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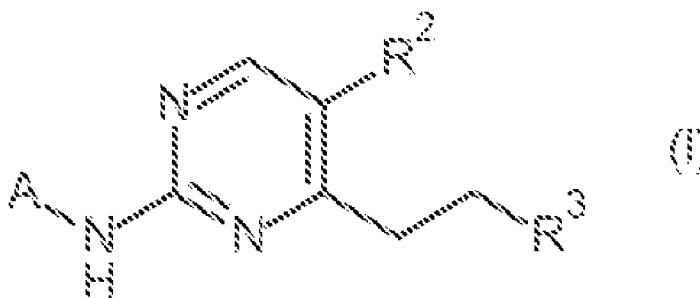
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[Continued on next page]

(54) Title: VEGFR3 INHIBITORS



(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 as well as the treatment of diseases ameliorated by the control and/or inhibition of lymphangiogenesis.



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GW, KM, ML, MR, NE, SN, TD, TG).

— *with international search report (Art. 21(3))*

— *with amended claims (Art. 19(1))*

VEGFR3 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 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, as well as the treatment of diseases ameliorated by the control and/or inhibition of lymphangiogenesis.

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).

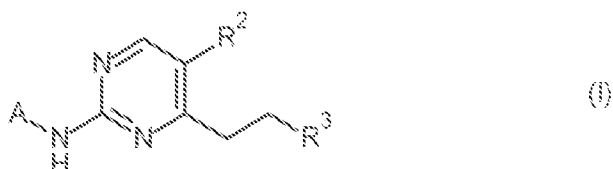
Accordingly, compounds that inhibit VEGFR3 may be useful for the prevention and/or treatment of rejection in renal transplantation.

Co-pending application PCT/GB2012/000175 discloses compounds which inhibit FAK and VEGFR3.

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 FAK and/or VEGFR2.

In a first aspect, the present invention provides compounds of the following formula (I) or isomers, salts, solvates or prodrugs thereof:



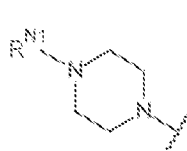
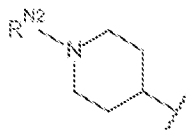
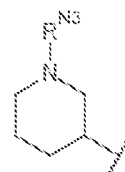
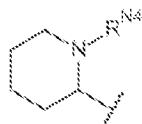
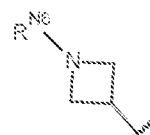
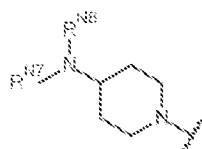
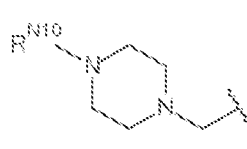
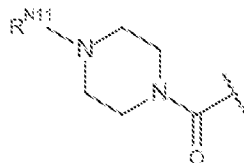
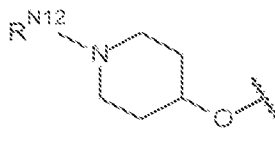
wherein:

A is an optionally substituted 5-10 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; and

A may bear a single substituent R^{1A} which is not *alpha* to the NH group, and may optionally further bear one, two or three substituents R^{1C}, where R^{1A} is selected from:

- (i) CH(R^{C1})NHZ¹, where R^{C1} is selected from H, C₁₋₂ alkyl and Z¹ is selected from H, C₁₋₃ alkyl optionally substituted by OH, C(=O)OC₁₋₃ alkyl and C(=O)Me;
- (ii) XNHZ², where X is selected from CMe₂, cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidene and Z² is selected from H, C₁₋₃ alkyl optionally substituted by OH, C(=O)OC₁₋₃ alkyl and C(=O)Me;

6

(iii) a group selected from R^{1A1} to R^{1A11} : (R^{1A1})  (R^{1A2})  (R^{1A3})  (R^{1A4})  (R^{1A5})  (R^{1A6})  (R^{1A7})  (R^{1A8})  (R^{1A9})  (R^{1A10})  (R^{1A11})

wherein:

 R^{N1} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$; R^{N2} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;5 R^{N3} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$; R^{N4} is selected from H and CH_3 ; R^{N5} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$; R^{N6} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$; R^{N7} and R^{N8} are independently selected from H and CH_3 ;10 R^{N9} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$; R^{N10} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$; R^{N11} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$; and R^{N12} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;and where each R^{10} is independently selected from:15 (i) C_{1-3} alkyl;(ii) CF_3 ;

- (iii) F;
- (iv) Cl;
- (v) O-(C₁₋₃ alkyl);
- (vi) CN; and
- (vii) =O;

R² is selected from H, halo, C₁₋₄ alkyl, CF₃, CF₂H, CN and methoxy;

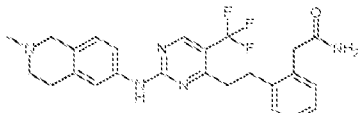
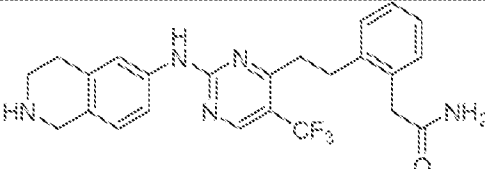
R³ is selected from substituted phenyl and a substituted 6 membered heteroaryl group,

where the heteroaryl ring system contains 1 or 2 N heteroatoms, where

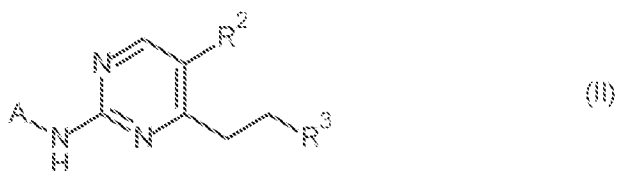
R⁴ bears a substituent R⁶ either *alpha* or *beta* to the -C₂H₄- group, and may additionally bear further substituents selected from F, methyl and CF₃; and

R⁴ is -CH₂-C(O)N(R^{N13})Z³, where R^{N13} is selected from H and CH₃; and Z³ is selected from H, CH₃ and OCH₃.

In some embodiments, the compounds of the first aspect of the present invention are of formula (i) as defined above with the proviso that the compound is not :

C21	
C32	

In a second aspect, the present invention provides compounds of the following formula (II) or isomers, salts, solvates or prodrugs thereof:



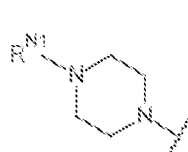
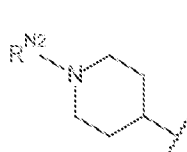
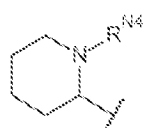
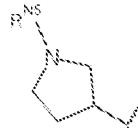
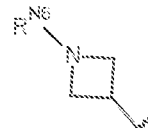
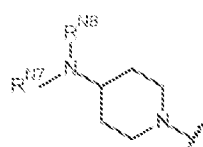
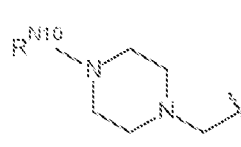
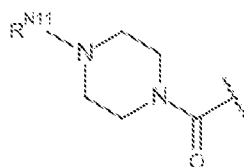
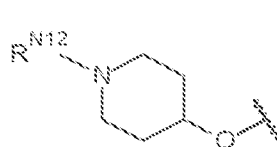
wherein:

A is optionally substituted phenyl;

when A is optionally substituted phenyl, A may bear a substituent R^{1A} which is not *alpha* to the NH group and may optionally further bear one or two substituents R^{1B} which are not *alpha* to the NH group, where R^{1A} is selected from:

- (i) CH(R^{C1})NHZ¹, where R^{C1} is selected from H, C₁₋₂ alkyl and Z¹ is selected from H, C₁₋₃ alkyl optionally substituted by OH, C(=O)OC₁₋₃ alkyl and C(=O)Me;

- (ii) XNHZ^2 , where X is selected from CMe_2 , cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidene and Z^2 is selected from H, C_{1-3} alkyl optionally substituted by OH, $\text{C}(=\text{O})\text{OC}_{1-3}$ alkyl and $\text{C}(=\text{O})\text{Me}$;
- (iii) a group selected from R^{1A1} to R^{1A11} :

 (R^{1A1})  (R^{1A2})  (R^{1A3})  (R^{1A4})  (R^{1A5})  (R^{1A6})  (R^{1A7})  (R^{1A8})  (R^{1A9})  (R^{1A10})  (R^{1A11})

5 wherein:

R^{N1} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $\text{C}(=\text{O})\text{Me}$;

R^{N2} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $\text{C}(=\text{O})\text{Me}$;

R^{N3} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $\text{C}(=\text{O})\text{Me}$;

R^{N4} is selected from H and CH_3 ;

10 R^{N5} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $\text{C}(=\text{O})\text{Me}$;

R^{N6} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $\text{C}(=\text{O})\text{Me}$;

R^{N7} and R^{N8} are independently selected from H and CH_3 ;

R^{N9} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $\text{C}(=\text{O})\text{Me}$;

R^{N10} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $\text{C}(=\text{O})\text{Me}$;

15 R^{N11} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $\text{C}(=\text{O})\text{Me}$; and

R^{N12} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $\text{C}(=\text{O})\text{Me}$;

and where each R^{1B} is independently selected from:

- (i) C_{1-3} alkyl;
- (ii) CF_3 ;
- (iii) F;
- (iv) Cl;
- (v) $O-(C_{1-3} \text{ alkyl})$; and
- (vi) CN;

R^2 is selected from H, halo, C_{1-4} alkyl, CF_3 , CF_2H , CN and methoxy;

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, 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 ; and

R^4 is $-CH_2-C(O)N(R^{N13})Z^3$, where R^{N13} is selected from H and CH_3 ; and Z^3 is selected from H, CH_3 and OCH_3 .

