methanol/chloroform (1/9). The residue was purified by PTLC with methanol/chloroform (1/9) to give the titled product (11 mg, 25%). $^1$H

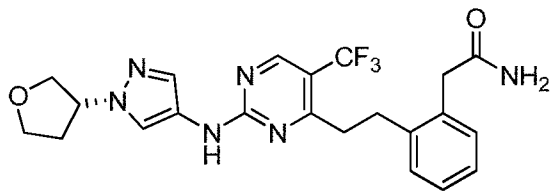
NMR (500MHz, DMSO-$d_6$) 10.12 (s, 1H), 8.59 (m, 1H), 8.04 (s, 1H), 7.57 (s, 1H), 7.41 (s, 1H), 7.24-7.14 (m, 4H), 6.88 (m, 1H), 4.32 (m, 1H), 3.47 (s, 2H), 3.13-2.72 (m, 6H), 2.41-1.55 (m, 6H), 0.97 (m, 7H). LCMS (Method 1) Rt 2.508 min, ESIMS *m/z* [M+H]+ 516.3.

**Example C16: 2-(2-(2-(1-(1-acetylpiperidin-3-yl)-1H-pyrazol-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide**



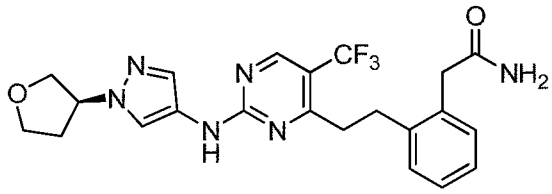
Acetyl chloride (12 uL, 0.170 mmol) was added to a solution of **D4** (40 mg, 0.085 mmol) and triethylamine (47 uL, 0.340 mmol) in DCM (2 mL) and the resulting reaction mixture was stirred at room temperature for 18 h. The solvent was removed and the residue filtered through a short plug of amino bonded silica eluting with methanol/chloroform (1/9). The solvent was removed from the filtrate and the residue purified by PTLC using methanol/chloroform (1/9) to give the titled product (28 mg, 64%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.15 (m, 1H), 8.60 (m, 1H), 8.02 (m, 1H), 7.61 (m, 1H), 7.40 (s, 1H), 7.23-7.15 (m, 4H), 6.87 (m, 1H), 4.50-4.29 (m, 1H), 4.10 (s, 1H), 3.93-3.74 (m, 1H), 3.48-2.77 (m, 8H), 2.08-1.94 (m, 5H), 1.76 (m,1H), 1.57-1.44 (m, 1H). LCMS (Method 1) Rt 1.840 min, ESIMS *m/z* [M+H]+ 516.2.

**Example C17: (R)-2-(2-(2-(1-(tetrahydrofuran-3-yl)-1H-pyrazol-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide**



A solution of **B15** (100 mg, 0.653 mmol) and **A7** (253 mg, 0.653 mmol) in dioxane (5 mL) was stirred at 40°C for 7 d. The solvent was removed from the mixture and the residue filtered through a plug of amino bonded silica eluting with methanol/chloroform (1/9). The product was purified by flash chromatography eluting with tetrahydrofuran/dichloromethane (3/7) to give the title compound (190 mg, 63%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.15 (s, 1H), 8.60 (m, 1H), 8.00 (m, 1H), 7.58 (s, 1H), 7.40 (s, 1H), 7.23-7.14 (m, 4H), 6.89 (s, 1H), 4.99 (m, 1H), 3.95 (m, 2H), 3.85 (m, 1H), 3.78 (m, 1H), 3.48 (s, 2H), 3.13-2.97 (m, 4H), 2.34 (m, 1H), 2.20 (m, 1H). LCMS (Method 1) Rt 1.964 min. ESIMS *m/z* $[M+H]^+$ 461.2.

**Example C18: (S)-2-(2-(2-(2-(1-(tetrahydrofuran-3-yl)-1H-pyrazol-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide**



A solution of **B16** (100 mg, 0.653 mmol) and **A7** (253 mg, 0.653 mmol) in dioxane (5 mL) was stirred at 40 °C for 7 d. The solvent was removed from the mixture and the residue filtered through a plug of amino bonded silica eluting with methanol/chloroform (1/9). The product was purified by flash chromatography eluting with tetrahydrofuran/dichloromethane (4/6) to give the title compound (206 mg, 69%). $^1$H NMR (500MHz, DMSO-$d_6$) 10.15 (s, 1H), 8.60 (m, 1H), 8.00 (m, 1H), 7.58 (s, 1H), 7.40 (s, 1H), 7.23-7.14 (m, 4H), 6.89 (s, 1H), 4.99 (m, 1H), 3.95 (m, 2H), 3.85 (m, 1H), 3.78 (m, 1H), 3.48 (s, 2H), 3.13-2.97 (m, 4H), 2.34 (m, 1H), 2.20 (m, 1H). LCMS (Method 1) Rt 1.972 min. ESIMS *m/z* $[M+H]^+$ 461.2.

**Biological Assays**

The activity of compounds of the invention can be profiled using the following assays.

*P1: Quantification of FAK phosphorylation inhibition by cellular assay*

The human Phospho-FAK (y397) DuoSet IC ELISA (R& D Systems ) is used to determine the inhibition of phosphorylation of FAK in MDA-MB-231 breast cancer cells after exposure to the FAK inhibitor compound of interest.

Briefly, cells are exposed to a 9 point dilution series of FAK inhibitor for 1 hour in normal cellular conditions. Cellular proteins are then lysed and collected in the presence of protease and phosphatase inhibitors and used for analysis. After total FAK protein is captured on the test plate, a detection antibody specific to FAK phosphorylated at the Tyr397 position is used. The presence of the secondary protein is then quantitated using a substrate specific to the Streptavidin-HRP tag associated with the antibody. The lysates are tested in triplicate wells of a 384 well plate generally with an n=3.

*P2: Aldefluor/cancer stem cell screening assay*

The Aldefluor assay kit (Stem Cell Technologies) is used to determine the expression of Aldehyde Dehydrogenase (ALDH) in MBA-MB-231 breast cancer cells after exposure to the FAK inhibitor compound of interest. Briefly, cells are treated in monolayer culture for 4 days

with nanomolar to micromolar concentration range. Cells are removed from the plate with trypsin and stained with 7-amino-actinomycin D (cell viability marker) and the Aldefluor reagent according to the manufacturer's protocol. Flow cytometry is then utilized to determine the percentage of viable cells that are positive for ALDH. The treatment is performed in 6 well plates, with one technical replicate per experiment, and generally n=2 or 3.

*P3: Subcutaneous tumor growth inhibition models*

Female Balb/c nude mice at 6 to 8 weeks old are subcutaneously inoculated with human cancer cell lines derived from patient derived xenografts or cell lines. Tumors are grown to an average size (150mm3) and randomized into groups before commencing treatment as described for each study. Tumor measurements are taken with digital calipers and tumor volume calculated as volume (mm3) = length (mm) x width (mm) x height (mm). Animal health is monitored daily, animal weight and tumor measurements taken 3 times per week. Animals are euthanized when tumor volume reaches ethical limits. Tumors will also be analyzed for cancer stem cell content and FAK phosphorylation inhibition in treated versus untreated groups

Compounds of the formula 1, including C3, C4, C5, C6, C7, C10 show activity against FAK in assay P1 with $IC_{50}$<5 μM.

*P4. VEGFR3 Phospho ELISA assay*

Compounds of the invention may be tested for *in vitro* activity in the following assay:

Adult human dermal lymphatic microvascular endothelial cells (HMVEC-dLyAD) (Cat# CC-2810, Lonza) were seeded into clear-bottom, TC treated 12 well plates (Cat # 665180, Greiner Bio-One) in EGM-2MV (Cat# CC-3202, Lonza) at 180,000 cells/well (volume 1 mL), and the plates incubated at 37 °C and 5% $CO_2$ for 6 hours. The media was replaced with EBM-2 (Cat # CC-3156, Lonza) + 0.1% BSA (Cat# A8412, Sigma) and cells incubated for a further period (overnight at 37 °C and 5% $CO_2$).

96 well Maxisorp immuno plates (Cat # 439454, Nunc) were coated with 100 μL of Total VEGFR3 capture antibody (Part # 841888, Human Total VEGFR3/FLT4 ELISA Kit, Cat # DYC3491, R&D Systems), or Phospho VEGFR3 Capture antibody (Part # 841885, Human

Phospho VEGFR3/FLT4 ELISA Kit, Cat# DYC2724, R&D Systems). The plates were covered and incubated at room temperature overnight.
The coating antibody was flicked out and the plates washed three times with Wash Buffer (Phosphate buffered saline (137 mM NaCl, 2.7 nM KCl, 8.1 nM $Na_2HPO_4$, 1.5 mL $KH_2PO_4$, pH 7.2-7.4), 0.05% Tween 20). 300 µL of blocking buffer (5% v/v Tween 20, 5% w/v sucrose in PBS) was then added to wells and plate incubated for 2 hours at room temperature. Blocking solution is flicked out and plates washed three times and tapped dry.

Compound dilution series were prepared in EBM-2 (Cat # CC-3156, Lonza) + 0.1% BSA (Cat# A8412, Sigma) with constant 0.1% DMSO concentration. 439 µL of sample or vehicle control was added to the cell monolayers. Cells are treated for 1 hour at 37 °C and 5% $CO_2$. 250 ng/mL Recombinant human VEGFC (Cat # 2179-VC, R & D Systems) added to wells and plates incubated for an additional 10 minutes at 37 °C and 5% $CO_2$.

The media and compounds were removed and the cell monolayer washed once in Dulbecco's Phosphate Buffered Saline (Cat # 21600-044, Invitrogen). 130 µL of Lysis buffer added to wells and cell lysate harvested and transferred to tubes and stored on ice. Complete lysis buffer was prepared by adding 10 µL Protease Inhibitor Cocktail (Cat # P8340, Sigma-Aldrich), 10 µL PMSF (Phenylmethanesulfonyl fluoride, Cat # P7626, Sigma-Aldrich, prepared as 500mM DMSO stock), 5uL Phosphatase Inhibitor Cocktail (100x) (Cat # 5870 Cell Signaling) per 1 mL of PathScan Sandwich ELISA Lysis Buffer (1X) (Cat # 7018 Cell Signaling) .

The harvested samples were then diluted 1:2 in IC Diluent #18 (5% Tween 20/PBS) and 100µL transferred to the Total and Phospho VEGFR3 coated, blocked and washed 96 well plates and incubated for 2 hours at room temperature. The plates were then washed three times in wash buffer as described above and tapped dry.
For detection of Total VEGFR3 100 µL of Detection antibody (Total VEGFR3 Detection Antibody Part# 841888 in Total VEGFR3 kit) diluted in IC Diluent #1 (1% w/v BSA (Cat # A7906, Sigma-Aldrich)/PBS) was added to wells and the plate incubated for 2 hours at room temperature. The plate was then washed three times in wash buffer and tapped dry. 100 µL of streptavidin-HPR diluted in IC diluent #1 Streptavidin-HRP, Part # 890803 in Total VEGFR3 kit) was added to wells and incubated at room temperature for 20 minutes followed by washing as described above.100 µL Substrate solution (3,3',5,5'-Tetramethylbenzidine (TMB) Liquid Substrate System for ELISA, Cat # T0440, Sigma-Aldrich) was added and the

plate incubated for 20 minutes in the dark at room temperature followed by the addition of 50 µL stop solution (2 M $H_2SO_4$).

Total VEGFR3 levels were quantified using a Multiskan Ascent plate reader and Ascent software fitted with 450 nm filter.

For detection of Phospho VEGFR3, 100 µL of Detection antibody (Anti-Phospho-Tyrosine-HRP Detection Antibody, Part # 841403 in Phospho VEGFR3 kit) was diluted in IC Diluent #1 (1% w/v BSA/PBS), added to the wells and the plate incubated for 2 hours at room temperature. The plate was then washed three times in wash buffer as described above and tapped dry. 100 µL Substrate solution (3,3',5,5'-Tetramethylbenzidine (TMB) Liquid Substrate System for ELISA, Cat # T0440, Sigma-Aldrich) was added and the plate incubated for 20 minutes in the dark at room temperature followed by the addition of 50 µL stop solution (2 M $H_2SO_4$).

Phospho VEGFR3 levels were quantified using a Multiscan ascent plate reader and ascent software fitted with 450 nm filter.

$IC_{50}$ values are determined by first calculating the level of phospho VEGFR3 relative to Total VEGFR3 according to the following formula:

$$SRP = \frac{SP}{ST}$$

Where SRP is the Sample Relative Phospho level, SP is Phospho VEGFR3 reading and ST is Total VEGFR3 reading.

Percent inhibition (%I) for each lysate relative to vehicle control (VEGFC stimulated) is then calculated according to the following formula:

$$\%I = \frac{SRP\ Vehicle - SRP\ Test}{SRP\ Vehicle} * 100$$

Where SRP is the Sample Relative Phospho level as calculated above.

%I is plotted against compound concentration and data fitted using a Sigmoidal dose response with IC50 determined from curve.

*VEGFR3 Phospho ELISA assay results*

| Compound | $IC_{50}$ (nM) |
|---|---|
| C1 | 11 |
| C2 | 40 |
| C4 | 126 |

| | |
|---|---|
| C5 | 21 |
| C6 | 15 |
| C7 | 31 |
| C9 | 217 |
| C10 | 144 |
| C11 | 30 |
| C12 | 18 |
| C13 | 9 |
| C14 | 64 |
| C15 | 47 |
| C16 | 21 |
| C17 | 42 |
| C18 | 44 |

*P5. VEGFR2 Phospho ELISA assay*

Compounds of the invention may be tested for *in vitro* activity in the following assay:

Adult human umbilical vein endothelial cells (HUVEC) (Cat# CC-2519, Lonza) were seeded into clear-bottom, TC treated 12 well plates (Cat # 665180, Greiner Bio-One) in EGM-2 (Cat# CC-3162, Lonza) at 180,000 cells/well (volume 1 mL), and the plates incubated at 37 °C and 5% $CO_2$ for 6 hours. The media was replaced with EBM-2 (Cat # CC-3156, Lonza) + 0.1% BSA (Cat# A8412, Sigma) and cells incubated for a further period (overnight at 37 °C and 5% $CO_2$).

96 well Maxisorp immuno plates (Cat # 439454, Nunc) were coated with 100 µL of Total VEGFR2 capture antibody (Part # 841434, Human Total VEGFR2/FLT4 ELISA Kit, Cat # DYC1780, R&D Systems), or Phospho VEGFR2 Capture antibody (Part # 841419, Human Phospho VEGFR2/FLT4 ELISA Kit, Cat# DYC1766, R&D Systems). The plates were covered and incubated at room temperature overnight.

The coating antibody was flicked out and the plates washed three times with Wash Buffer (Phosphate buffered saline (137 mM NaCl, 2.7 nM KCl, 8.1 nM $Na_2HPO_4$, 1.5 mL $KH_2PO_4$, pH 7.2-7.4), 0.05% Tween 20). 300 µL of Blocking buffer (1% v/v BSA (Cat# A8412, Sigma) in PBS) was then added to wells and plate incubated for 2 hours at room temperature. Blocking solution is flicked out and plates washed three times and tapped dry.

Compound dilution series were prepared in EBM-2 (Cat # CC-3156, Lonza) + 0.1% BSA (Cat# A8412, Sigma) with constant 0.1% DMSO concentration. 427.5 µL of sample or vehicle control was added to the cell monolayers. Cells are treated for 1 hour at 37 °C and 5% $CO_2$. 50 ng/mL Recombinant human VEGF (Cat # 293-VC, R & D Systems) added to wells and plates incubated for an additional 10 minutes at 37 °C and 5% $CO_2$.