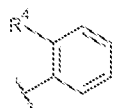
In some embodiments, the compounds of the second aspect of the present invention are of formula (II) or isomers, salts, solvates or prodrugs thereof as defined above with the proviso that the compound is not any of the following compounds:

C1		C17	
C2		C18	
C3		C19	
C4		C20	
C5		C21	
C6		C22	

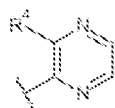
C7		C23	
C8		C24	
C9		C25	
C10		C26	
C11		C27	
C12		C28	
C13		C29	
C14		C30	
C15		C31	
C16			

In some embodiments, the compounds of the second aspect are of formula (II) as defined above with the proviso that:

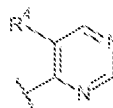
when R^3 is selected from:



;

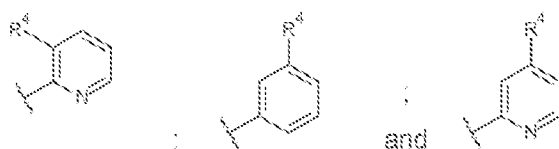


;

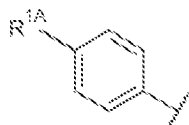


;

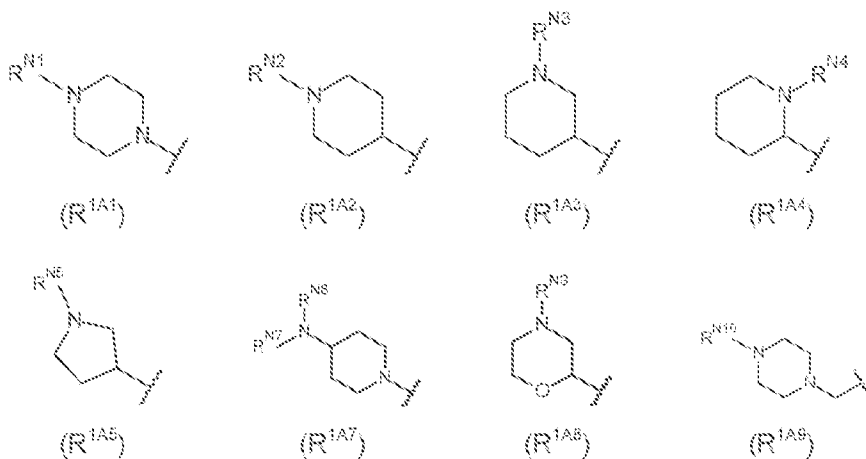
11



A is either:



where R^{1A} is selected from



and R^{N1} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

R^{N2} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

5 R^{N3} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

R^{N4} is selected from H and CH_3 ;

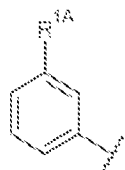
R^{N5} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

R^{N7} and R^{N8} are independently selected from H and CH_3 ;

R^{N9} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

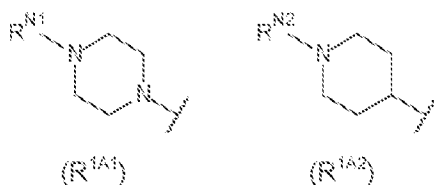
10 R^{N10} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

or



where R^{1A} is

12

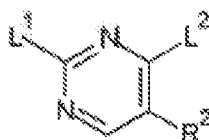


and R^{N1} is selected from H, C₁₋₃ alkyl, and C(=O)Me;

R^{N2} is selected from H, C₁₋₃ alkyl, and C(=O)Me;

then R² is not selected from CF₃, halo, CF₂H and CN.

- 5 A third aspect of the invention provides a process for the preparation of a compound of formula (I) or formula (II) or isomers, salts, solvates or prodrugs thereof of either the first aspect or the second aspect, comprising reacting a compound of formula F1



F1

with a compound of formula A-NH₂ to displace the group L¹ and with a compound of formula HCER³ to displace the group L²; or

with a compound of formula HCER³ to displace the group L² and with a compound of formula A-NH₂ to displace the group L¹,

wherein A, R² and R³ are as defined in formula (I) or (II) above and L¹ and L² are leaving groups.

15 A fourth aspect of the invention provides a pharmaceutical agent comprising a compound of the formula (I) or formula (II) or isomers, salts, solvates or prodrugs thereof of either the first aspect or the second aspect.

20 There is also provided use of a compound of formula (I) or formula (II) or isomers, salts, solvates, protected forms or prodrugs thereof of either the first aspect or the second aspect as a pharmaceutical agent.

25 There is further provided a compound of formula (I) or formula (II) or isomers, salts, solvates or prodrugs thereof of either the first aspect or the second aspect for use as a pharmaceutical agent.

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

5 A fifth aspect of the present invention provides a composition comprising a compound of formula (I) or formula (II) or an isomer, salt, solvate or prodrug thereof of either the first aspect or the second aspect and a pharmaceutically acceptable carrier or diluent.

10 A sixth aspect of the invention provides a compound of formula (I) or formula (II) or an isomer, salt, solvate or prodrug thereof of either the first aspect or the second aspect, agent of the fourth aspect or composition of the fifth aspect for use in a method of therapy.

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

20 An eighth aspect of the invention provides for the use of a compound of formula (I) or formula (II) or an isomer, salt, solvate or prodrug thereof of either the first aspect or the second aspect, agent of the fourth aspect or composition of the fifth aspect in the preparation of a medicament for treating cancer. The eighth aspect of the invention also provides a compound of formula (I) or formula (II) or an isomer, salt, solvate or prodrug thereof of either the first aspect or the second aspect, agent of the fourth aspect or composition of the fifth aspect for use in the method of treatment of cancer.

30 A further aspect of the invention provides a compound of formula (I) or formula (II) or an isomer, salt, solvate or prodrug thereof of either the first aspect or the second aspect, agent of the fourth aspect or composition of the fifth aspect for use in a method of treatment of the human or animal body, preferably in the form of a pharmaceutical composition.

35 Another aspect of the invention 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 formula (II) or an isomer, salt, solvate or prodrug thereof of either the first aspect or the second aspect, agent of the fourth aspect or composition of the fifth aspect.

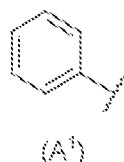
A still further aspect of the invention provides an anti-cancer treatment comprising a compound of formula (I) or formula (II) or an isomer, salt, solvate or prodrug thereof of either the first aspect or the second aspect, agent of the fourth aspect or composition of the fifth aspect and an anti-tumour agent.

Each of the groups A, and R^1 to R^4 from the first and second aspects of the invention will be discussed in more detail below.

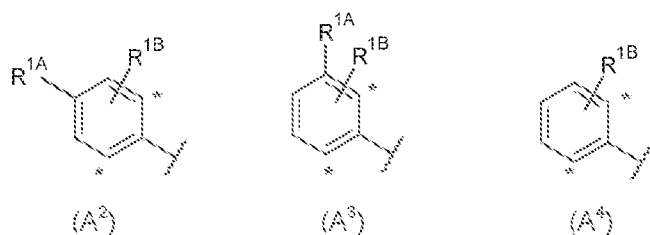
A

A is selected from optionally substituted phenyl (in the second aspect of the invention) and an optionally substituted 5-10 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom (in the first aspect of the invention), in which the heteroaryl ring system contains 1 to 4 heteroatoms selected from N, O and S.

If A is unsubstituted phenyl, it has the structure:



If A is substituted phenyl, the R^{1A} group can either be *meta* or *para*, and so A can have the structures:



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

When A is a 5-10 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, it 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:

- 5 N₁: pyrrole (azole) (5-membered), pyridine (azine) (6-membered);
 O₁: furan (oxole) (5-membered);
 S₁: thiophene (thiole) (5-membered);
 N₁O₁: oxazole (5-membered), isoxazole (5-membered), isoxazine (6-membered);
 N₂O₁: oxadiazole (furazan) (5-membered),
 10 N₃O₁: oxatriazole (5-membered);
 N₁S₁: thiazole (5-membered), isothiazole (5-membered);
 N₂: 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);
 15 N₃: triazole (5-membered), triazine (6-membered); and,
 N₄: tetrazole (5-membered).

Examples of heteroaryl groups which comprise fused rings, include, but are not limited to, those derived from:

- 20 9-membered (with 2 fused rings) derived from benzofuran (O₁), isobenzofuran (O₁), indole (N₁), isoindole (N₁), indolizine (N₁), indoline (N₁), isoindoline (N₁), purine (N₄) (e.g., adenine, guanine), benzimidazole (N₂), indazole (N₂), benzoxazole (N₁O₁), benzisoxazole (N₁O₁), benzodioxole (O₂), benzofurazan (N₂O₁), benzotriazole (N₃), benzothiofuran (S₁), benzothiazole (N₁S₁), benzothiadiazole (N₂S);
 25 10-membered (with 2 fused rings) derived from chromene (O₁), isochromene (O₁), chroman (O₁), isochroman (O₁), benzodioxan (O₂), quinoline (N₁), isoquinoline (N₁), quinolizine (N₁), benzoxazine (N₁O₁), benzodiazine (N₂), pyridopyridine (N₂), quinoxaline (N₂), quinazoline (N₂), cinnoline (N₂), phthalazine (N₂), naphthyridine (N₂), pteridine (N₄).

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

- 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
 35 heteroatoms selected from N, O and S. Preferably the heteroatoms are N atoms.

If A is 6-membered heteroaryl, the R^{1A} group can either be *meta* or *para* to the NH group. If A is 5-membered heteroaryl or a 7 to 10 membered heteroaryl, the R^{1A} group is not *alpha* to the -NH- group. Thus, when A is 5-membered heteroaryl, the R^{1A} group is *beta* to the -NH- group

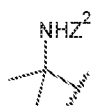
R^{1A}

R^{1A} may have one of the following structures:

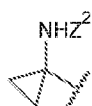
CH_2NHZ^1 ;

$CH(CH_3)NHZ^1$;

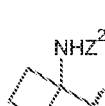
$CH(C_2H_5)NHZ^1$;



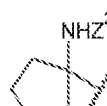
(R^{1A1})



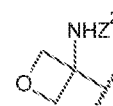
(R^{1A2})



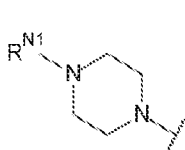
(R^{1A3})



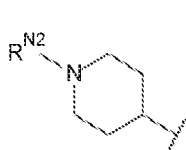
(R^{1A4})



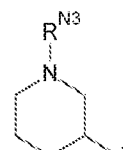
(R^{1A5})



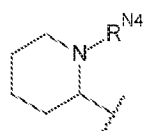
(R^{1A6})



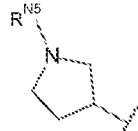
(R^{1A7})



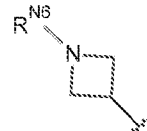
(R^{1A8})



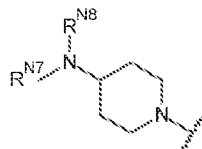
(R^{1A9})



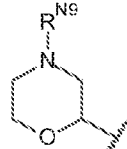
(R^{1A10})



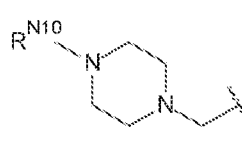
(R^{1A11})



(R^{1A12})

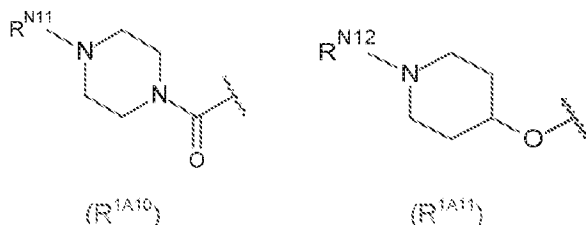


(R^{1A13})



(R^{1A14})

17



wherein:

R^{N1} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N2} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

5 R^{N3} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N4} is selected from H and CH₃;

R^{N5} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N6} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N7} and R^{N8} are independently selected from H and CH₃;

10 R^{N9} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N10} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N11} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me; and

R^{N12} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me.

15 Each of R^{N1}, R^{N2}, R^{N3}, R^{N5}, R^{N6}, R^{N9}, R^{N10}, R^{N11} and R^{N12} is independently selected from H, C₁₋₄ alkyl (i.e. methyl, ethyl, prop-1-yl, prop-2-yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl), C₃₋₄ cycloalkyl (i.e. cyclopropyl, methylcyclopropyl, cyclobutyl) and C(=O)Me. Each of R^{N4}, R^{N7} and R^{N8} is independently selected from either H or methyl.

20 Each of Z¹ and Z² is independently selected from H, C₁₋₃ alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl), optionally substituted by OH, C(=O)OC₁₋₃ 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.

R^{1B}

25 Each R^{1B} group may be C₁₋₃ alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl), CF₃, F, Cl, O-C₁₋₃ alkyl (i.e. methoxy, ethoxy, prop-1-oxy and prop-2-oxy) or CN. These groups may be 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).

30

18

 R^{1C}

Each R^{1C} group may be C_{1-3} alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl), CF_3 , F, Cl, O-
 C_{1-3} alkyl (i.e. methoxy, ethoxy, prop-1-oxy and prop-2-oxy), CN or =O. These groups may be
 substituted at any available ring position on A. There may be up to 3 R^{1C} groups (i.e. 1, 2 or
 3) depending on the nature of A, and in particular on the number of ring atoms and ring
 heteroatoms, as well as whether R^{1A} is present.

 R^2

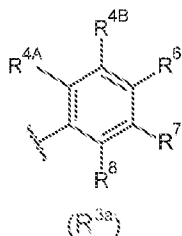
R^2 is selected from H, halo (i.e. F, Cl, Br, I), C_{1-4} alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-
 yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl), CF_3 , CF_2H , CN and methoxy.

In some embodiments, the halo group is either F or Cl.

 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.

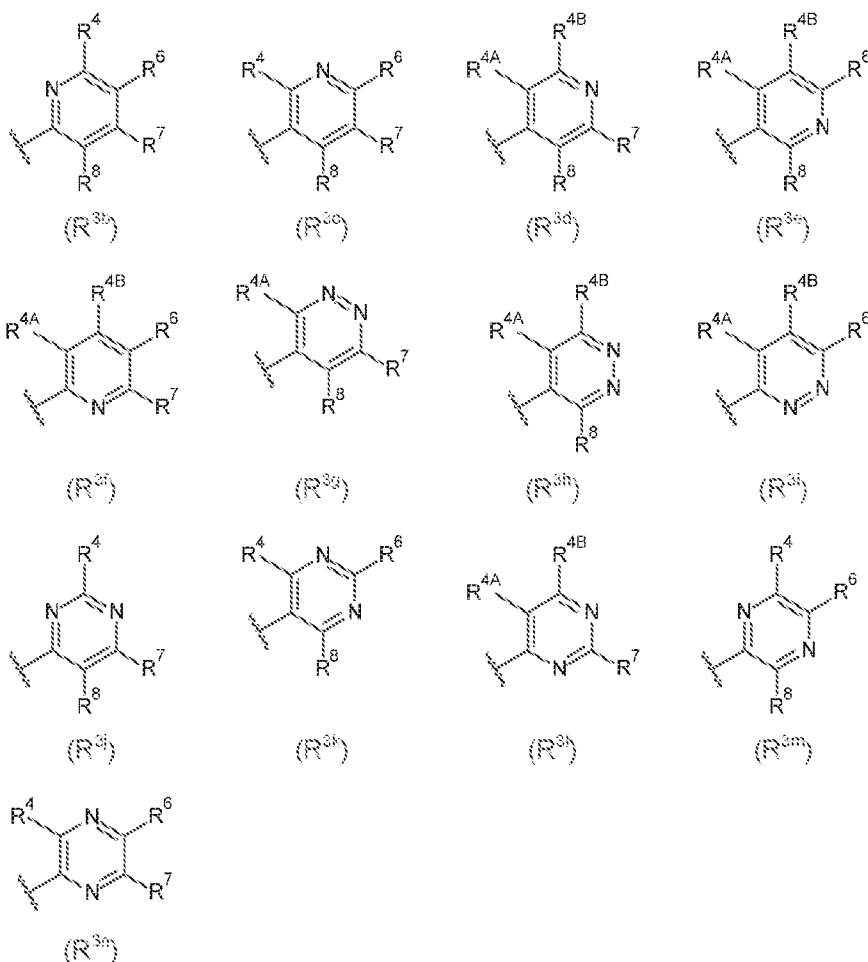
When R^3 is substituted phenyl, it has the structure:



where R^5 , 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:
 pyridyl; pyridazinyl (1,2-diazinyl); pyrimidinyl (1,3-diazinyl); and pyrazinyl (1,4-diazinyl).

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



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*.

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 upto 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 heteroatoms.

R^4
 R^4 is $-CH_2-C(O)N(R^{N10})Z^3$.

R^{N13} is selected from H and CH_2 , and Z^3 is selected from H, CH_2 or OCH_3 . Thus, R^4 is selected from:

- (i) $-CH_2-C(O)NH_2$;
- (ii) $-CH_2-C(O)NHMe$;
- 5 (iii) $-CH_2-C(O)NMe_2$;
- (iv) $-CH_2-C(O)N(OMe)H$; and
- (v) $-CH_2-C(O)N(OMe)Me$.