The media and compounds were removed and the cell monolayer washed once in Dulbecco's Phosphate Buffered Saline (Cat # 21600-044, Invitrogen). 130 µL of Lysis buffer added to wells and cell lysate harvested and transferred to tubes and stored on ice. Complete lysis buffer was prepared by adding 10 µL Protease Inhibitor Cocktail (Cat # P8340, Sigma-Aldrich), 10 µL PMSF (Phenylmethanesulfonyl fluoride, Cat # P7626, Sigma-Aldrich, prepared as 500 mM DMSO stock), 5uL Phosphatase Inhibitor Cocktail (100x) (Cat # 5870 Cell Signaling) per 1 mL of PathScan Sandwich ELISA Lysis Buffer (1X) (Cat # 7018 Cell Signaling) ).

The harvested samples were then diluted 1:2 in IC Diluent #12 (1% NP-40, 20 nM Tris (pH 8.0), 137 mM NaCl, 10% glycerol, 2 mM EDTA, 1 mM activated sodium orthovanadate) and 100 µL transferred to the Total and Phospho VEGFR2 coated, blocked and washed 96 well plates and incubated for 2 hours at room temperature. The plates were then washed three times in wash buffer as described above and tapped dry.

For detection of Total VEGFR2 100 µL of Detection antibody (Total VEGFR2 Detection Antibody Part# 841435 in Total VEGFR2 kit) diluted in IC Diluent #14 (20 mM Tris, 137 mM $CaCl_2$, 0.05% Tween20, 0.1% BSA) was added to wells and the plate incubated for 2 hours at room temperature. The plate was then washed three times in wash buffer and tapped dry. 100 µL of streptavidin-HPR diluted in IC diluent #14 Streptavidin-HRP, Part # 890803 in Total VEGFR2 kit) was added to wells and incubated at room temperature for 20 minutes followed by washing as described above.100 µL Substrate solution (3,3',5,5'-Tetramethylbenzidine (TMB) Liquid Substrate System for ELISA, Cat # T0440, Sigma-Aldrich) was added and the plate incubated for 20 minutes in the dark at room temperature followed by the addition of 50 µL stop solution (2 M $H_2SO_4$).

Total VEGFR2 levels were quantified using a Multiskan Ascent plate reader and Ascent software fitted with 450 nm filter.

For detection of Phospho VEGFR2, 100 µL of Detection antibody (Anti-Phospho-Tyrosine-HRP Detection Antibody, Part # 841403 in Phospho VEGFR2 kit) was diluted in IC Diluent 14 (20 mM Tris, 137 mM $CaCl_2$, 0.05% Tween20, 0.1% BSA), was added to the wells and the plate incubated for 2 hours at room temperature. The plate was then washed three times in wash buffer as described above and tapped dry. 100 µL Substrate solution (3,3',5,5'-Tetramethylbenzidine (TMB) Liquid Substrate System for ELISA, Cat # T0440, Sigma-Aldrich) was added and the plate incubated for 20 minutes in the dark at room temperature followed by the addition of 50 µL stop solution (2 M $H_2SO_4$).

Phospho VEGFR2 levels were quantified using a Multiscan ascent plate reader and ascent software fitted with 450 nm filter.

$IC_{50}$ values are determined by first calculating the level of phospho VEGFR2 relative to Total VEGFR2 according to the following formula:

$$SRP = \frac{SP}{ST}$$

where SRP is the Sample Relative Phospho level, SP is Phospho VEGFR2 reading and ST is Total VEGFR2 reading.

Percent inhibition (%I) for each lysate relative to vehicle control (VEGF-A stimulated) is then calculated according to the following formula:

$$\%I = \frac{SRP\,Vehicle - SRP\,Test}{SRP\,Vehicle} * 100$$

where SRP is the Sample Relative Phospho level as calculated above.

%I is plotted against compound concentration and data fitted using a Sigmoidal dose response with $IC_{50}$ determined from plotted curve.

*VEGFR2 Phospho ELISA assay results*

| **Compound** | **$IC_{50}$ (nM)** |
|---|---|
| C1 | 2144 |
| C5 | 602 |
| C6 | 455 |
| C7 | 584 |
| C8 | 1210 |
| C11 | 1238 |
| C12 | 598 |
| C13 | 776 |

| | |
|---|---|
| C17 | 1728 |
| C18 | 1766 |

*P6. B16F10 Melanoma mouse model*

*In-life study*

Female BALB/c nu/nu mice at 6 to 8 weeks are inoculated with 4 x $10^5$ murine B16F10 melanoma cells (ATCC CRL-6475) in Matrigel® suspension sub-dermally in the ear. 24 hours following inoculation treatment commences via oral gavage twice daily for 14 days. Animals are monitored daily for health, weight changes and the appearance and number of satellite lesions tracking down the ear.

On day 15 mice are sacrificed and ears removed and fixed in 4% paraformaldehyde. Ears are washed twice in PBS prior to being photographed then stored in PBS for whole mount immunohistochemistry analysis. Draining lymph nodes (superficial cervicals) are removed, examined for the presence of metastatic lesions and photographed prior to freezing in OTC medium.

Primary lesion size is determined through measurement of length and width. Lesion volume is calculated using the following equation ($V=W \times L^2)/2$).

*Whole mount Immunohistochemistry for lymphatic and blood vessels*

Cartilage is removed from the edge of the paraformaldehyde fixed ear prior to the ear being separated into the dorsal (with primary lesion) and ventral sections. Dorsal ear sections are premeablised in 0.3% Triton-x100 in PBS for 1 hour at $4^0$C followed by blocking overnight at $4^0$C in 1% BSA/0.3% Triton-x100/PBS on rotating wheel.

Ears are then incubated for 24 hours in the primary antibody (Mouse LYVE-1 Biotinylated affinity 6402 purified pAB, R&D Systems, Cat # BAF2125 or Rat Anti-mouse CD31 (PECAM) Clone 390, eBioscience, Cat # 14-0311) at $4^0$C on rotating wheel followed by 6 x 1 hour washes in 0.3% Triton-x100/PBS at $4^0$C.

Ear are then incubated for 24 hours in the secondary detection reagent (Streptavidin Cy3 Conjugate, Sigma-Aldrich Cat # S-6402 or Alexa Fluor 488 Goat Anti-Rat IgI (H+L) Antibody, Invitrogen Molecular Probes Cat # A11006) at $4^0$C on rotating wheel followed by 6 x 1 hour washes in 0.3% Triton-x100/PBS at $4^0$C.

Ear sections are refixed in 4% paraformaldehyde for 20 minutes then washed twice in PBS prior to mounting in whole mount slide with Prolong Gold antifade reagent with Dapi (Invitrogen Molecular Probes Cat# P36935).

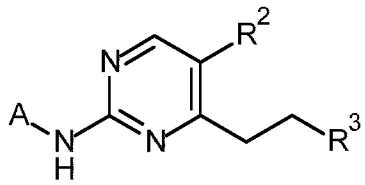
Representative images of ears are taken on a Olympus BX51 microscope with DP72 CCD camera and associated software.

*P7. Caki-1 Tumor model*

Female BALB/c nu/nu mice at 6 to 8 weeks injected subcutaneously (s.c.) with the human renal cancer cell line Caki-1 (ATCC HTB-46). Cells are resuspended in Dulbecco's PBS (Sigma-Aldrich) and $5 \times 10^6$ cells are injected s.c near the third mammary fat pad. Tumors are grown to an average size of 150 $mm^3$ prior to commencement of treatment. Treatment can consist of a repeat oral gavage at varying doses dose. Tumour growth and animal health is monitored over the course of the study. Tumor growth is represented as mean tumor volume in $mm^3$. Animals are euthanized and tumors excised for either histologic examination including development of lymphatic vessels and blood vessels within the tumor and target engagement (phosphorylated VEGFR3) using immunohistochemistry or alternatively using tumor lysates to quantitate in situ inhibition of the target (phosphorylated VEGFR3).

**CLAIMS**

1. A compound of the formula (I) or stereoisomers, salts, solvates or prodrugs thereof:



(I)

wherein:

A is an optionally substituted 5 to 10 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl group contains 1 to 4 heteroatoms selected from N, O and S;

A may optionally bear a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

wherein when A is a 9 or 10 membered heteroaryl group, the substitutent $R^{1A}$ must be present;

where $R^{1A}$ is selected from:

(i) $CH(R^{C1})NHZ^1$, where $R^{C1}$ is selected from H, $C_{1-3}$ alkyl, $C_{3-5}$ cycloalkyl and oxetanyl, and $Z^1$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(ii) $XNHZ^2$, where X is selected from $CF_2$, $CMe_2$, cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidine, and $Z^2$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(iii) a substituted 3-6 membered cycloalkyl; and

(iv) an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N, O and S;

each $R^{1B}$ is independently selected from $O\text{-}C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from $O\text{-}C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, $O\text{-}(C_{1-3}$ alkyl), $O\text{-}(CH_2)n\text{-}C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the $-C_2H_4-$ group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

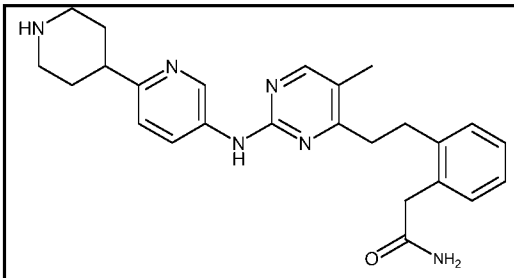
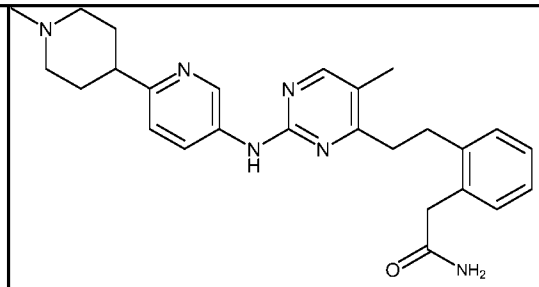
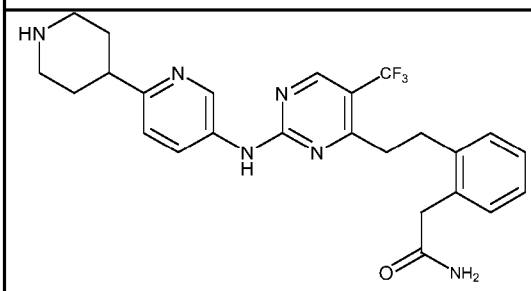
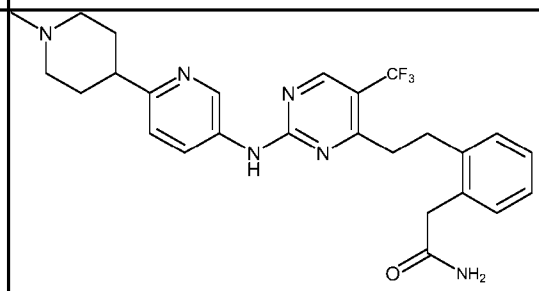
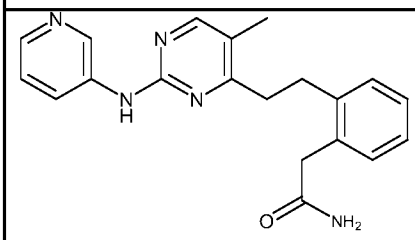
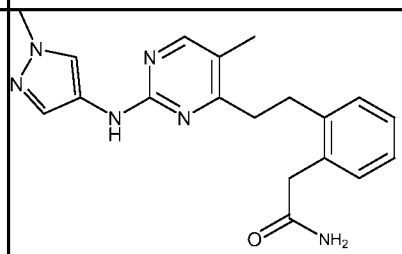
$R^4$ is selected from:

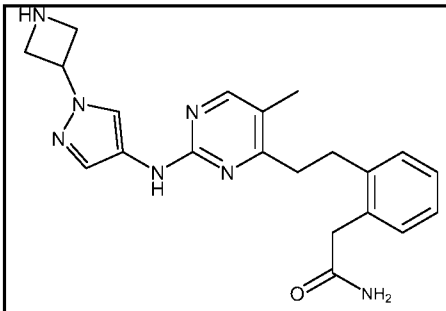
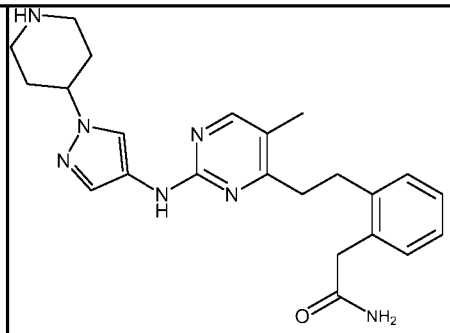
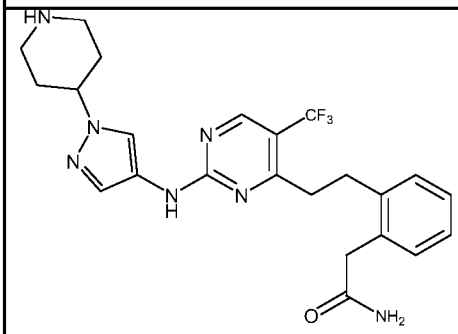
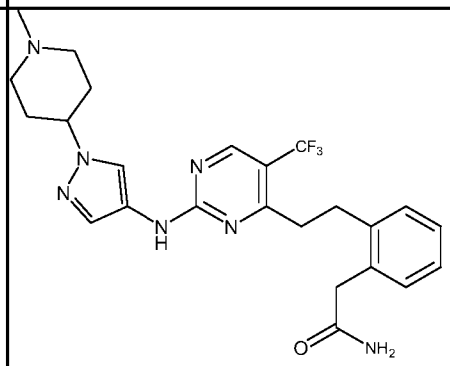
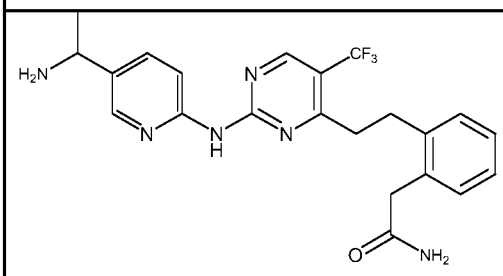
(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

2. A compound according to claim 1, with the proviso that it is not any one of the following compounds or Boc-protected intermediates thereof:

| | |
|---|---|
|  <br>2-(2-(2-(5-methyl-2-((6-(piperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (4) |  <br>2-(2-(2-(5-methyl-2-((6-(1-methylpiperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (5) |
|  <br>*2-(2-(2-(2-((6-(piperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (13)* |  <br>2-(2-(2-(2-((6-(1-methylpiperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (14) |
|  <br>2-(2-(2-(5-methyl-2-(pyridin-3-ylamino)pyrimidin-4-yl)ethyl)phenyl)acetamide (24) |  <br>2-(2-(2-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (28) |

| | |
|---|---|
|  <br>*2-(2-(2-(2-((1-(azetidin-3-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (30)* |  <br>2-(2-(2-(5-Methyl-2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (33) |
|  <br>2-(2-(2-(2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (35) |  <br>2-(2-(2-(2-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (36) |
|  <br>2-(2-(2-(2-((6-(1-aminoethyl)pyridin-3-yl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (40) | |

3. A compound according to claim 1 or 2, wherein A is a substituted 5 to 10 membered heteroaryl group.

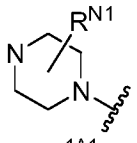
4. A compound according to claim 1 or 2, wherein A is an optionally substituted 5 or 6-membered heteroaryl group.

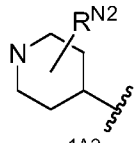
5. A compound according to claim 1 or 2, wherein A is an optionally substituted 5 to 10 membered heteroaryl group containing 1 or 2 N heteroatoms.

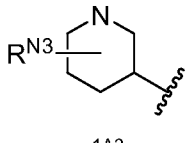
6. A compound according to any one of claims 1 to 5, wherein A is an optionally substituted pyrrole, pyridine, imidazole, pyrazole, pyridazine, pyrimidine or pyrazine.

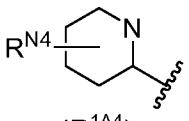
7. A compound according any one of claims 1 to 6, wherein A bears a substituent $R^{1A}$.

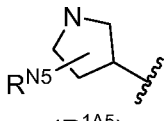
8. A compound according to claim 7, wherein $R^{1A}$ is an optionally substituted 4 to 6 membered non-aromatic heterocycle selected from:

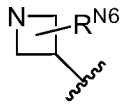

($R^{1A1}$)

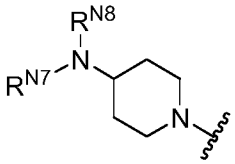

($R^{1A2}$)

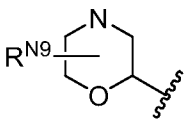

($R^{1A3}$)

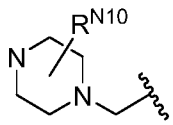

($R^{1A4}$)

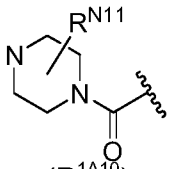

($R^{1A5}$)

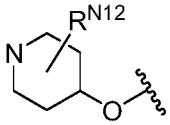

($R^{1A6}$)

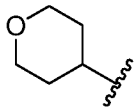

($R^{1A7}$)

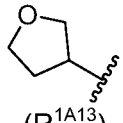

($R^{1A8}$)

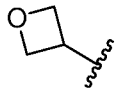

($R^{1A9}$)


($R^{1A10}$)


($R^{1A11}$)


($R^{1A12}$)


($R^{1A13}$)

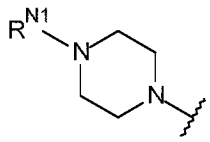

($R^{1A14}$)

wherein:

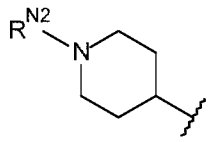
each of $R^{N1}$, $R^{N2}$, $R^{N3}$, $R^{N4}$, $R^{N5}$, $R^{N6}$, $R^{N9}$, $R^{N10}$, $R^{N11}$ and $R^{N12}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups; and.

each of $R^{N7}$ and $R^{N8}$ is independently selected from H and methyl.

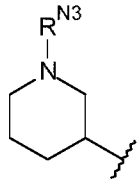
9. A compound according to claim 7, wherein $R^{1A}$ is an optionally substituted 4 to 6 membered non-aromatic heterocycle selected from:



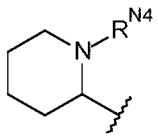
($R^{1A1}$)



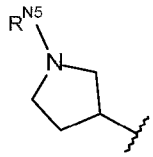
($R^{1A2}$)



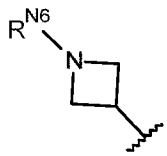
($R^{1A3}$)



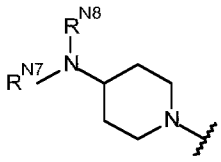
($R^{1A4}$)



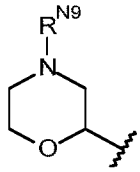
($R^{1A5}$)



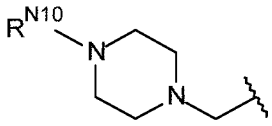
($R^{1A6}$)



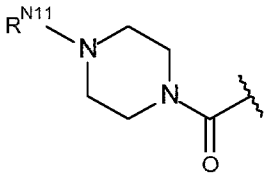
($R^{1A7}$)



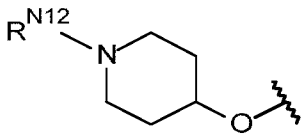
($R^{1A8}$)



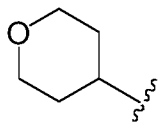
($R^{1A9}$)



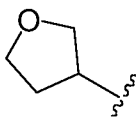
($R^{1A10}$)



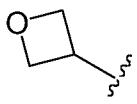
($R^{1A11}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

each of $R^{N1}$, $R^{N2}$, $R^{N3}$, $R^{N4}$, $R^{N5}$, $R^{N6}$, $R^{N9}$, $R^{N10}$, $R^{N11}$ and $R^{N12}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups; and.

each of $R^{N7}$ and $R^{N8}$ is independently selected from H and methyl.

10. A compound according to any one of claims 1 to 9, wherein when

A is substituted pyridinyl,

$R^2$ is $CF_3$ or $CH_3$,

$R^3$ is substituted phenyl and bears a substituent $R^4$ alpha to the $–C_2H_4$- group,

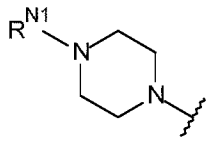
$R^4$ is $–CH_2$-C(O)-$NH_2$

A bears a substituent $R^{1A}$ selected from:

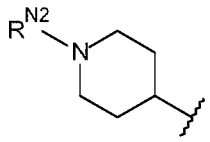
(i) $CH(R^{C1})NHZ^1$, where $R^{C1}$ is selected from H, $C_{2-3}$ alkyl, $C_{3-5}$ cycloalkyl and oxetanyl, and $Z^1$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(ii) $XNHZ^2$, where X is selected from $CF_2$, $CMe_2$, cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidine, and $Z^2$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me; and

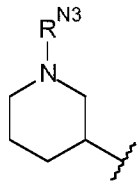
(iii) a substituted 3-6 membered cycloalkyl selected from:



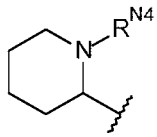
($R^{1A1}$)



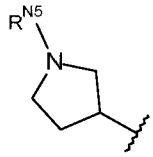
($R^{1A2}$)



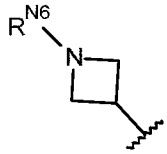
($R^{1A3}$)



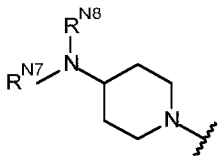
($R^{1A4}$)



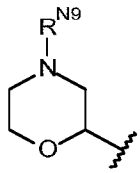
($R^{1A5}$)



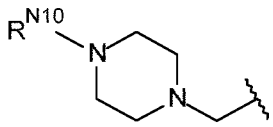
($R^{1A6}$)



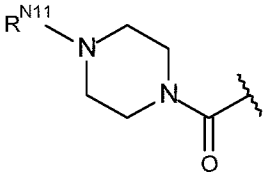
($R^{1A7}$)



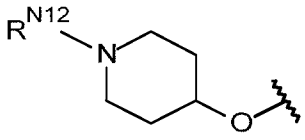
($R^{1A8}$)



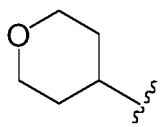
($R^{1A9}$)



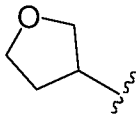
($R^{1A10}$)

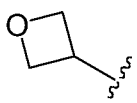


($R^{1A11}$)



($R^{1A12}$)





($R^{1A13}$) ($R^{1A14}$)

wherein:

$R^{N2}$ is independently selected from $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

each of $R^{N1}$, $R^{N3}$, $R^{N4}$, $R^{N5}$, $R^{N6}$, $R^{N9}$, $R^{N10}$, $R^{N11}$ and $R^{N12}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups; and.

each of $R^{N7}$ and $R^{N8}$ is independently selected from H and methyl.

11. A compound according to any one of claims 1 to 9, wherein when

A is substituted pyrazolyl,

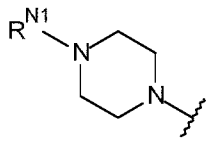
$R^2$ is $CF_3$ or $CH_3$,

$R^3$ is substituted phenyl and bears a substituent $R^4$ alpha to the $–C_2H_4$- group,

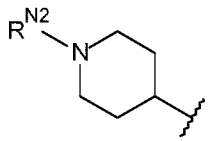
$R^4$ is $–CH_2$-C(O)-$NH_2$

A bears a substituent $R^{1A}$ selected from:

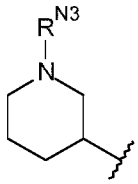
(iii) a substituted 3-6 membered cycloalkyl selected from:



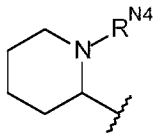
($R^{1A1}$)



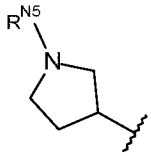
($R^{1A2}$)



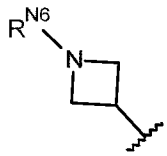
($R^{1A3}$)



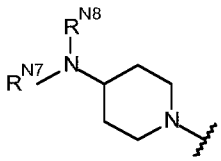
($R^{1A4}$)



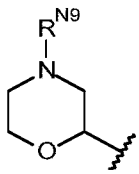
($R^{1A5}$)



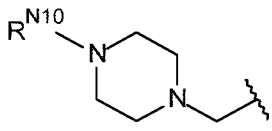
($R^{1A6}$)



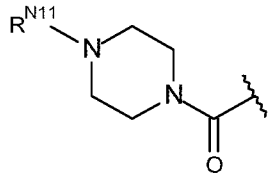
($R^{1A7}$)



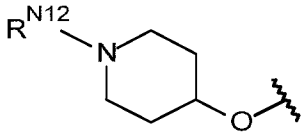
($R^{1A8}$)



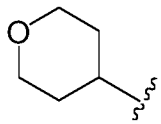
($R^{1A9}$)



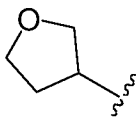
($R^{1A10}$)



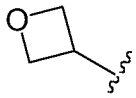
($R^{1A11}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

$R^{N2}$ is independently selected from $C_{2-4}$ alkylCN, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^{N6}$ is independently selected from $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

each of $R^{N1}$, $R^{N3}$, $R^{N4}$, $R^{N5}$, $R^{N9}$, $R^{N10}$, $R^{N11}$ and $R^{N12}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups; and.

each of $R^{N7}$ and $R^{N8}$ is independently selected from H and methyl.

12. A compound according to any one of claims 1 to 11, wherein $R^3$ is substituted phenyl.

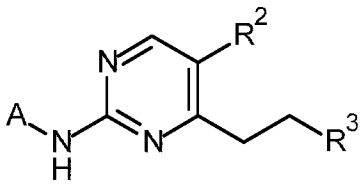
13. A compound according to any one of claims 1 to 12, wherein $R^4$ is selected from:

(i) $CH_2$-$C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $CH_3$; and $Z^4$ is selected from H, $CH_3$ and $OCH_3$; and

(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $CH_3$; and $Z^4$ is selected from H, $CH_3$ and $OCH_3$.

14. A compound according to any one of claims 1 to 13, wherein $R^3$ is substituted phenyl; and $R^4$ is $CH_2$-$C(O)N(R^{N13})Z^4$ where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl ; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

15. A compound of the formula (IC) or stereoisomers, salts, solvates or prodrugs thereof:



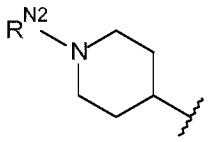
(IC)

wherein:

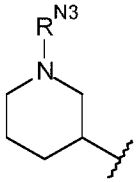
A is an optionally substituted 5 or 6 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl group contains 1 or 2 N heteroatoms;

A bears a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

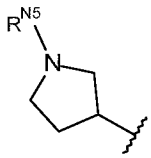
where $R^{1A}$ is selected from



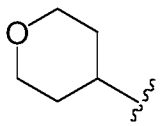
($R^{1A2}$)



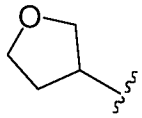
($R^{1A3}$)



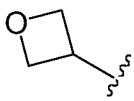
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

each of $R^{N2}$, $R^{N3}$ and $R^{N5}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1B}$ is independently selected from $O\text{-}C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from $O\text{-}C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, $O\text{-}(C_{1-3}$ alkyl), $O\text{-}(CH_2)n\text{-}C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$

either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

$R^4$ is selected from:

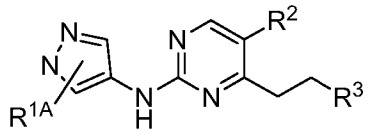
(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

16. A compound according to any one of claims 1 to 15, wherein $R^{1B}$ is absent.

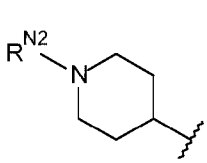
17. A compound of formula (IE) or stereoisomers, salts, solvates, or prodrugs thereof:



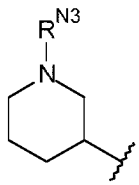
(IE)

wherein:

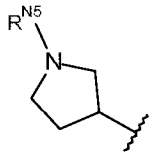
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



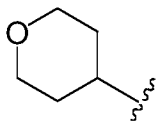
($R^{1A2}$)



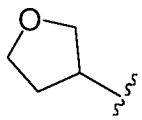
($R^{1A3}$)



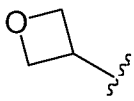
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

each of $R^{N2}$ and $R^{N5}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, C(=O)$C_{1-4}$ alkyl and C(=O)$C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^{N3}$ is selected from H, $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, C(=O)$C_{1-4}$ alkyl and C(=O)$C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-($CH_2$)n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

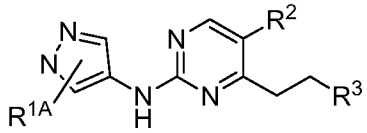
$R^4$ is selected from:

(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

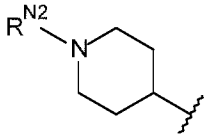
18. A compound of formula (IG) or stereoisomers, salts, solvates, or prodrugs thereof:



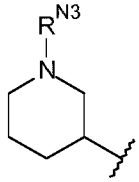
(IG)

wherein:

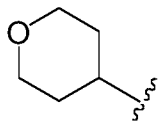
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



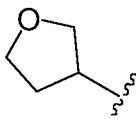
($R^{1A2}$)



($R^{1A3}$)



($R^{1A12}$)



($R^{1A13}$)

wherein:

$R^{N2}$ is independently selected from $C_{2-3}$ alkyl, $C_3$ alkenyl, and C(=O)$C_1$ alkyl;

$R^{N3}$ is $C_1$ alkyl;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-($CH_2$)n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

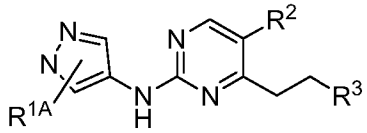
$R^4$ is selected from:

(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

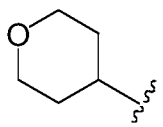
19. A compound of formula (IH) or stereoisomers, salts, solvates, or prodrugs thereof:



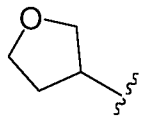
(IH)

wherein:

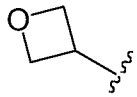
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-($CH_2$)n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

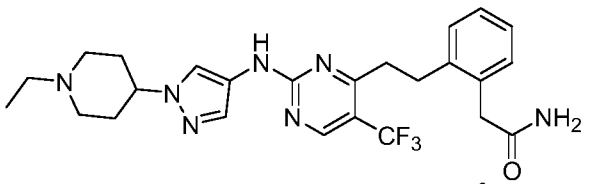
$R^4$ is selected from:

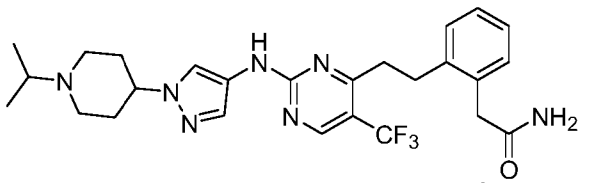
(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

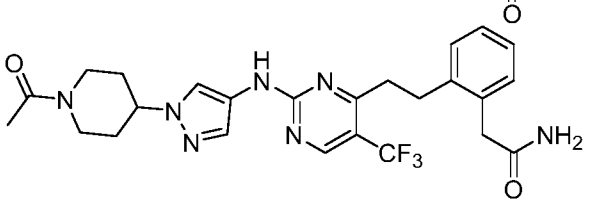
(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

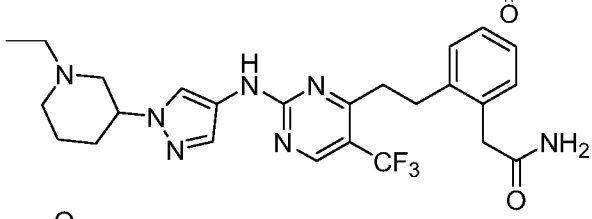
(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