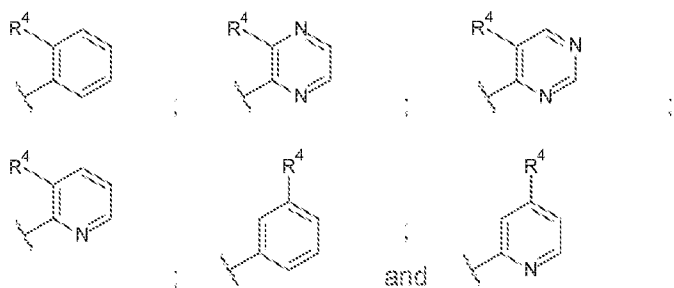
Proviso

- 10 In some embodiments of the second aspect, compounds of WO2012/110773 are disclaimed from the present application (C1 – C32 below):

C1		C17	
C2		C18	
C3		C19	
C4		C20	
C5		C21	
C6		C22	
C7		C23	
C8		C24	
C9		C25	

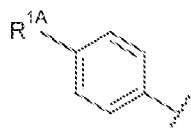
C10		C26	
C11		C27	
C12		C28	
C13		C29	
C14		C30	
C15		C31	
C16		C32	

In other embodiments of the second aspect, the compounds of the present invention do not include those disclosed in WO2012/110773, which is incorporated herein by reference. In particular, when R^3 is selected from:



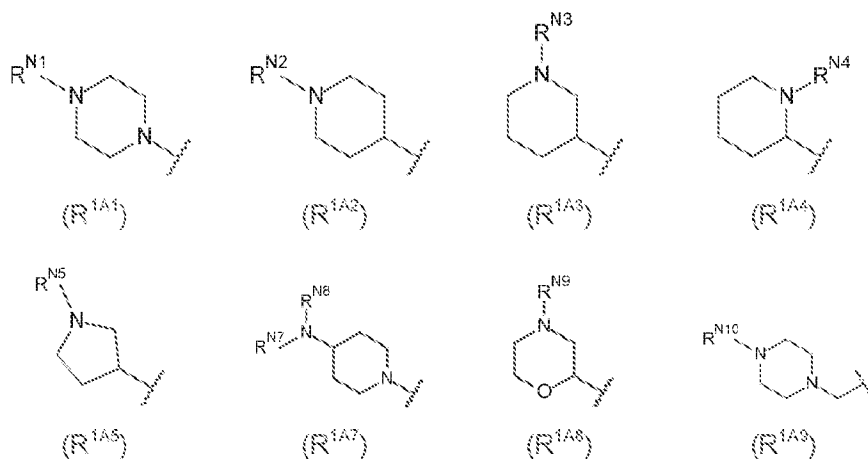
5

A is either:



where R^{1A} is selected from

22



and R^{N1} is selected from H, C₁₋₃ alkyl, and C(=O)Me;

R^{N2} is selected from H, C₁₋₃ alkyl, and C(=O)Me;

R^{N3} is selected from H, C₁₋₃ alkyl, and C(=O)Me;

R^{N4} is selected from H and CH₃;

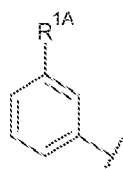
5 R^{N6} is selected from H, C₁₋₃ alkyl, and C(=O)Me;

R^{N7} and R^{N8} are independently selected from H and CH₃;

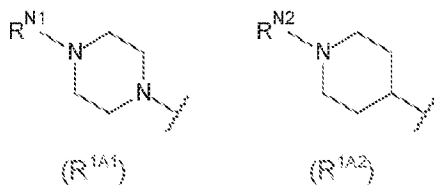
R^{N9} is selected from H, C₁₋₃ alkyl, and C(=O)Me;

R^{N10} is selected from H, C₁₋₃ alkyl, and C(=O)Me;

or



10 where R^{1A} is



and R^{N1} is selected from H, C₁₋₃ alkyl, and C(=O)Me;

R^{N2} is selected from H, C₁₋₃ alkyl, and C(=O)Me;

then R² is not selected from CF₃, halo, CF₂H and CN.

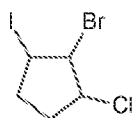
15 *Includes Other Forms*

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:



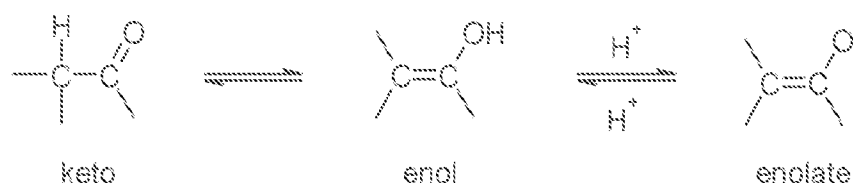
wherein the bromo group is *alpha* to the chloro group, and the iodo group is *beta* to the chloro group.

Isomers, Salts, Solvates, Protected Forms, and Prodrugs

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, *cis*- and *trans*-forms; *E*- and *Z*-forms; *c*-, *l*-, 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/hydroxyazo, and nitro/aci-nitro.



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 ^1H , ^2H (D), and ^3H (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., $-\text{COOH}$ may be $-\text{COO}^-$), 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

fromethamine, 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, pantoic, tartaric, citric, gluconic, ascorbic, maleic, hydroxymaleic, phenylacetic, glutamic, aspartic, benzoic, cinnamic, pyruvic, salicylic, sulfanilic, 2-acetoxybenzoic, 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
 5 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 ($>NO^+$).

15 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
 20 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
 25 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
 30 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 C_{1-7} 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-carboxyloxyethyl; 1-(benzoyloxy)ethyl; 1-isopropoxy-carboxyloxyethyl; 1-isopropoxy-carboxyloxyethyl; 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).

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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.

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Selectivity

The selectivity of the compounds for inhibiting VEGFR3 over other kinases, such as FAK and/or VEGFR2 can be demonstrated by cellular assay results (see, for example, the VEGFR3 and VEGFR2 assays described below).

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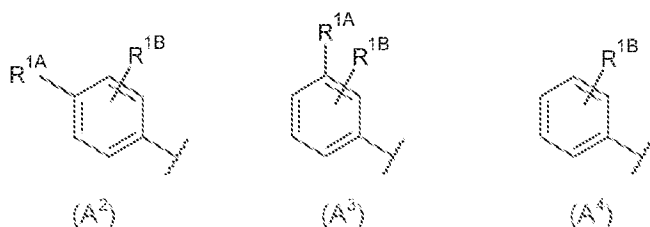
Further Embodiments

The following embodiments and preferences relate to both first and second aspects of the invention and may be combined with one another as appropriate.

20

A

In the second aspect, A is optionally substituted phenyl and can have the structures:

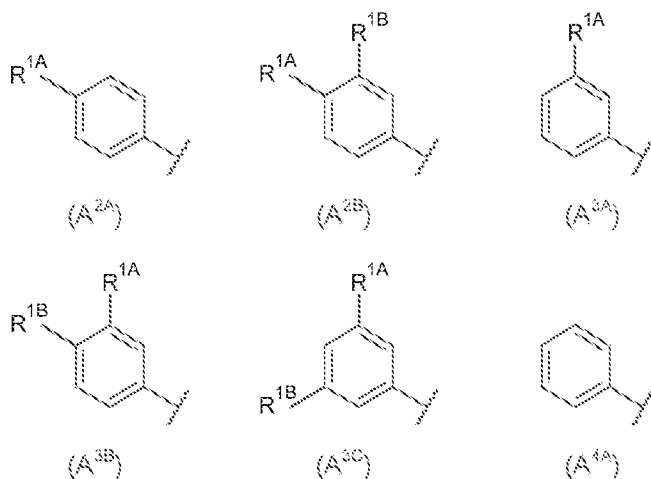


where the R^{1b} group cannot be *alpha* the connection point to the rest of the compound.

25

In these embodiments (i.e. when A is phenyl), it may be preferred that either there are no R^{1b} substituents, or a single R^{1b} substituent. If there is a single R^{1b} substituent it is may be *meta* or *para*, so further preferred A groups include:

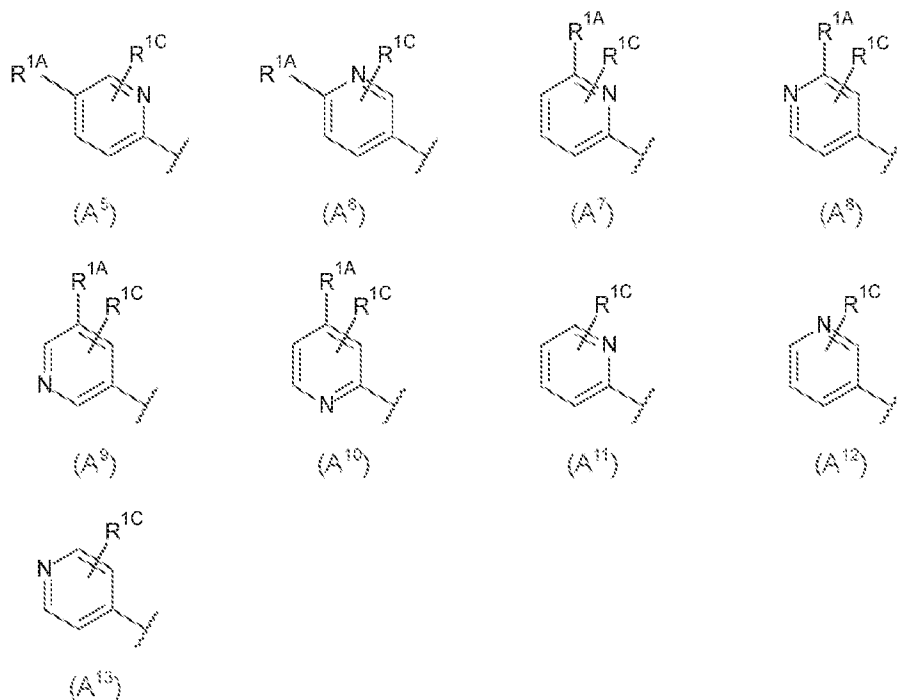
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In some embodiments of the first aspect, A is an optionally substituted 6 membered heteroaryl group. 6 membered heteroaryl groups include, but are not limited to: pyridyl, isoxaziny, pyridaziny, pyrimidinyl, pyraziny and triazinyl.