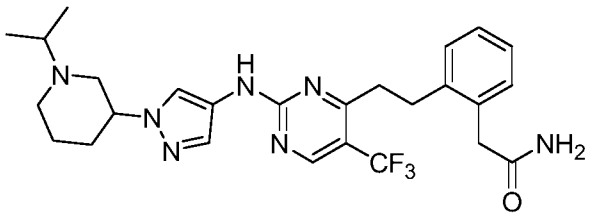
20. A compound selected from any one of the following compounds, or stereoisomers, salts, solvates or prodrugs thereof:

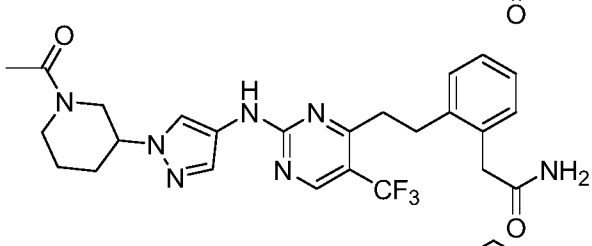


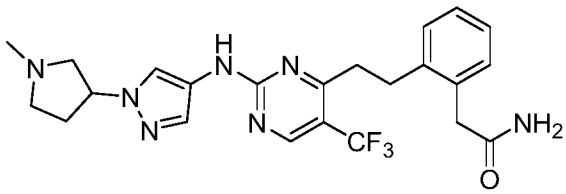


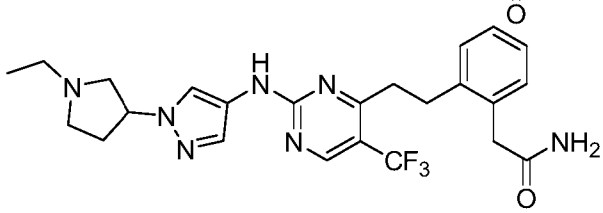


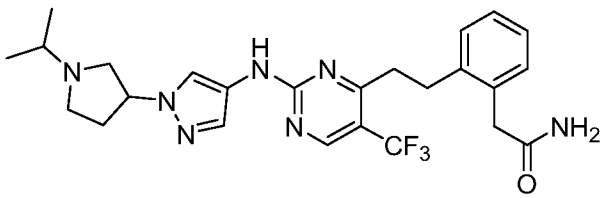


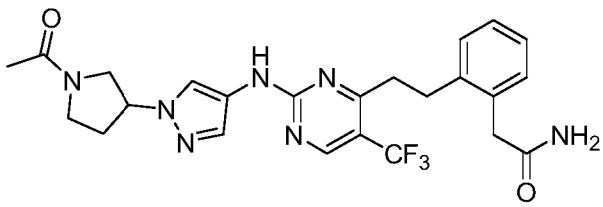


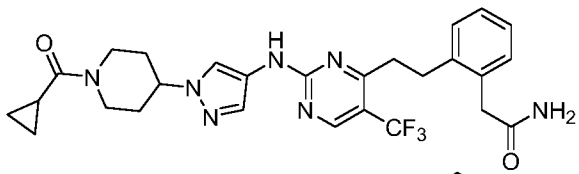


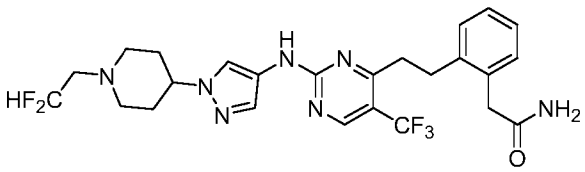


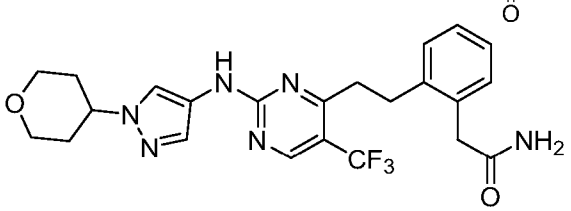


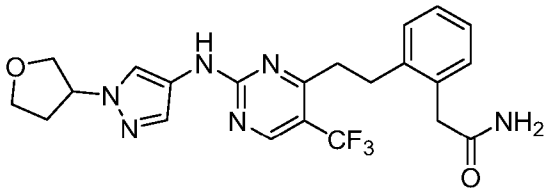


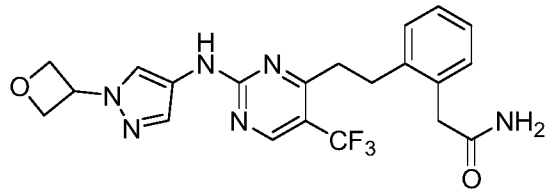


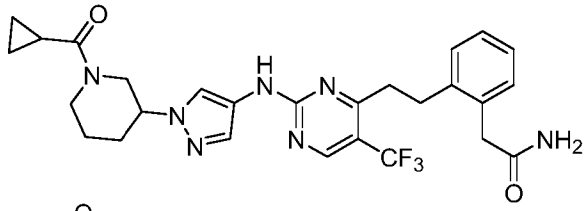


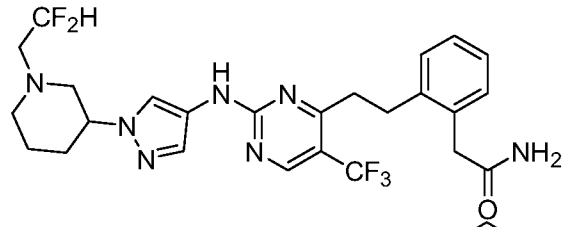


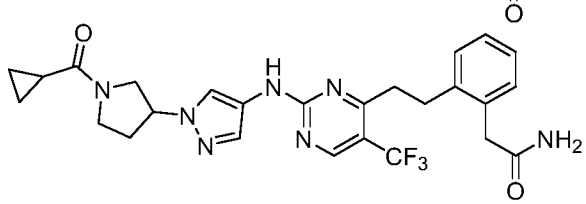


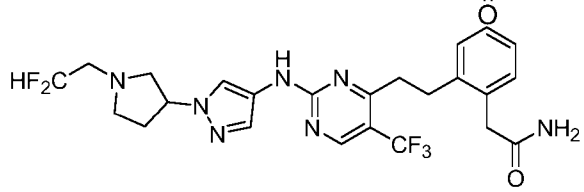


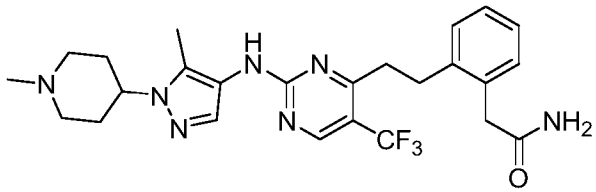


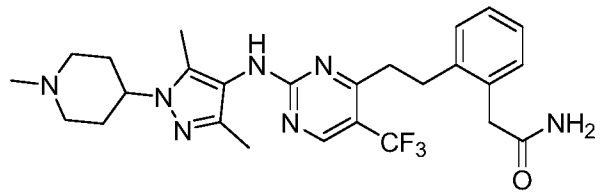


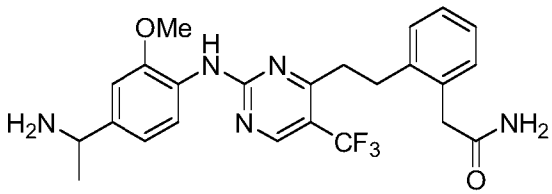


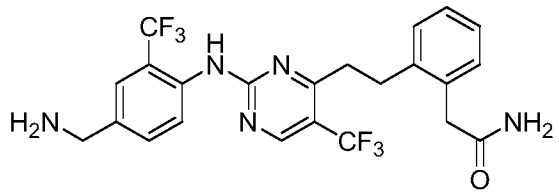


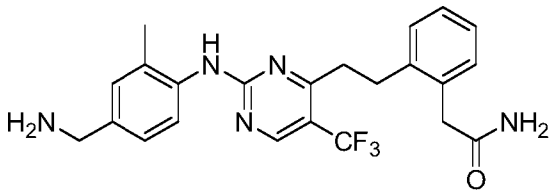


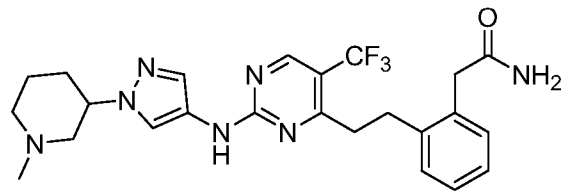


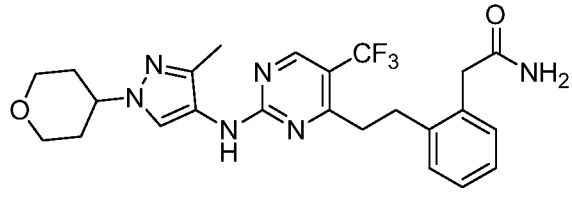


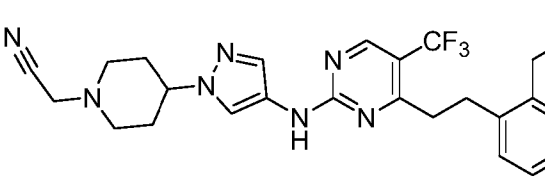


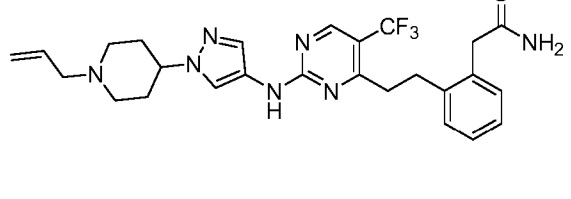


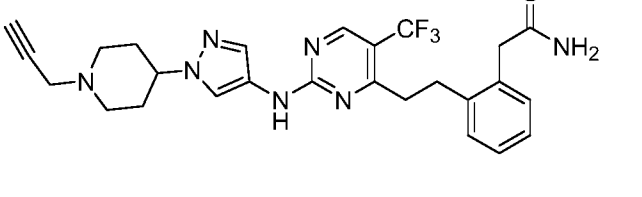


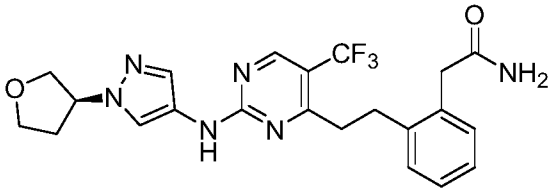


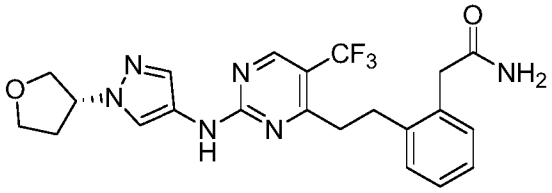




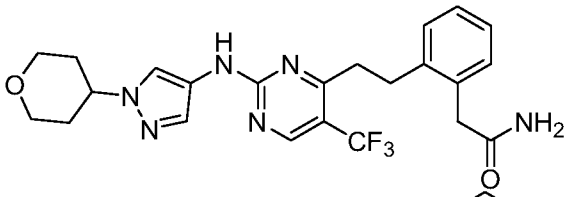


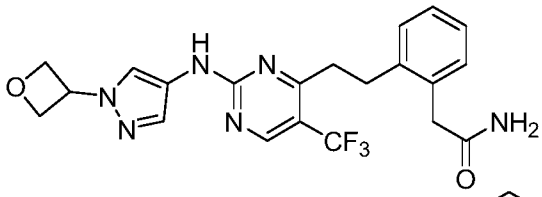


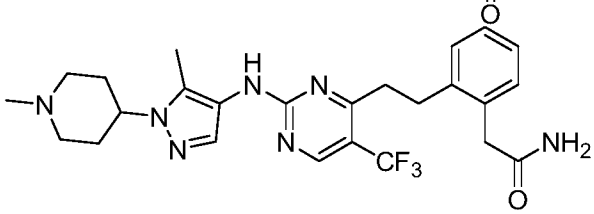


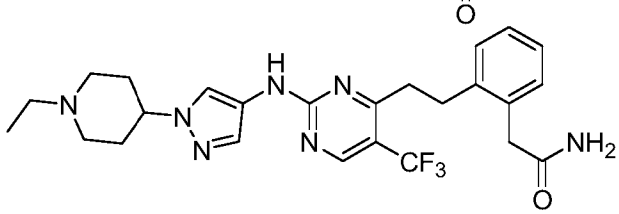


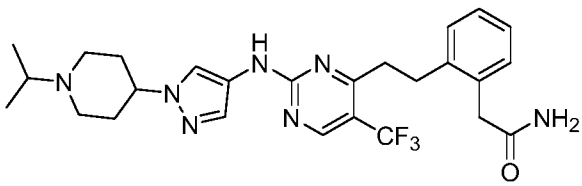
21. A compound selected from any one of the following compounds, or stereoisomers, salts, solvates or prodrugs thereof:

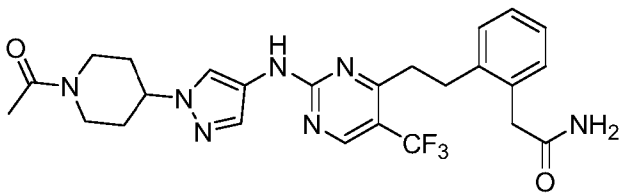


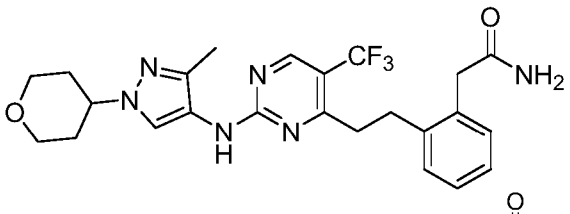


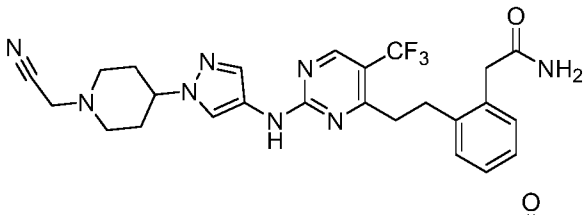


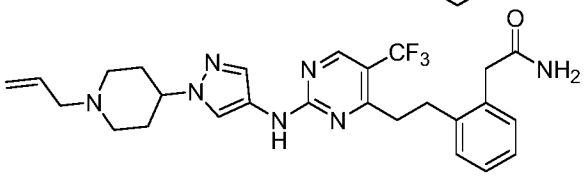


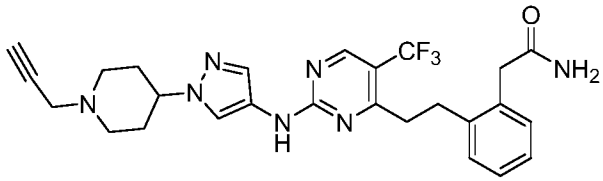


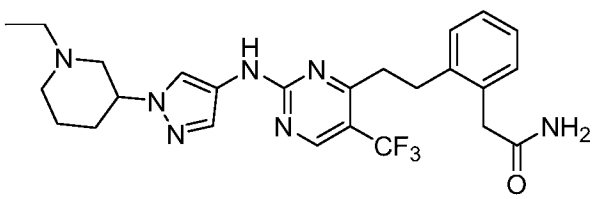


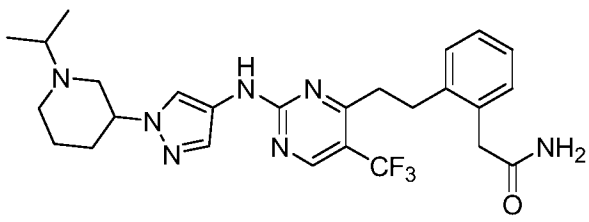


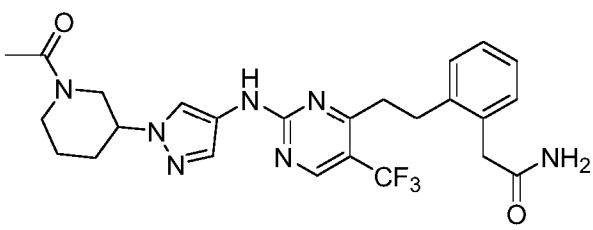


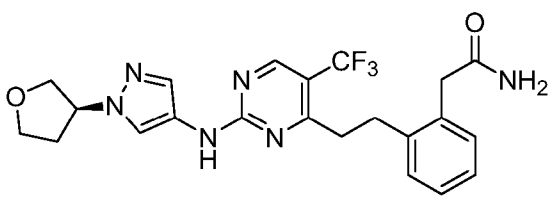


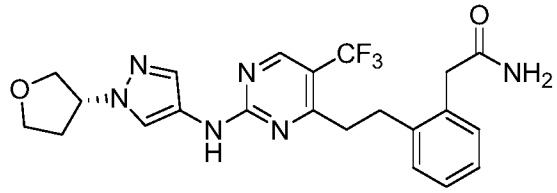




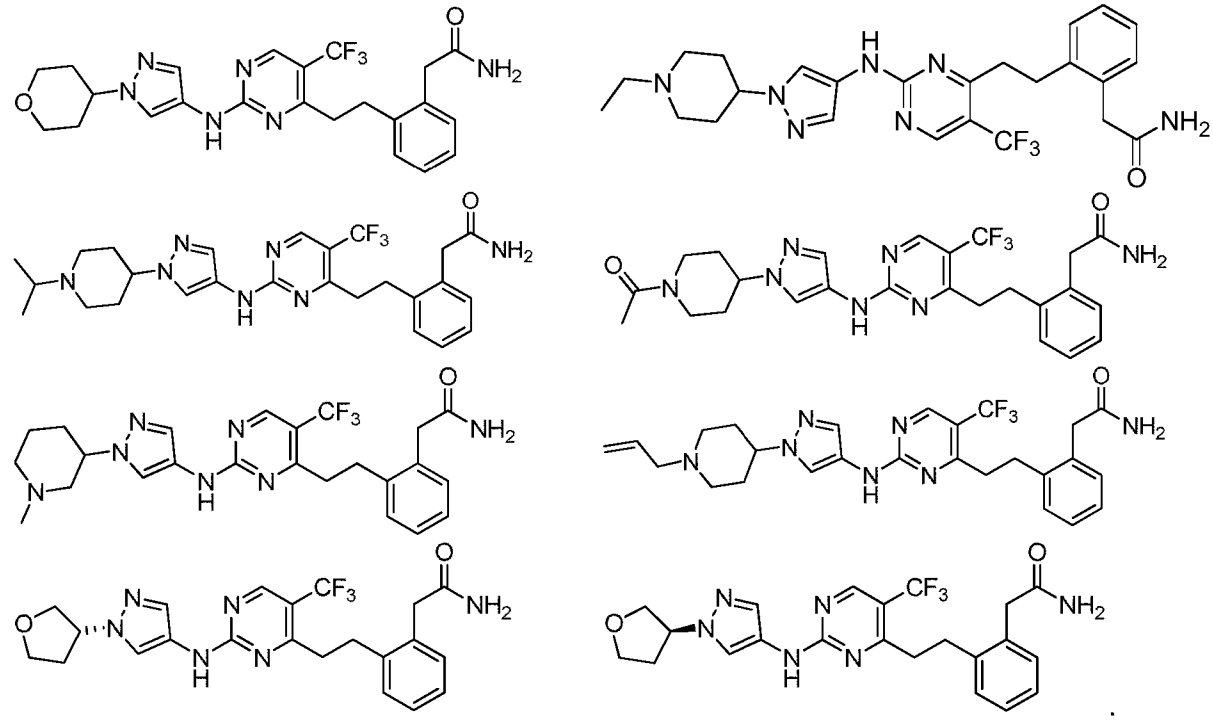




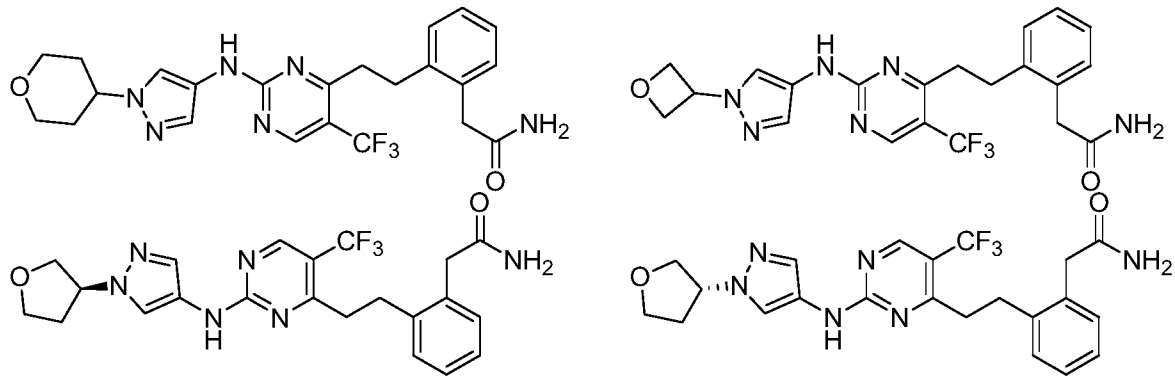




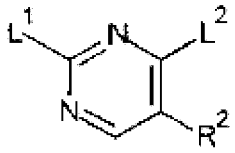
22. A compound selected from any one of the following compounds, or stereoisomers, salts, solvates or prodrugs thereof:



23. A compound selected from any one of the following compounds, or stereoisomers, salts, solvates or prodrugs thereof:



24. A process for the preparation of a compound according to any one of claims 1 to 23 or stereoisomers, salts, solvates or prodrug thereof, comprising reacting a compound of formula F1



F1

with a compound of formula A-$NH_2$ to displace the group $L^1$ and with a compound of formula $HC\equiv R^3$ to displace the group $L^2$, or
with a compound of formula $HC\equiv R^3$ to displace the group $L^2$ and with a compound of formula A-$NH_2$ to displace the group $L^1$,
wherein A, $R^2$ and $R^3$ are as defined in claim 1 and $L^1$ and $L^2$ are leaving groups.

25. A pharmaceutical agent comprising a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23.

26. A composition comprising a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, and a pharmaceutically acceptable carrier or diluents.

27. A composition according to claim 26, wherein the composition further comprising an anti-tumour agent selected from the group consisting of antiproliferative drugs, antineoplastic drugs, cytostatic agents, anti-invasion agents, inhibitors of growth factor function, antiangiogenic agents, antilymphangiogenic agents, vascular damaging agents, and combinations thereof.

28. A compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23 agent according to claim 25 or composition according to claim 26 for use in a method of therapy.

29. The use of a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 in the preparation of a medicament for treating a disease ameliorated by the inhibition of FAK.

30. The use of a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim

26 in the preparation of a medicament for treating a disease ameliorated by the inhibition of VEGFR3.

31. The use of a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 in the preparation of a medicament for treating cancer.

32. The use of a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 in the preparation of a medicament for inhibiting supressing or reducing lymphangiogenesis.

33. A compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 for use in a method of treatment of a disease ameliorated by the inhibition of FAK.

34. A compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 for use in a method of treatment of a disease ameliorated by the inhibition of VEGFR3.

35. A compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 for use in the method for treating cancer.

36. A compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 for use in the method for inhibiting, supressing or reducing lymphangiogenesis.

37. A compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 for use in a method of treatment of the human or animal body.

38. A method of inhibiting FAK *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26.

39. A method of inhibiting VEGFR3 *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26.

40. The use of claim 31 or the compound or stereoisomer, salt, solvate or prodrug thereof of claim 35, wherein the cancer is selected from bone cancer, brain stem glioma, breast cancer, cancer of the adrenal gland, cancer of the anal region, cancer of the bladder, cancer of the endocrine system, cancer of the oesophagus, cancer of the brain, cancer of the head or neck, cancer of the kidney or ureter, cancer of the liver, cancer of the parathyroid gland, cancer of the penis, cancer of the small intestine, cancer of the thyroid gland, cancer of the urethra, carcinoma of the cervix, carcinoma of the endometrium, carcinoma of the fallopian tubes, carcinoma of the renal pelvis, carcinoma of the vagina, carcinoma of the vulva, chronic or acute leukemia, acute myelogenous leukemia, colon cancer, melanoma such as cutaneous or intraocular melanoma, haemetological malignancies, Hodgkin's disease, lung cancer, non-small cell lung cancer (NSCLC), mesothelioma, lymphocytic lymphomas, neoplasms of the central nervous system (CNS), ovarian cancer, pancreatic cancer, pituitary adenoma, primary CNS lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, sarcoma of soft tissue, skin cancer, spinal axis tumors, stomach cancer, uterine cancer, hepatocellular carcinoma, small cell lung carcinoma, sarcoma, osteosarcoma, cervical cancer, colon cancer, neuroblastoma, head and neck cancer, hematopoietic cancer and mesothelioma.

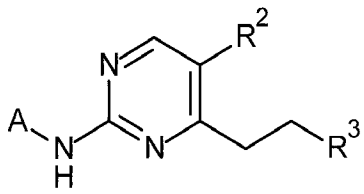
41. The use of claim 32 or the compound or stereoisomer, salt, solvate or prodrug thereof of claim 36, wherein inhibiting, supressing or reducing lymphangiogenesis prevents and/or treats diseases of conditions selected from eye diseases, skin inflammations, rejection in renal transplantation, rheumatoid arthritis, diabetic retinopathy, cardiovascular diseases, autoimmune disease, fibrosis, restenosis, diabetes mellitus, thrombosis, glomerulonephritis and neurodegeneration.

42. An anti-cancer agent comprising a compound or an stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 and an anti-tumour agent.

AMENDED CLAIMS
received by the International Bureau on 27 July 2015 (27.07.2015)

**CLAIMS**

1. A compound of the formula (I) or stereoisomers, salts, solvates or prodrugs thereof:



(I)

wherein:

A is an optionally substituted 5 to 10 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl group contains 1 to 4 heteroatoms selected from N, O and S;

A may optionally bear a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

wherein when A is a 9 or 10 membered heteroaryl group, the substitutent $R^{1A}$ must be present;

where $R^{1A}$ is selected from:

(i) $CH(R^{C1})NHZ^1$, where $R^{C1}$ is selected from H, $C_{1-3}$ alkyl, $C_{3-5}$ cycloalkyl and oxetanyl, and $Z^1$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(ii) $XNHZ^2$, where X is selected from $CF_2$, $CMe_2$, cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidine, and $Z^2$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

(iii) a substituted 3-6 membered cycloalkyl; and

(iv) an optionally substituted 4 to 6 membered non-aromatic heterocycle containing 1 to 2 heteroatoms selected from N, O and S;

each $R^{1B}$ is independently selected from $O\text{-}C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from $O\text{-}C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, $O\text{-}(C_{1-3}$ alkyl), $O\text{-}(CH_2)n\text{-}C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, and cyano where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the $-C_2H_4-$ group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

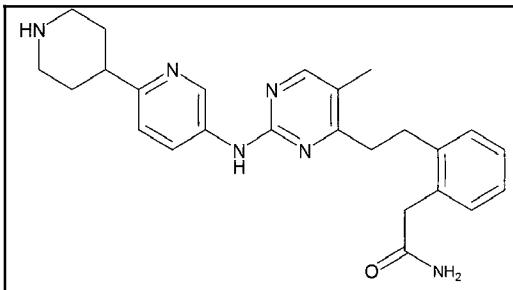
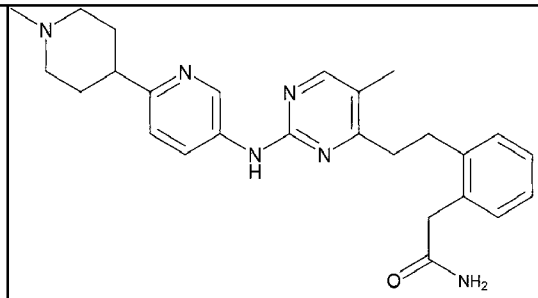
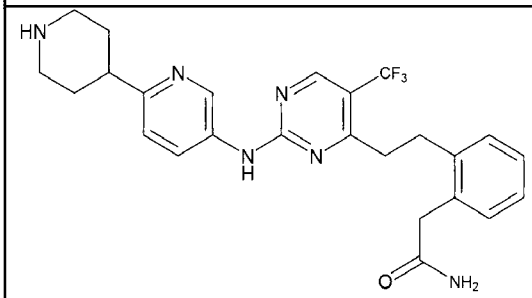
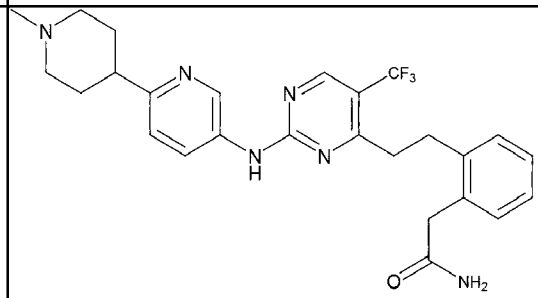
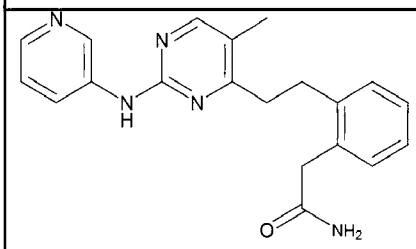
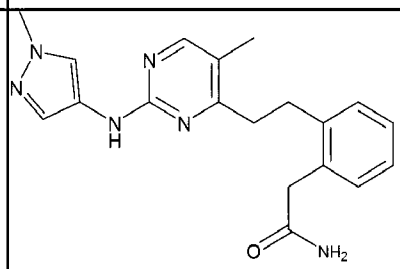
$R^4$ is selected from:

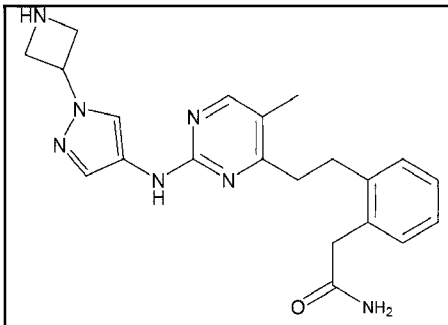
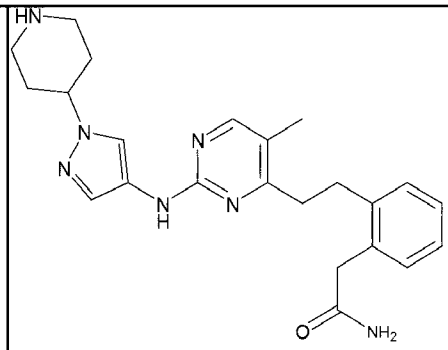
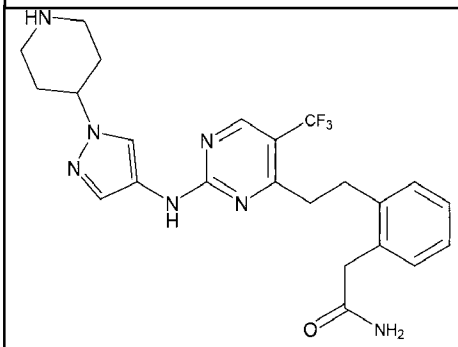
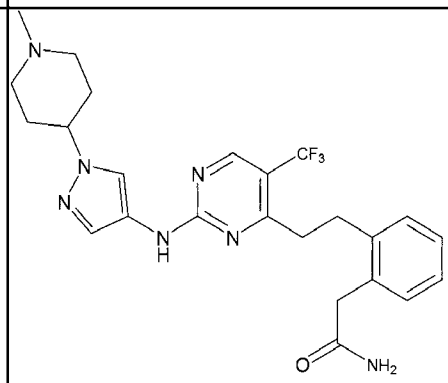
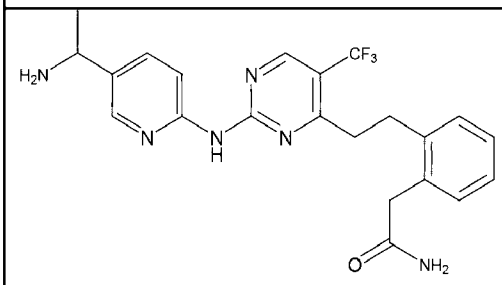
(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

2. A compound according to claim 1, with the proviso that it is not any one of the following compounds or Boc-protected intermediates thereof:

| | |
|---|---|
|  <br>2-(2-(2-(5-methyl-2-((6-(piperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (4) |  <br>2-(2-(2-(5-methyl-2-((6-(1-methylpiperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (5) |
|  <br>*2-(2-(2-(2-((6-(piperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (13)* |  <br>2-(2-(2-(2-((6-(1-methylpiperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (14) |
|  <br>2-(2-(2-(5-methyl-2-(pyridin-3-ylamino)pyrimidin-4-yl)ethyl)phenyl)acetamide (24) |  <br>2-(2-(2-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (28) |

| | |
|---|---|
|  <br>*2-(2-(2-(2-((1-(azetidin-3-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (30)* |  <br>2-(2-(2-(5-Methyl-2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (33) |
|  <br>2-(2-(2-(2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (35) |  <br>2-(2-(2-(2-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (36) |
|  <br>2-(2-(2-(2-((6-(1-aminoethyl)pyridin-3-yl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (40) | |

3. A compound according to claim 1 or 2, wherein A is a substituted 5 to 10 membered heteroaryl group.

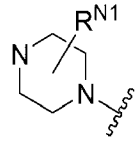
4. A compound according to claim 1 or 2, wherein A is an optionally substituted 5 or 6-membered heteroaryl group.