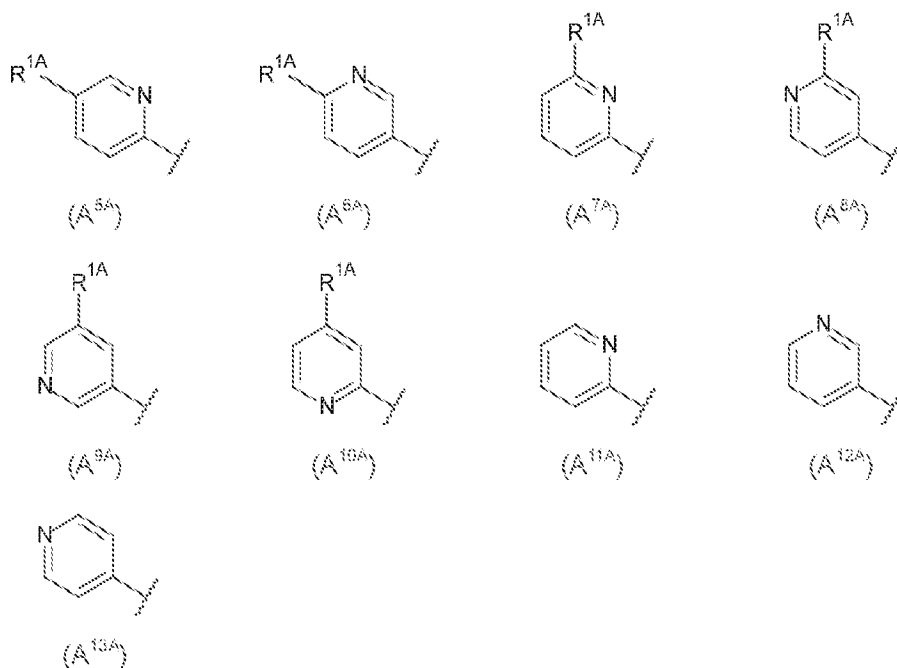
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In these embodiments, it may be preferred that A is pyridyl, which can have the structures:



In these embodiments, it is preferred that when R^{1A} is present R^{1C} is not an oxo (=O) group. Of these structures, A⁶ may be further preferred.

In these embodiments (i.e. when A is 6 membered heteroaryl group), it may be preferred that there are no R^{1C} substituents. Thus, when A is pyridyl and there are no R^{1C} groups, it may have the structures:



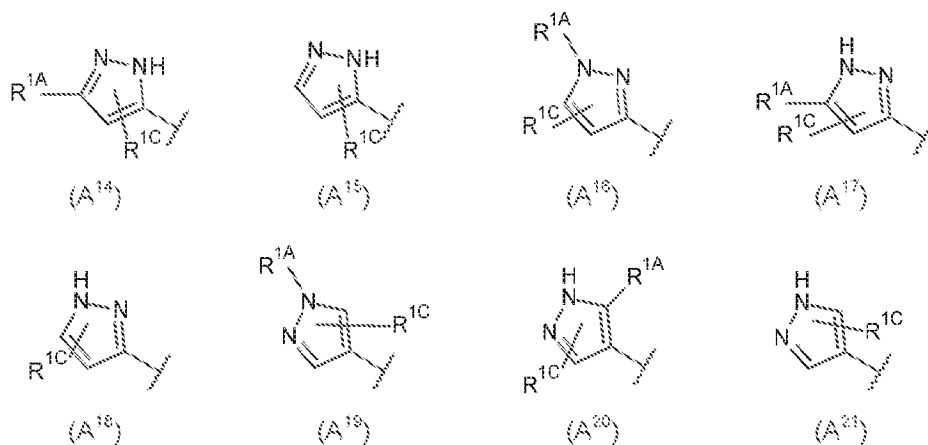
Of these structures A^{6A} may be further preferred.

5

In some embodiments of the first aspect, A is an optionally substituted 5 membered heteroaryl group. 5 membered heteroaryl groups include, but are not limited to: pyrrolyl; furanyl; thiophenyl; oxazolyl; isoxazolyl; oxadiazolyl; oxatriazolyl; thiazolyl; isothiazolyl; imidazolyl; pyrazolyl; triazolyl and tetrazolyl.

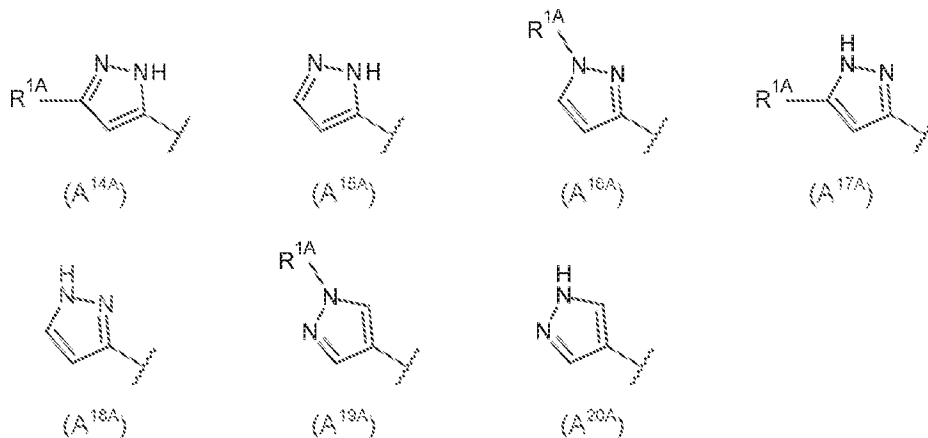
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In these embodiments, it may be preferred that A is pyrazolyl, which can have the structures:



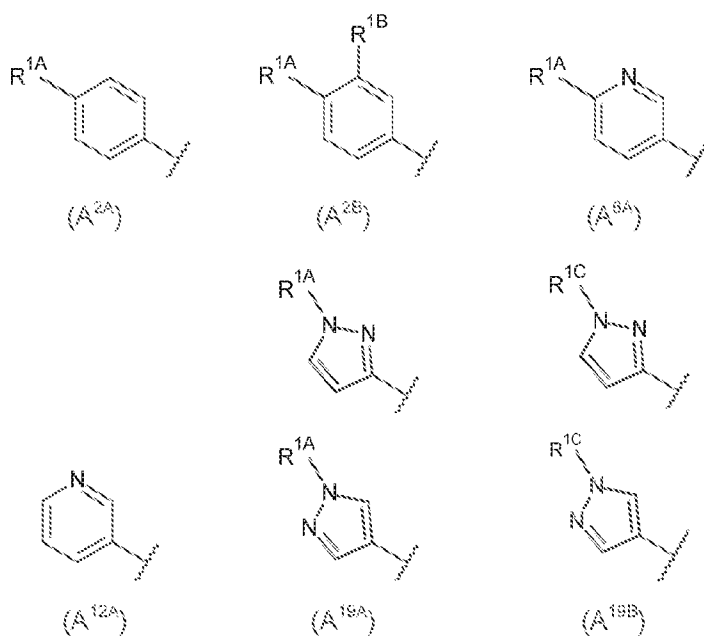
In these embodiments, it is preferred that R^{1C} is not an oxo (=O) group. Of these structures A^{16} and A^{18} may be further preferred.

In these embodiments (i.e. when A is a 5 membered heteroraryl group), it may be preferred that there are no R^{1C} substituents. Thus, when A is pyrazolyl and there are no R^{1C} groups, it may have the structures:



Of these structures A^{19A} may be further preferred.

Thus particularly preferred structures for A include:



R^{1A}

In some embodiments where R^{1A} is $CH(R^{C1})NHZ^1$, Z^1 may be any one of:

(i) H;

- (ii) C_{1-3} alkyl optionally substituted by OH, preferably Me, or CH_2CH_2OH ;
- (iii) $C(=O)OC_{1-3}$ alkyl, preferably $C(=O)OMe$; and
- (iv) $C(=O)Me$.