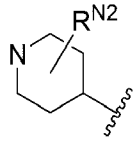
5. A compound according to claim 1 or 2, wherein A is an optionally substituted 5 to 10 membered heteroaryl group containing 1 or 2 N heteroatoms.

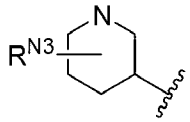
6. A compound according to any one of claims 1 to 5, wherein A is an optionally substituted pyrrole, pyridine, imidazole, pyrazole, pyridazine, pyrimidine or pyrazine.

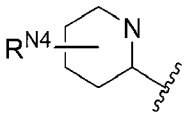
7. A compound according any one of claims 1 to 6, wherein A bears a substituent $R^{1A}$.

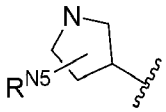
8. A compound according to claim 7, wherein $R^{1A}$ is an optionally substituted 4 to 6 membered non-aromatic heterocycle selected from:

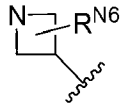

($R^{1A1}$)

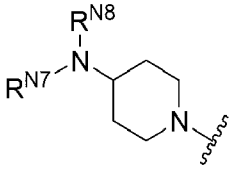

($R^{1A2}$)

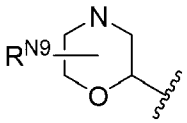

($R^{1A3}$)

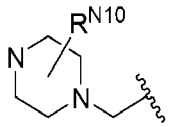

($R^{1A4}$)

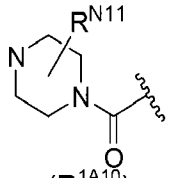

($R^{1A5}$)

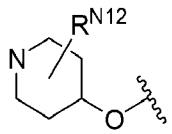

($R^{1A6}$)

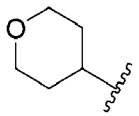

($R^{1A7}$)

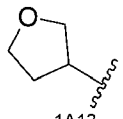

($R^{1A8}$)

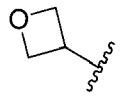

($R^{1A9}$)


($R^{1A10}$)


($R^{1A11}$)


($R^{1A12}$)


($R^{1A13}$)

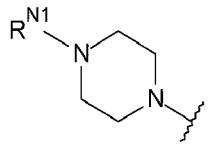

($R^{1A14}$)

wherein:

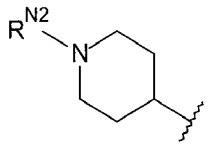
each of $R^{N1}$, $R^{N2}$, $R^{N3}$, $R^{N4}$, $R^{N5}$, $R^{N6}$, $R^{N9}$, $R^{N10}$, $R^{N11}$ and $R^{N12}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups; and.

each of $R^{N7}$ and $R^{N8}$ is independently selected from H and methyl.

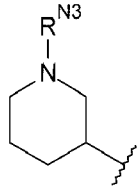
9. A compound according to claim 7, wherein $R^{1A}$ is an optionally substituted 4 to 6 membered non-aromatic heterocycle selected from:



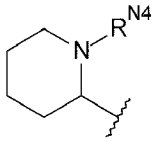
($R^{1A1}$)



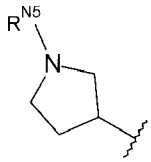
($R^{1A2}$)



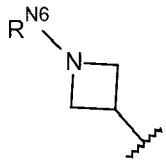
($R^{1A3}$)



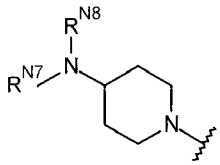
($R^{1A4}$)



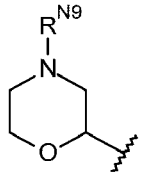
($R^{1A5}$)



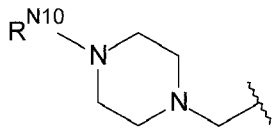
($R^{1A6}$)



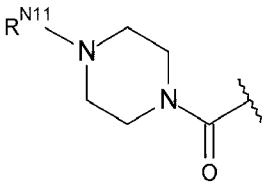
($R^{1A7}$)



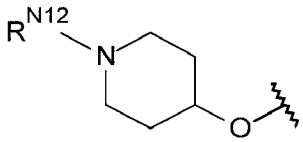
($R^{1A8}$)



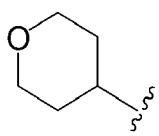
($R^{1A9}$)



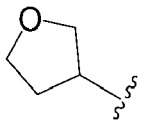
($R^{1A10}$)



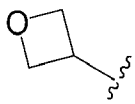
($R^{1A11}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

each of $R^{N1}$, $R^{N2}$, $R^{N3}$, $R^{N4}$, $R^{N5}$, $R^{N6}$, $R^{N9}$, $R^{N10}$, $R^{N11}$ and $R^{N12}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups; and.

each of $R^{N7}$ and $R^{N8}$ is independently selected from H and methyl.

10. A compound according to any one of claims 1 to 9, wherein when

A is substituted pyridinyl,

$R^2$ is $CF_3$ or $CH_3$,

$R^3$ is substituted phenyl and bears a substituent $R^4$ alpha to the $-C_2H_4-$ group,

$R^4$ is $-CH_2-C(O)-NH_2$

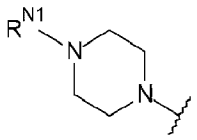
A bears a substituent $R^{1A}$ selected from:

(i) $CH(R^{C1})NHZ^1$, where $R^{C1}$ is selected from H, $C_{2-3}$ alkyl, $C_{3-5}$ cycloalkyl and oxetanyl, and $Z^1$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me;

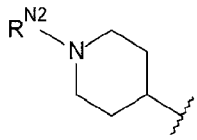
(ii) $XNHZ^2$, where X is selected from $CF_2$, $CMe_2$, cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidine, and $Z^2$ is selected from H, $C(=O)OC_{1-3}$ alkyl and C(=O)Me; and

(iii) a substituted 3-6 membered cycloalkyl; and

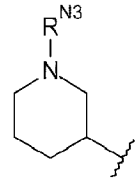
(iv) an optionally substituted 4 to 6 membered non-aromatic heterocycle selected from:



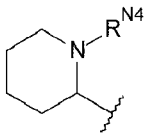
($R^{1A1}$)



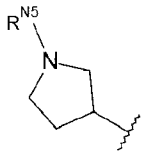
($R^{1A2}$)



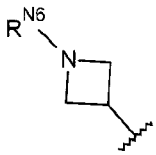
($R^{1A3}$)



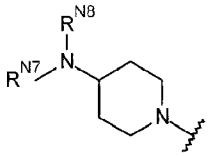
($R^{1A4}$)



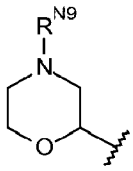
($R^{1A5}$)



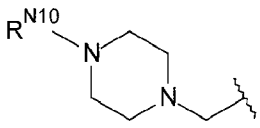
($R^{1A6}$)



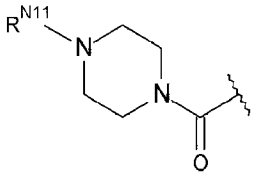
($R^{1A7}$)



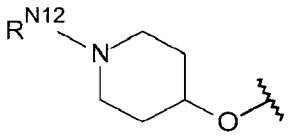
($R^{1A8}$)



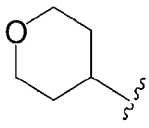
($R^{1A9}$)



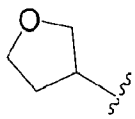
($R^{1A10}$)



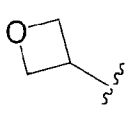
($R^{1A11}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

$R^{N2}$ is independently selected from $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

each of $R^{N1}$, $R^{N3}$, $R^{N4}$, $R^{N5}$, $R^{N6}$, $R^{N9}$, $R^{N10}$, $R^{N11}$ and $R^{N12}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups; and.

each of $R^{N7}$ and $R^{N8}$ is independently selected from H and methyl.

11. A compound according to any one of claims 1 to 9, wherein when

A is substituted pyrazolyl,

$R^2$ is $CF_3$ or $CH_3$,

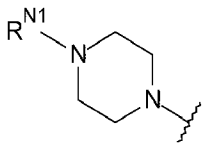
$R^3$ is substituted phenyl and bears a substituent $R^4$ alpha to the $–C_2H_4$- group,

$R^4$ is $–CH_2$-C(O)-$NH_2$

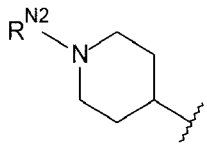
A bears a substituent $R^{1A}$ selected from:

(iii) a substituted 3-6 membered cycloalkyl; and

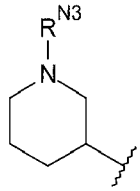
(iv) an optionally substituted4 to 6 membered non-aromatic heterocycle selected from:



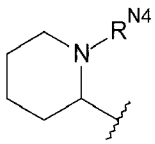
($R^{1A1}$)



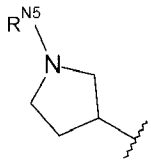
($R^{1A2}$)



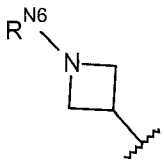
($R^{1A3}$)



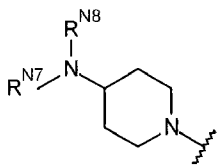
($R^{1A4}$)



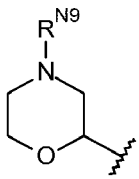
($R^{1A5}$)



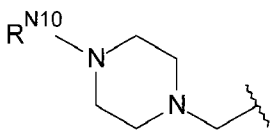
($R^{1A6}$)



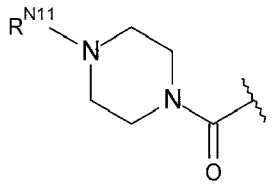
($R^{1A7}$)



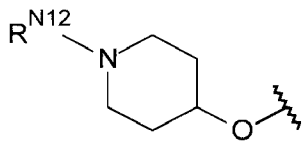
($R^{1A8}$)



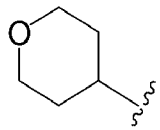
($R^{1A9}$)



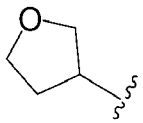
($R^{1A10}$)



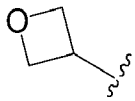
($R^{1A11}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

$R^{N2}$ is independently selected from $C_{2-4}$ alkylCN, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^{N6}$ is independently selected from $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

each of $R^{N1}$, $R^{N3}$, $R^{N4}$, $R^{N5}$, $R^{N9}$, $R^{N10}$, $R^{N11}$ and $R^{N12}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups; and.

each of $R^{N7}$ and $R^{N8}$ is independently selected from H and methyl.

12. A compound according to any one of claims 1 to 11, wherein $R^3$ is substituted phenyl.

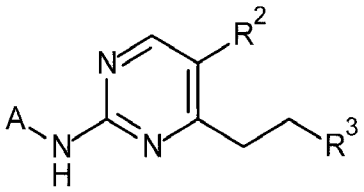
13. A compound according to any one of claims 1 to 12, wherein $R^4$ is selected from:

(i) $CH_2$-$C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $CH_3$; and $Z^4$ is selected from H, $CH_3$ and $OCH_3$; and

(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $CH_3$; and $Z^4$ is selected from H, $CH_3$ and $OCH_3$.

14. A compound according to any one of claims 1 to 13, wherein $R^3$ is substituted phenyl; and $R^4$ is $CH_2$-$C(O)N(R^{N13})Z^4$ where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl ; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

15. A compound of the formula (IC) or stereoisomers, salts, solvates or prodrugs thereof:



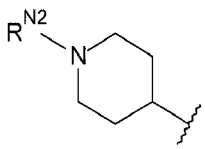
(IC)

wherein:

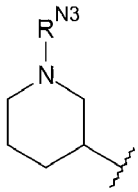
A is an optionally substituted 5 or 6 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl group contains 1 or 2 N heteroatoms;

A bears a substituent $R^{1A}$ which is not alpha to the NH group, A may optionally bear one or two substituents $R^{1B}$ which are alpha to the NH group, and A may optionally bear one or two further substituents $R^{1C}$ which are not alpha to the NH group,

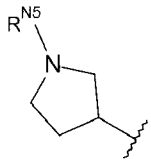
where $R^{1A}$ is selected from



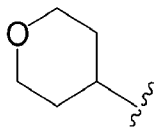
($R^{1A2}$)



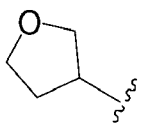
($R^{1A3}$)



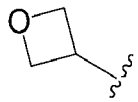
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

each of $R^{N2}$, $R^{N3}$ and $R^{N5}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C(=O)C_{1-4}$ alkyl and $C(=O)C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1B}$ is independently selected from $O\text{-}C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo and cyano, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

each $R^{1C}$ is independently selected from $O\text{-}C_{1-2}$ alkyl, $C_{1-2}$ alkyl, halo, cyano and hydroxyl, where the $C_{1-2}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, $O\text{-}(C_{1-3}$ alkyl), $O\text{-}(CH_2)n\text{-}C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$

either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

$R^4$ is selected from:

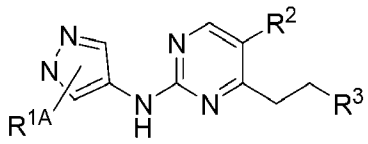
(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

16. A compound according to any one of claims 1 to 15, wherein $R^{1B}$ is absent.

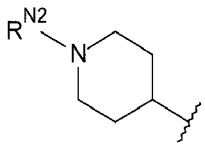
17. A compound of formula (IE) or stereoisomers, salts, solvates, or prodrugs thereof:



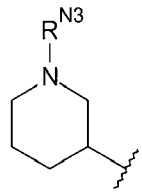
(IE)

wherein:

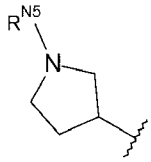
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



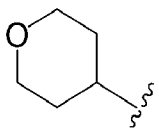
($R^{1A2}$)



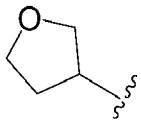
($R^{1A3}$)



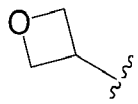
($R^{1A5}$)



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

wherein:

each of $R^{N2}$ and $R^{N5}$ is independently selected from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, C(=O)$C_{1-4}$ alkyl and C(=O)$C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^{N3}$ is selected from H, $C_{2-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkylCN, $C_{3-4}$ cycloalkyl, C(=O)$C_{1-4}$ alkyl and C(=O)$C_{3-4}$ cycloalkyl, where the $C_{1-4}$ alkyl group may be substituted by one or more fluoro groups;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-($CH_2$)n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

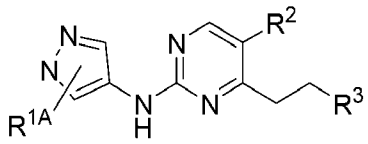
$R^4$ is selected from:

(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

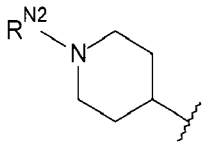
18. A compound of formula (IG) or stereoisomers, salts, solvates, or prodrugs thereof:



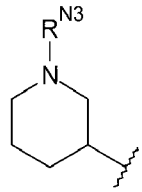
(IG)

wherein:

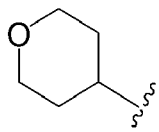
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



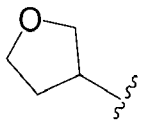
($R^{1A2}$)



($R^{1A3}$)



($R^{1A12}$)



($R^{1A13}$)

wherein:

$R^{N2}$ is independently selected from $C_{2-3}$ alkyl, $C_3$ alkenyl, and C(=O)$C_1$ alkyl;

$R^{N3}$ is $C_1$ alkyl;

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-($CH_2$)n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

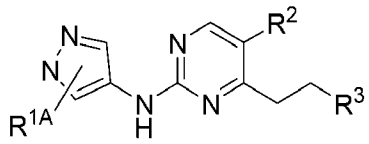
$R^4$ is selected from:

(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

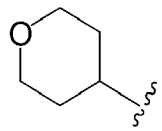
19. A compound of formula (IH) or stereoisomers, salts, solvates, or prodrugs thereof:



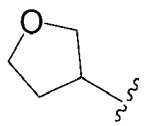
(IH)

wherein:

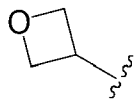
the substituent $R^{1A}$ is not alpha to the NH group, and is selected from:



($R^{1A12}$)



($R^{1A13}$)



($R^{1A14}$)

$R^2$ is selected from H, halo, $C_{1-3}$ alkyl, O-($C_{1-3}$ alkyl), O-($CH_2$)n-$C_{3-4}$ cycloalkyl, oxetanyl, $C_{3-4}$ cycloalkyl, $SO_2C_{1-3}$ alkyl, cyano and $OCH_2$-cyclopropyl where the $C_{1-3}$ alkyl group may be substituted by one or more fluoro groups and the group n is 0 or 1;

$R^3$ is selected from substituted phenyl and a substituted 6-membered heteroaryl group, where the heteroaryl group contains 1 or 2 N heteroatoms, where $R^3$ bears a substituent $R^4$ either alpha or beta to the -$C_2H_4$- group, and may additionally bear further substituents selected from F, methyl and $CF_3$;

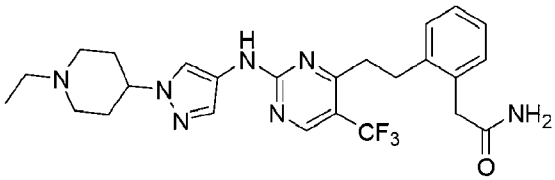
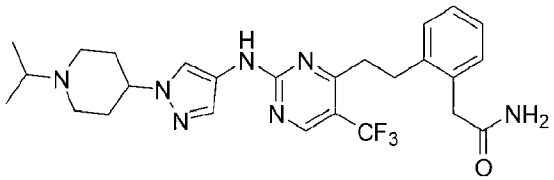
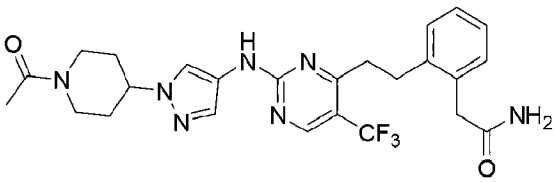
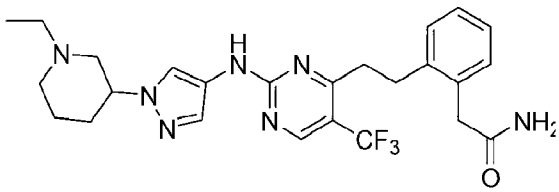
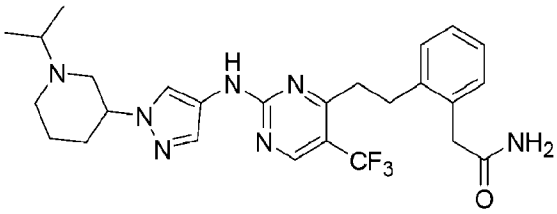
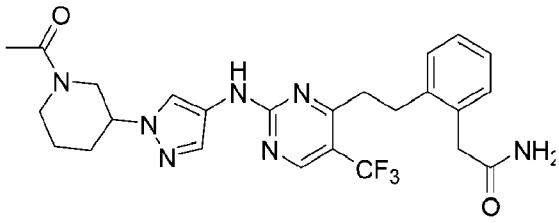
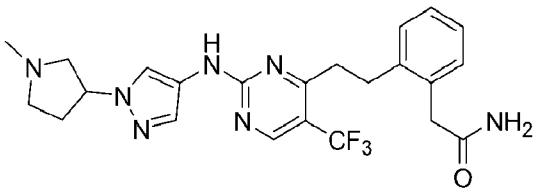
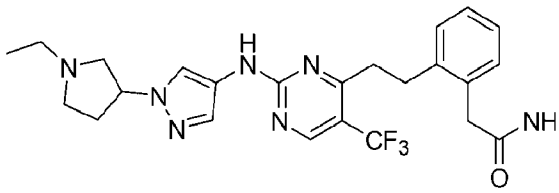
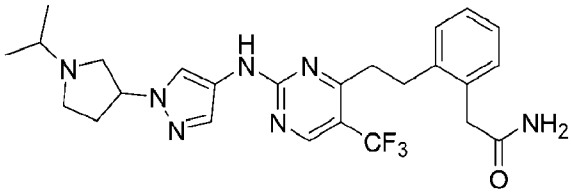
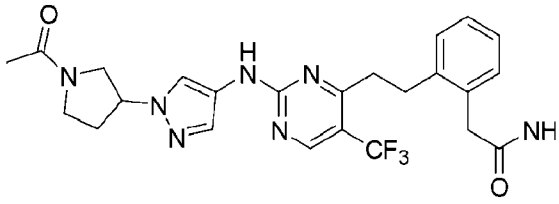
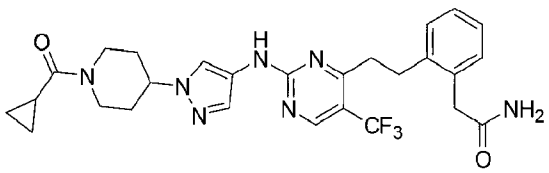
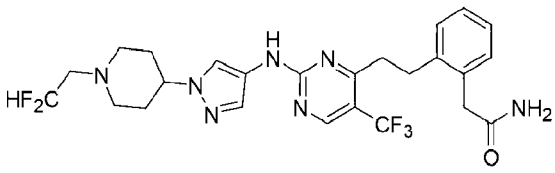
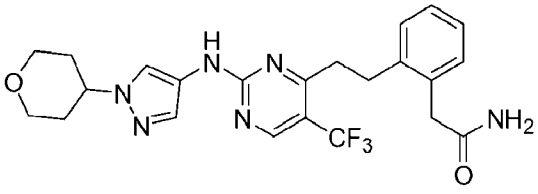
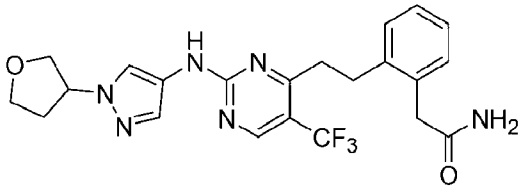
$R^4$ is selected from:

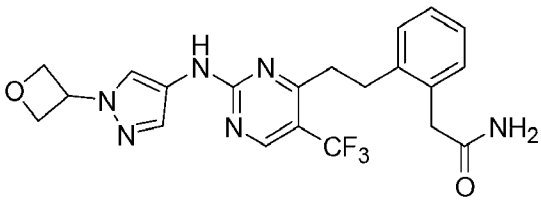
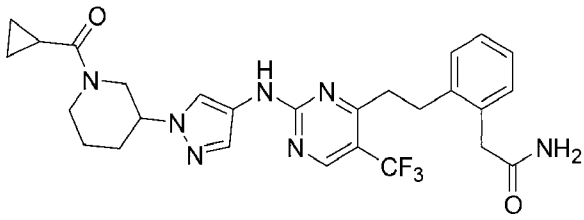
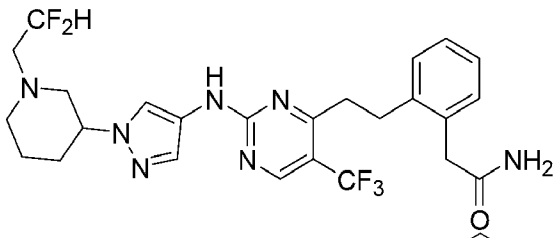
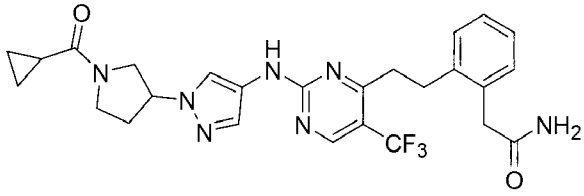
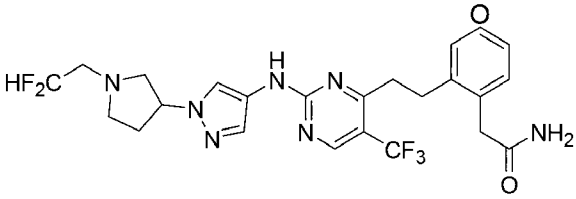
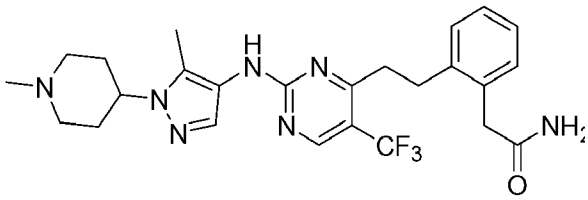
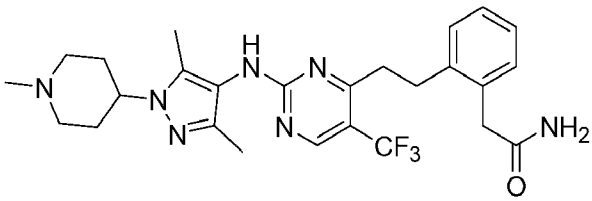
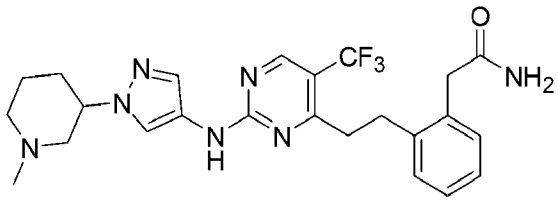
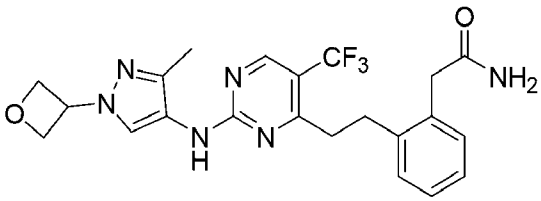
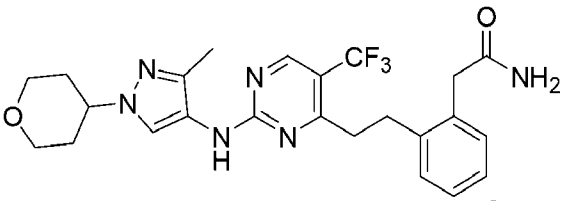
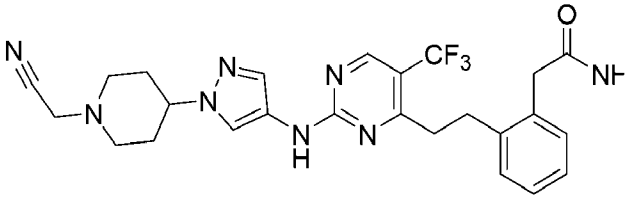
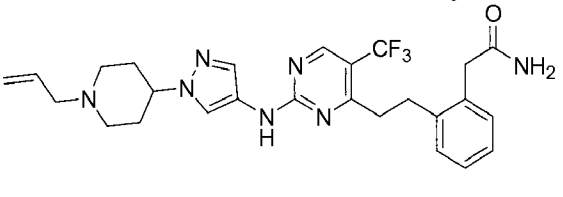
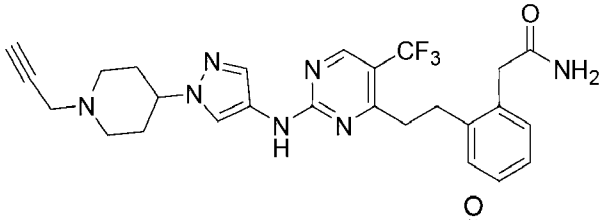
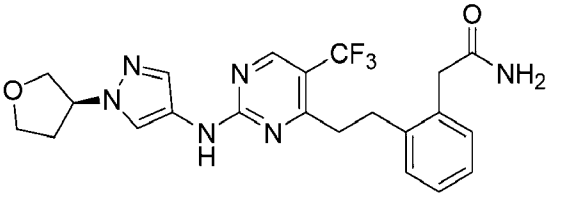
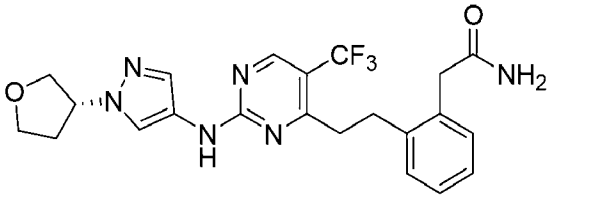
(i) $CH_2$-C(O)N($R^{N13}$)$Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$;

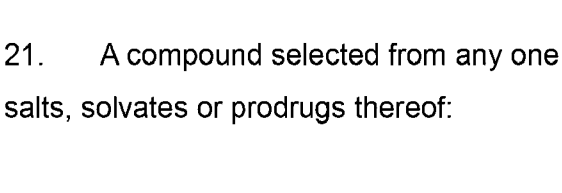
(ii) $NR^{N14}(SO_2)R^{S1}$, where $R^{N14}$ is selected from H and $C_{1-3}$ alkyl, and $R^{S1}$ is selected from $C_{1-3}$ alkyl; and

(iii) $C(O)N(R^{N13})Z^4$, where $R^{N13}$ is selected from H and $C_{1-2}$ alkyl; and $Z^4$ is selected from H, $C_{1-2}$ alkyl and $OCH_3$.