5 In some of these embodiments, Z^1 may be selected from H, CH_2CH_2OH and $C(=O)Me$.
 Thus, in these embodiments, R^{1A} is selected from: CH_2NH_2 ; $CH(CH_3)NH_2$; $CH(C_2H_5)NH_2$;
 $CH_2NHCH_2CH_2OH$; $CH(CH_2)NHCH_2CH_2OH$; and $CH(C_2H_5)NHCH_2CH_2OH$.
 In some embodiments where R^{1A} is $CH(R^{C1})NHZ^1$, R^{C1} may be selected from H and methyl.
 Thus, in these embodiments, R^{1A} is selected from: CH_2NHZ^1 ; and $CH(CH_3)NHZ^1$.

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In some embodiments where R^{1A} is $CH(R^{C1})NHZ^1$, Z^1 may be selected from H and CH_2CH_2OH and R^{C1} may be selected from H and methyl. Thus, in these embodiments, R^{1A} is selected from: CH_2NH_2 ; $CH_2NHCH_2CH_2OH$; $CH(CH_3)NH_2$; and $CH(CH_3)NHCH_2CH_2OH$.

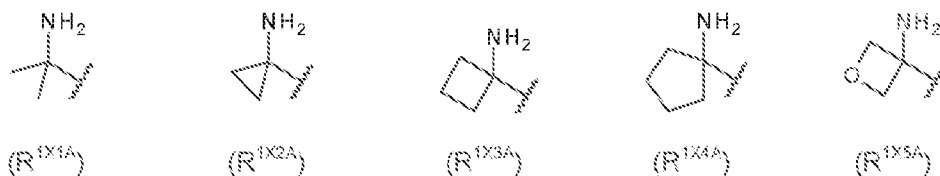
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In some embodiments where R^{1A} is $XNHZ^2$, Z^2 may be any one of:

- (i) H;
- (ii) C_{1-3} alkyl optionally substituted by OH, preferably Me, or CH_2CH_2OH ;
- (iii) $C(=O)OC_{1-3}$ alkyl, preferably $C(=O)OMe$; and
- (iv) $C(=O)Me$.

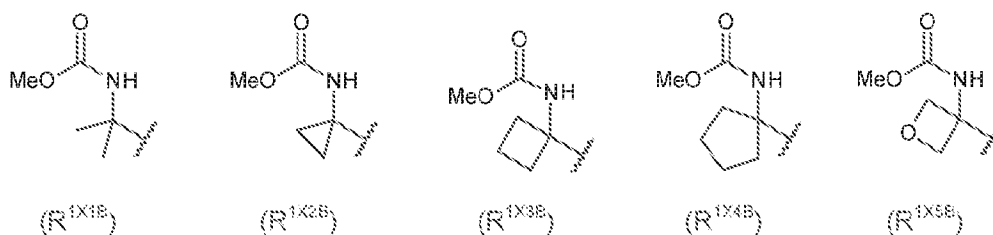
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In some embodiments where R^{1A} is $XNHZ^2$, Z^2 may be H. Thus, in these embodiments, R^{1A} has the structures:

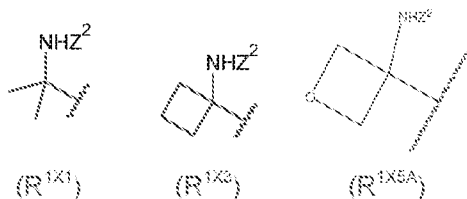


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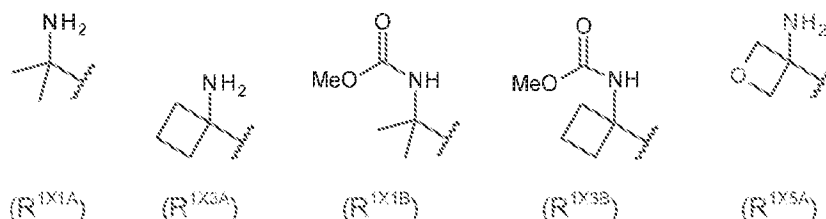
In some embodiments where R^{1A} is $XNHZ^2$, Z^2 may be $C(=O)OMe$. Thus, in these embodiments, R^{1A} has the structures:



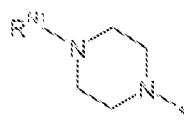
In some embodiments where R^{1A} is $XNHZ^2$, X may be selected from CMe_2 , and cyclobutylidene. Thus, in these embodiments, R^{1A} has the structures:



In some embodiments where R^{1A} is $XNHZ^2$, Z^2 may be selected from H and $C(=O)OMe$, and X may be selected from CMe_2 , and cyclobutylidene. Thus, in these embodiments, R^{1A} has the structures:

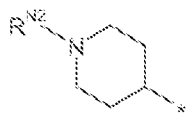


In some embodiments, R^{1A} is:



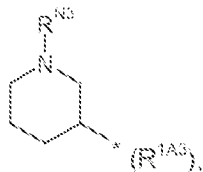
wherein R^{N1} is selected from H, C_{1-4} alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl), C_{3-4} cycloalkyl (i.e. cyclopropyl, methylcyclopropyl, cyclobutyl) and $C(=O)Me$. In some of these embodiments, it may be preferred that R^{N1} is $C(=O)Me$. In others of these embodiments, it may be preferred that R^{N1} is H, methyl or ethyl.

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



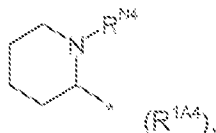
wherein R^{N2} is selected from H, C_{1-4} alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl), C_{3-4} cycloalkyl (i.e. cyclopropyl, methylcyclopropyl, cyclobutyl) and $C(=O)Me$. In some of these embodiments, it may be preferred that R^{N2} is $C(=O)Me$. In others of these embodiments, it may be preferred that R^{N2} is H, methyl or ethyl, more preferably H or methyl.

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



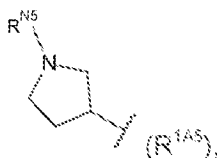
wherein R^{N3} is selected from H, C_{1-4} alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl), C_{3-4} cycloalkyl (i.e. cyclopropyl, methylcyclopropyl, cyclobutyl) and $C(=O)Me$. In some of these embodiments, it may be preferred that R^{N3} is $C(=O)Me$. In others of these embodiments, it may be preferred that R^{N3} is H, methyl or ethyl, more preferably H or methyl.

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



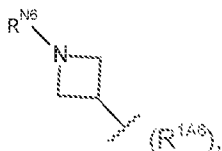
wherein R^{N4} is selected from H or methyl. In some of these embodiments, it may be preferred that R^{N4} is H.

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



wherein R^{N5} is selected from H, C_{1-4} alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl), C_{3-4} cycloalkyl (i.e. cyclopropyl, methylcyclopropyl, cyclobutyl) and $C(=O)Me$. In some of these embodiments, it may be preferred that R^{N5} is $C(=O)Me$. In others of these embodiments, it may be preferred that R^{N5} is H, methyl or ethyl, more preferably H or methyl.

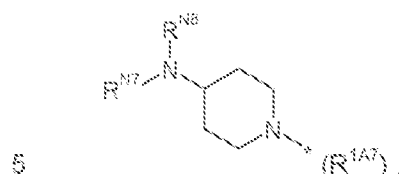
In some embodiments, R^{1A} is:



wherein R^{N6} is selected from H, C_{1-4} alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl), C_{3-4} cycloalkyl (i.e. cyclopropyl, methylcyclopropyl, cyclobutyl) and $C(=O)Me$. In some of these embodiments, it may be preferred that R^{N6} is $C(=O)Me$. In

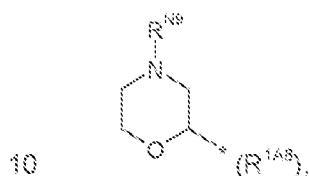
others of these embodiments, it may be preferred that R^{N8} is H, methyl or ethyl, more preferably H or methyl.

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



wherein R^{N7} and R^{N8} are both H or both methyl. In some of these embodiments, it may be preferred that R^{N7} and R^{N8} are both H.

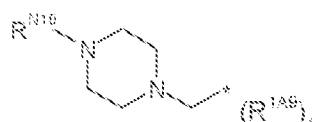
In some embodiments, R^{1A} is:



wherein R^{N9} is selected from H, C_{1-4} alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl), C_{3-4} cycloalkyl (i.e. cyclopropyl, methylcyclopropyl, cyclobutyl) and $C(=O)Me$. In some of these embodiments, it may be preferred that R^{N9} is $C(=O)Me$. In others of these embodiments, it may be preferred that R^{N9} is H, methyl or ethyl, more preferably H or methyl.

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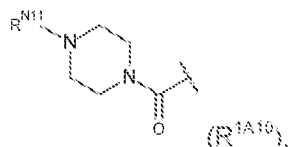
In some embodiments, R^{1A} is:



wherein R^{N10} is selected from H, C_{1-4} alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl), C_{3-4} cycloalkyl (i.e. cyclopropyl, methylcyclopropyl, cyclobutyl) and $C(=O)Me$. In some of these embodiments, it may be preferred that R^{N10} is $C(=O)Me$. In others of these embodiments, it may be preferred that R^{N10} is H, methyl or ethyl, more preferably H or methyl.