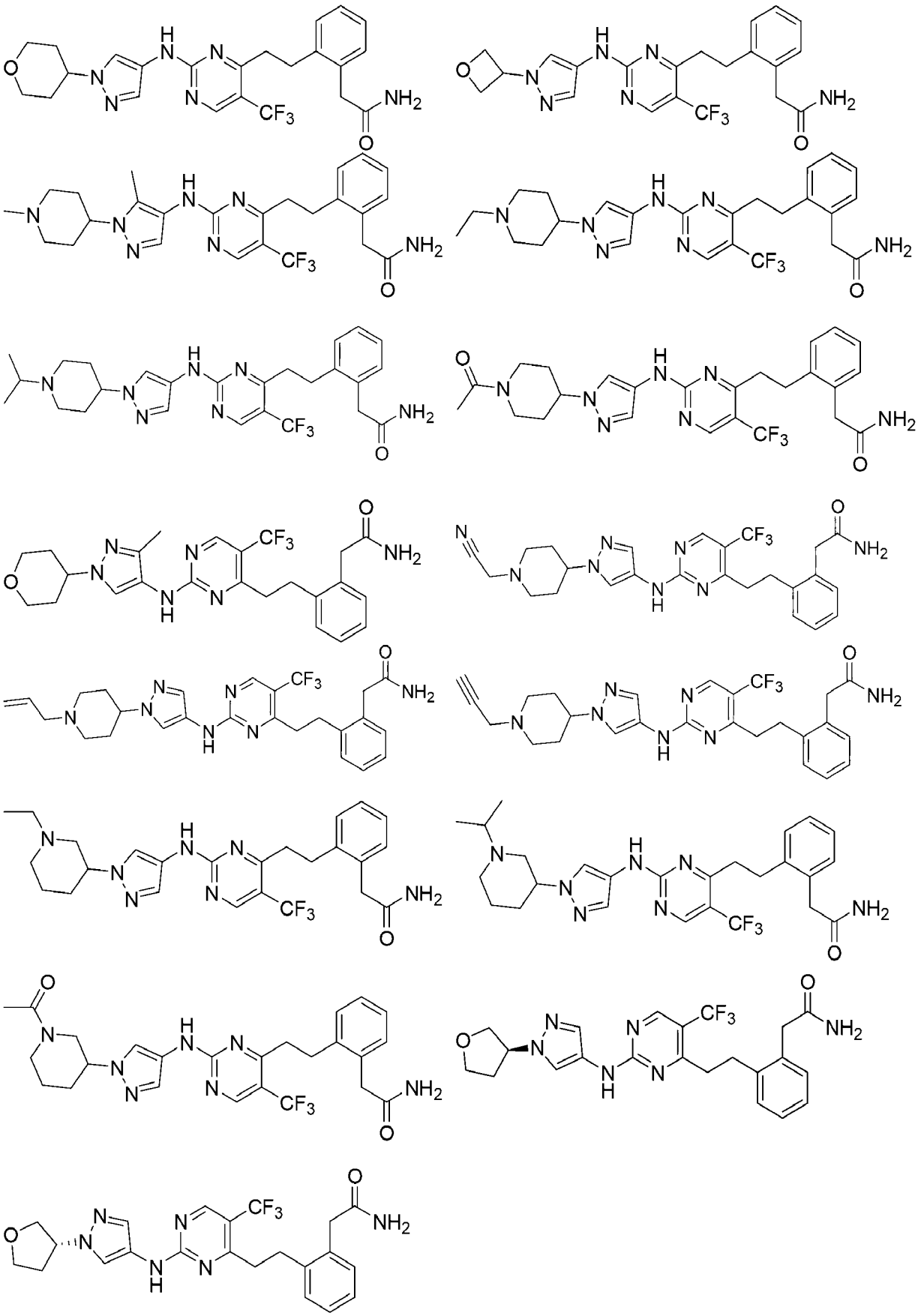
20. A compound selected from any one of the following compounds, or stereoisomers, salts, solvates or prodrugs thereof:

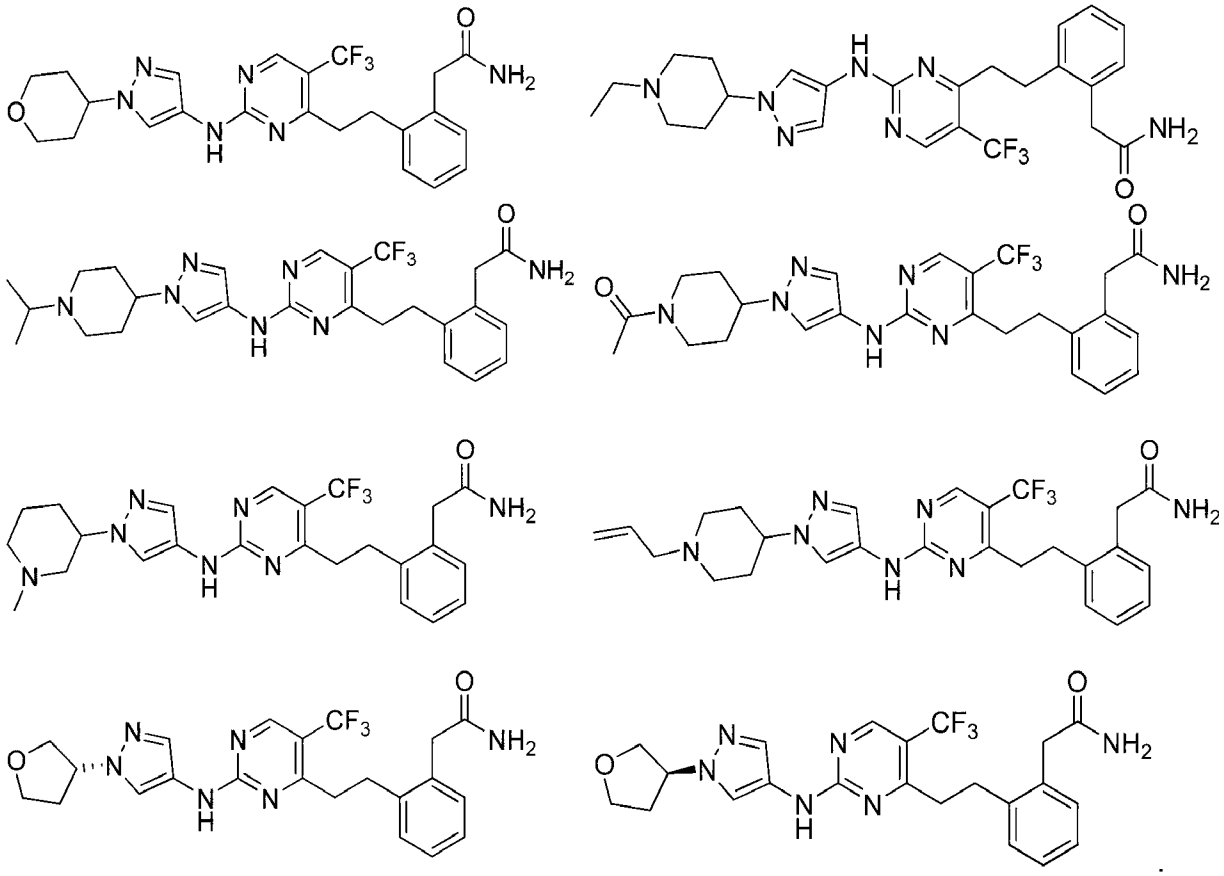


















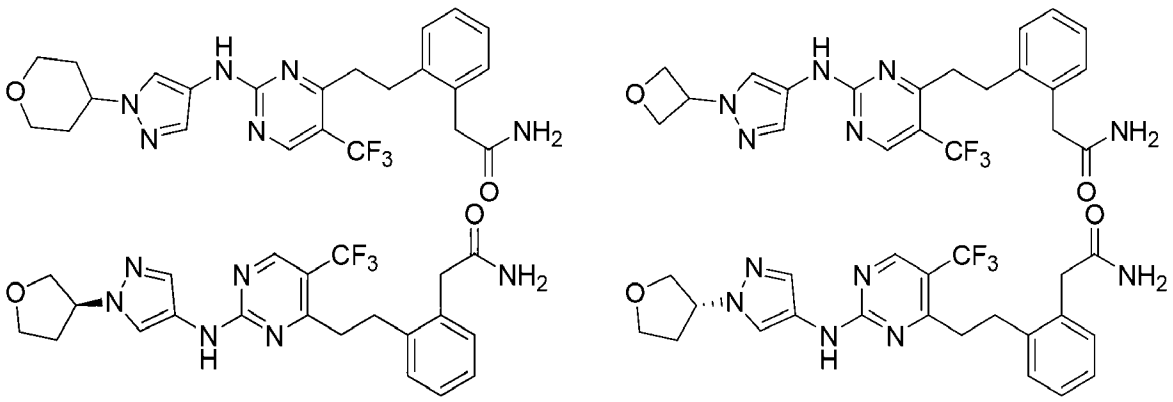
21. A compound selected from any one of the following compounds, or stereoisomers, salts, solvates or prodrugs thereof:



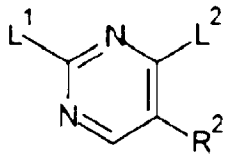
22. A compound selected from any one of the following compounds, or stereoisomers, salts, solvates or prodrugs thereof:



23. A compound selected from any one of the following compounds, or stereoisomers, salts, solvates or prodrugs thereof:



24. A process for the preparation of a compound according to any one of claims 1 to 23 or stereoisomers, salts, solvates or prodrug thereof, comprising reacting a compound of formula F1



F1

with a compound of formula A-$NH_2$ to displace the group $L^1$ and with a compound of formula $HC\equiv R^3$ to displace the group $L^2$, or
with a compound of formula $HC\equiv R^3$ to displace the group $L^2$ and with a compound of formula A-$NH_2$ to displace the group $L^1$,
wherein A, $R^2$ and $R^3$ are as defined in claim 1 and $L^1$ and $L^2$ are leaving groups.

25. A pharmaceutical agent comprising a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23.

26. A composition comprising a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, and a pharmaceutically acceptable carrier or diluents.

27. A composition according to claim 26, wherein the composition further comprising an anti-tumour agent selected from the group consisting of antiproliferative drugs, antineoplastic drugs, cytostatic agents, anti-invasion agents, inhibitors of growth factor function, antiangiogenic agents, antilymphangiogenic agents, vascular damaging agents, and combinations thereof.

28. A compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 for use in a method of therapy.

29. The use of a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 in the preparation of a medicament for treating a disease ameliorated by the inhibition of FAK.

30. The use of a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim

26 in the preparation of a medicament for treating a disease ameliorated by the inhibition of VEGFR3.

31. The use of a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 in the preparation of a medicament for treating cancer.

32. The use of a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 in the preparation of a medicament for inhibiting supressing or reducing lymphangiogenesis.

33. A compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 for use in a method of treatment of a disease ameliorated by the inhibition of FAK.

34. A compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 for use in a method of treatment of a disease ameliorated by the inhibition of VEGFR3.

35. A compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 for use in the method for treating cancer.

36. A compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 for use in the method for inhibiting, supressing or reducing lymphangiogenesis.

37. A compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 for use in a method of treatment of the human or animal body.

38. A method of inhibiting FAK *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26.

39. A method of inhibiting VEGFR3 *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound or a stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26.

40. The use of claim 31 or the compound or stereoisomer, salt, solvate or prodrug thereof of claim 35, wherein the cancer is selected from bone cancer, brain stem glioma, breast cancer, cancer of the adrenal gland, cancer of the anal region, cancer of the bladder, cancer of the endocrine system, cancer of the oesophagus, cancer of the brain, cancer of the head or neck, cancer of the kidney or ureter, cancer of the liver, cancer of the parathyroid gland, cancer of the penis, cancer of the small intestine, cancer of the thyroid gland, cancer of the urethra, carcinoma of the cervix, carcinoma of the endometrium, carcinoma of the fallopian tubes, carcinoma of the renal pelvis, carcinoma of the vagina, carcinoma of the vulva, chronic or acute leukemia, acute myelogenous leukemia, colon cancer, melanoma such as cutaneous or intraocular melanoma, haemetological malignancies, Hodgkin's disease, lung cancer, non-small cell lung cancer (NSCLC), mesothelioma, lymphocytic lymphomas, neoplasms of the central nervous system (CNS), ovarian cancer, pancreatic cancer, pituitary adenoma, primary CNS lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, sarcoma of soft tissue, skin cancer, spinal axis tumors, stomach cancer, uterine cancer, hepatocellular carcinoma, small cell lung carcinoma, sarcoma, osteosarcoma, cervical cancer, colon cancer, neuroblastoma, head and neck cancer, hematopoietic cancer and mesothelioma.

41. The use of claim 32 or the compound or stereoisomer, salt, solvate or prodrug thereof of claim 36, wherein inhibiting, supressing or reducing lymphangiogenesis prevents and/or treats diseases of conditions selected from eye diseases, skin inflammations, rejection in renal transplantation, rheumatoid arthritis, diabetic retinopathy, cardiovascular diseases, autoimmune disease, fibrosis, restenosis, diabetes mellitus, thrombosis, glomerulonephritis and neurodegeneration.

42. An anti-cancer agent comprising a compound or an stereoisomer, salt, solvate or prodrug thereof according to any one of claims 1 to 23, agent according to claim 25 or composition according to claim 26 and an anti-tumour agent.

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/AU2015/000089**

A. CLASSIFICATION OF SUBJECT MATTER

***C07D 403/14 (2006.01)*** ***C07D 401/04 (2006.01)*** ***C07D 401/12 (2006.01)*** ***C07D 401/14 (2006.01)*** ***C07D 403/04 (2006.01)***
***C07D 403/12 (2006.01)*** ***C07D 413/14 (2006.01)*** ***C07D 405/04 (2006.01)*** ***C07D 405/12 (2006.01)*** ***C07D 405/14 (2006.01)***
***C07D 407/04 (2006.01)*** ***C07D 407/12 (2006.01)*** ***C07D 407/14 (2006.01)*** ***A61K 31/505 (2006.01)*** ***A61K35/506 INVALID***
***A61P 35/00 (2006.01)***

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)

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)

Inventor and Applicant search:

Patentscope & Google: Bionomics Limited; Harvey, Andrew. J.; VEGFR3 Inhibitors.

STN Registry and CAplus: Substructure search based on compounds of formula (I)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| | Documents are listed in the continuation of Box C | |

[X] Further documents are listed in the continuation of Box C [X] 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
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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 |
|---|---|
| 28 May 2015 | 28 May 2015 |
| **Name and mailing address of the ISA/AU** | **Authorised officer** |
| AUSTRALIAN PATENT OFFICE<br>PO BOX 200, WODEN ACT 2606, AUSTRALIA<br>Email address: pct@ipaustralia.gov.au | Pina Potenza<br>AUSTRALIAN PATENT OFFICE<br>(ISO 9001 Quality Certified Service)<br>Telephone No. 0399359614 |

| INTERNATIONAL SEARCH REPORT<br>C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | International application No.<br>**PCT/AU2015/000089** |
|---|---|---|
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | WO 2012/022408 A1 (MERCK PATENT GMBH) 23 February 2012<br>& AU2011291110 A1<br>Abstract; Generic definition pages 7-9; Preparation process pages 9-10; Compounds "A107", "A108" and "A109" on pages 95-96 and 111; Claims 1, 9 and 10-12 | 1-42 |
| P,X | WO 2014/026242 A1 (CANCER THERAPEUTICS CRC PTY LIMITED) 20 February 2014<br>Abstract; Generic definition pages 5-7 and Claim 1; Preparation process page 12 and Claim 53; Examples 4-5, 13-14, 24, 28, 30, 33, 35-36, 40; Claims 1, 6-13, 21-48 | 1-42 |
| P,X | WO 2014/026243 A1 (CANCER THERAPEUTICS CRC PTY LIMITED) 20 February 2014<br>Abstract; Generic definition pages 5-8 and Claim 1; Preparation process page 10 and Claim 67; Examples 5-6, 9-22, 25-49, 51, 53-69, 72-77; Claims 1-78 | 1-42 |

| INTERNATIONAL SEARCH REPORT<br>Information on patent family members | International application No.<br>**PCT/AU2015/000089** |
|---|---|

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| **Patent Document/s Cited in Search Report** | | **Patent Family Member/s** | |
|---|---|---|---|
| **Publication Number** | **Publication Date** | **Publication Number** | **Publication Date** |
| WO 2012/022408 A1 | 23 February 2012 | AR 082722 A1 | 26 Dec 2012 |
| | | AU 2011291110 A1 | 04 Apr 2013 |
| | | AU 2011291110 B2 | 22 Jan 2015 |
| | | CA 2808540 A1 | 23 Feb 2012 |
| | | CN 103052627 A | 17 Apr 2013 |
| | | DE 102010034699 A1 | 23 Feb 2012 |
| | | EP 2606034 A1 | 26 Jun 2013 |
| | | JP 2013534227 A | 02 Sep 2013 |
| | | US 2013158005 A1 | 20 Jun 2013 |
| | | US 8906916 B2 | 09 Dec 2014 |
| WO 2014/026242 A1 | 20 February 2014 | AU 2013302319 A1 | 26 Feb 2015 |
| | | CA 2882270 A1 | 20 Feb 2014 |
| | | US 2014080798 A1 | 20 Mar 2014 |
| WO 2014/026243 A1 | 20 February 2014 | AU 2013302320 A1 | 26 Feb 2015 |
| | | CA 2882158 A1 | 20 Feb 2014 |
| | | US 2014073620 A1 | 13 Mar 2014 |

**End of Annex**

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.