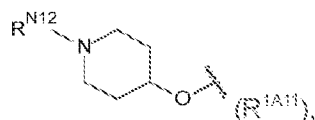
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In some embodiments, R^{1A} is:



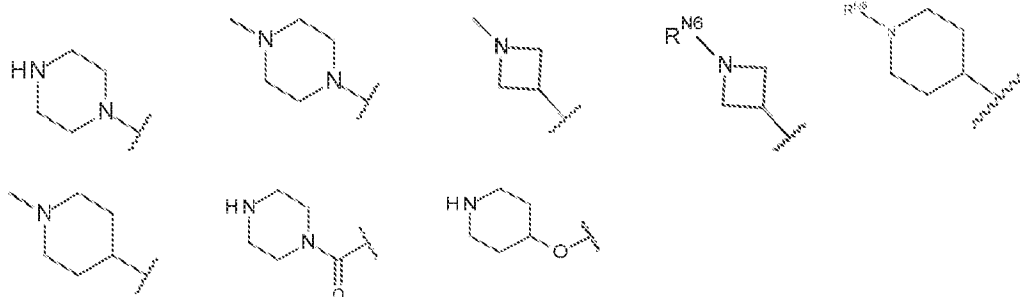
wherein R^{N11} is selected from H, C_{1-4} alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl), C_{3-4} cycloalkyl (i.e. cyclopropyl, methylcyclopropyl, cyclobutyl) and $C(=O)Me$. In some of these embodiments, it may be preferred that R^{N11} is $C(=O)Me$. In others of these embodiments, it may be preferred that R^{N11} is H, methyl or ethyl, more preferably H or methyl.

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



wherein R^{N12} is selected from H, C_{1-4} alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl), C_{3-4} cycloalkyl (i.e. cyclopropyl, methylcyclopropyl, cyclobutyl) and $C(=O)Me$. In some of these embodiments, it may be preferred that R^{N12} is $C(=O)Me$. In others of these embodiments, it may be preferred that R^{N12} is H, methyl or ethyl, more preferably H or methyl.

Particularly preferred R^{1A} groups include:



R^{1B} (Second aspect)

In some embodiments, no R^{1B} substituents are present.

In some embodiments, R^{1B} is preferably C_{1-3} alkyl and more preferably methyl.

In some embodiments, a single R^{1B} substituent is present. It may be C_{1-3} alkyl; CF_3 ; F; Cl; O-(C_{1-3} alkyl); and CN. In some of these embodiments, it is preferably F or C_{1-3} alkyl, and more preferably F or methyl.

5

R^{1C} (First aspect)

In some embodiments, no R^{1C} substituents are present.

In some embodiments, R^{1C} is preferably C_{1-3} alkyl and more preferably methyl.

10

In some embodiments, a single R^{1C} substituent is present. It may be C_{1-3} alkyl; CF_3 ; F; Cl; O-(C_{1-3} alkyl); CN; and =O. In some of these embodiments, it is preferably C_{1-3} alkyl, and more preferably methyl.

15

R^2

In some embodiments, R^2 is H.

In some embodiments, R^2 is halo (i.e. F, Cl, Br, I). In some of these embodiments, the halo group is either F or Cl.

20

In some embodiments, R^2 is C_{1-4} alkyl (i.e. methyl, ethyl, prop-1-yl and prop-2-yl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl). In some of these embodiments, the C_{1-4} alkyl group is methyl or ethyl, and methyl may be preferred.

25

In some embodiments, R^2 is selected from CF_3 and CF_2H . In some of these embodiments, R^2 is CF_3 .

In some embodiments, R^2 is CN.

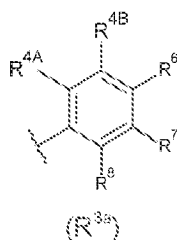
30

In some embodiments, R^2 is methoxy.

35

R^3

In some embodiments, R^3 is substituted phenyl, and therefore it has the structure:

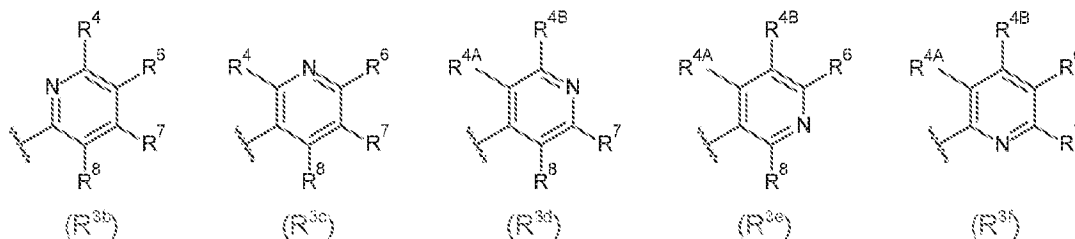


where R^6 , R^7 and R^8 are independently selected from H, F, methyl and CF_3 . One of R^{4A} and R^{4B} is R^4 , and the other is selected from H, F, methyl and CF_3 . In some of these
 5 embodiments, the group of R^{4A} and R^{4B} that is not R^4 , and R^6 , R^7 and R^8 are all H. In others
 of these embodiments, one of the group of R^{4A} and R^{4B} that is not R^4 , R^6 , R^7 and R^8 is not H,
 and therefore is F, methyl or CF_3 . The group that is not H may preferably be R^6 or R^7 .

In some embodiments, R^3 is substituted phenyl, R^{4B} , R^6 , R^7 and R^8 are all H, and R^{4A} is R^4 .

10

In some embodiments, R^3 is a substituted 6 membered heteroaryl group, where the
 heteroaryl ring system contains 1 or 2 N heteroatoms. In these embodiments, it may be
 preferred that R^3 is pyridyl, which can have the structures:



where R^6 , R^7 and R^8 (if present) are independently selected from H, F, methyl and CF_3 . One
 15 of R^{4A} and R^{4B} (if present) is R^4 , and the other is selected from H, F, methyl and CF_3 . Of
 these structures, R^{3d} and R^{3e} may be preferred. In some of these embodiments, the group of
 R^{4A} and R^{4B} that is not R^4 , and R^6 , R^7 and R^8 (if present) are all H. In others of these
 embodiments, one of the group of R^{4A} and R^{4B} that is not R^4 , R^6 , R^7 and R^8 (if present) is not
 H, and therefore is F, methyl or CF_3 . In some embodiments, it may be preferred that a F
 20 substituent is not alpha to a ring nitrogen atom.

 R^4

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

25

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

In some embodiments, R^{N13} is H.

In other embodiments, R^{N13} is Me.

5 In some embodiments, Z^3 is H.

In other embodiments, Z^3 is Me.

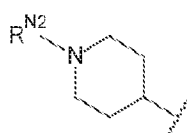
In other embodiments, Z^3 is OMe.

10 In some embodiments of the present invention the compounds of formula (I) are of formula (Ia) or isomers, salts, solvates, protected forms or prodrugs thereof wherein:

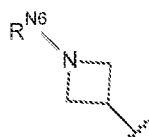
A is an optionally substituted 5 or 6 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl ring system contains 1 or 2 N atoms, and;

15 A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear a substituent 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 C_{1-2} alkyl and Z^1 is selected from H and C_{1-2} alkyl optionally substituted by OH,;
- (ii) $XNHZ^2$, where X is cyclobutylidene, and Z^2 is $C(=O)OC_{1-3}$ alkyl;
- (iii) a group selected from:



(R^{1A2})



(R^{1A6})

20 wherein:

R^{N2} is selected from H and C_{1-4} alkyl;

R^{N6} is H;

and where R^{1C} is C_{1-3} alkyl;

R^2 is selected from C_{1-4} alkyl and CF_3 ;

25 R^3 is substituted phenyl, where R^3 bears a substituent R^4 alpha to the $-C_2H_4-$ group, and may additionally bear a further substituent F; and

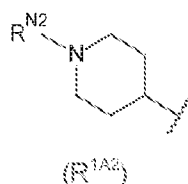
R^4 is $-CH_2-C(O)N(R^{N12})Z^3$, where R^{N12} is H; and Z^3 is H.

30 In some embodiments of the present invention the compounds of formula (I) are of formula (Ib) or isomers, salts, solvates, protected forms or prodrugs thereof 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 or 2 N atoms, and;

A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear a substituent R^{1C} which are not alpha to the NH group, where R^{1A} is R^{1A2} ;

5



wherein:

R^{N2} is selected from H and C₁₋₄ alkyl;

and where R^{1C} is C₁₋₃ alkyl;

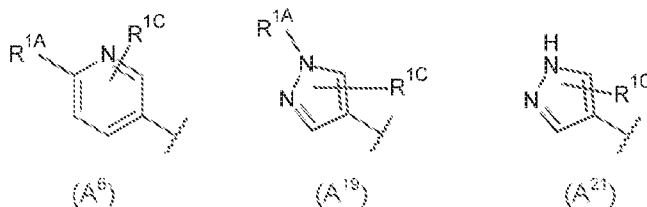
R^2 is selected from C₁₋₄ alkyl;

10

R^3 is substituted phenyl, where R^3 bears a substituent R^4 alpha to the -C₂H₄- group; and

R^4 is -CH₂-C(O)N(R^{N13})Z³, where R^{N13} is H; and Z³ is H.

In some embodiments of the present invention the compounds of formula (I) are of formula (Ic) or isomers, salts, solvates, protected forms or prodrugs thereof wherein:



15

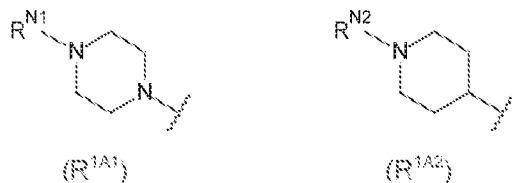
wherein R^{1A} is selected from:

(i) CH(R^{C1})NHZ¹, where R^{C1} is selected from H and methyl and Z¹ is selected from H and CH₂CH₂OH;

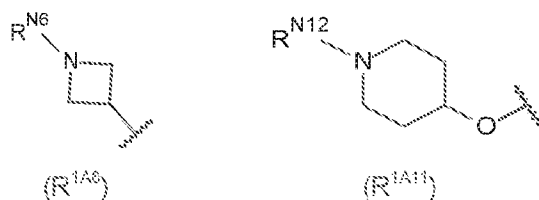
(ii) XNHZ², where X is selected from cyclobutylidene and oxetanylidene and Z² is selected from H and C(=O)OMe;

20

(iii) a group selected from R^{1A1} , R^{1A2} , R^{1A6} and R^{1A11} ;



40



wherein:

R^{N1} is selected from H and Me;

R^{N2} is selected from H and Me;

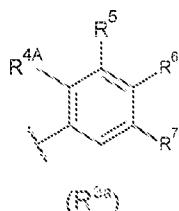
R^{N8} is selected from H and Me; and

5 R^{N12} is selected from H and Me;

and where there may be a single R^{1C} group which is methyl;

R^2 is selected from H, methyl and CF_3 ;

R^3 is:



where R^5 , R^6 and R^7 are independently selected from H, F, methyl and CF_3 , and only one of
10 them is not H; and

R^4 is $-CH_2-C(O)NH_2$.

In some embodiments of the present invention the compounds of formula (II) are of formula
(IIa) or isomers, salts, solvates, protected forms or prodrugs thereof wherein:

15 A is substituted phenyl;

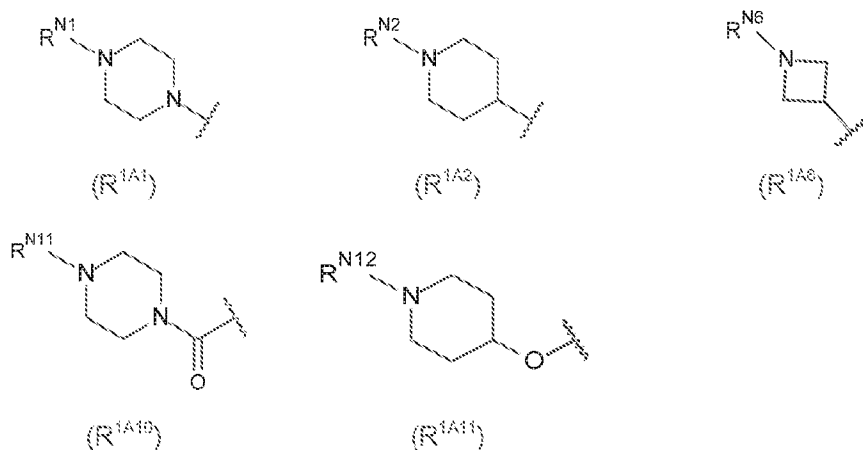
A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further
bear a substituent R^{1B} which is not alpha to the NH group, where R^{1A} is selected from:

(i) $CH(R^{C1})NHZ^1$, where R^{C1} is selected from H and C_{1-2} alkyl and Z^1 is selected from H,
 C_{1-3} alkyl optionally substituted by OH and $C(=O)Me$;

20 (ii) $XNHZ^2$, where X is selected from cyclobutylidene and oxetanylidene and Z^2 is
selected from H and $C(=O)OC_{1-3}$ alkyl;

(iii) a group selected from:

41



wherein:

R^{N1} is H;

R^{N2} is selected from H and C₁₋₄ alkyl;

R^{N6} is H;

5 R^{N11} is H; and

R^{N12} is H;

and where each R^{1B} is independently selected from:

(i) C₁₋₃ alkyl;

(iii) F;

10 R² is selected from H, halo, C₁₋₄ alkyl, CF₃ and methoxy;

R³ is substituted phenyl, where R³ bears a substituent R⁴ alpha to the -C₂H₄- group, and may additionally bear a further substituent selected from F, methyl and CF₃; and

R⁴ is -CH₂-C(O)N(R^{N13})Z³, where R^{N13} is H; and Z³ is H.

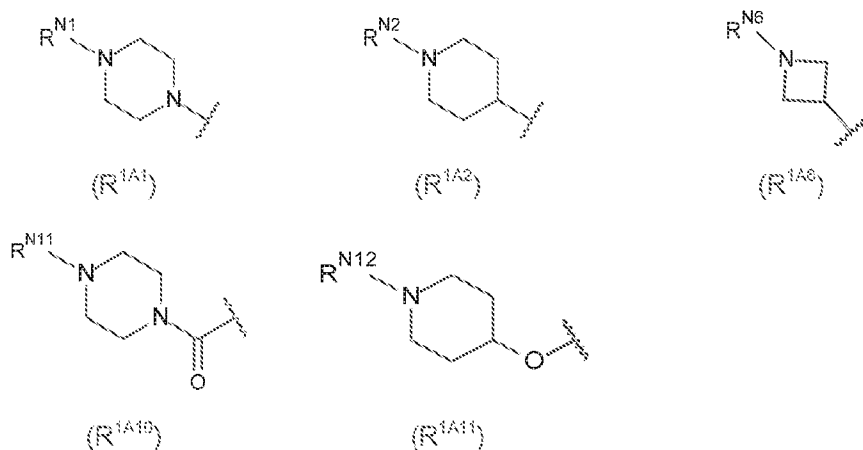
15 In some embodiments of the present invention the compounds of formula (II) are of formula (IIb) or isomers, salts, solvates, protected forms or prodrugs thereof wherein:

A is substituted phenyl;

A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear a substituent R^{1B} which is not alpha to the NH group, where R^{1A} is selected from:

- 20 (i) CH(R^{C1})NHZ¹, where R^{C1} is selected from H and C₁₋₂ alkyl and Z¹ is selected from H and C₁₋₂ alkyl optionally substituted by OH;
- (ii) XNHZ², where X is oxetanylidine and Z² is H;
- (iii) a group selected from:

42



wherein:

R^{N1} is H;

R^{N2} is selected from H and C₁₋₄ alkyl;

R^{N6} is H;

5 R^{N11} is H; and

R^{N12} is H;

and where each R^{1B} is C₁₋₂ alkyl;

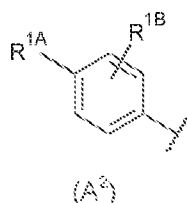
R² is selected from halo, C₁₋₄ alkyl, CF₃ and methoxy;

10 R³ is substituted phenyl, where R³ bears a substituent R⁴ alpha to the -C₂H₄- group, and may additionally bear a further substituent selected from methyl and CF₃; and

R⁴ is -CH₂-C(O)N(R^{N13})Z³, where R^{N13} is H; and Z³ is H.

In some embodiments of the present invention the compounds of formula (II) are of formula (IIc) or isomers, salts, solvates, protected forms or prodrugs thereof wherein:

15 A is:

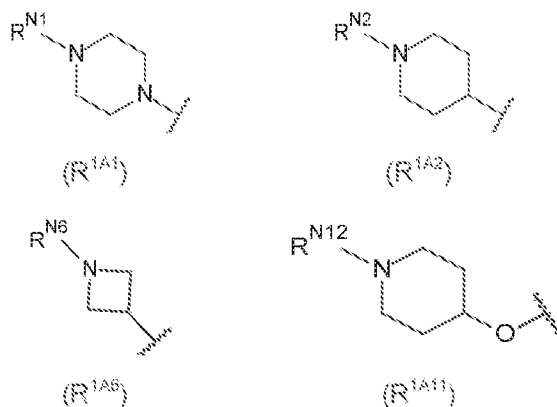


wherein R^{1A} is selected from:

- (i) CH(R^{C1})NHZ¹, where R^{C1} is selected from H and methyl and Z¹ is selected from H and CH₂CH₂OH;
- (ii) XNHZ², where X is selected from cyclobutylidene and oxetanylidene and Z² is selected from H and C(=O)OMe;
- (iii) a group selected from R^{1A1}, R^{1A2}, R^{1A6} and R^{1A11};

20

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wherein:

R^{N1} is selected from H and Me;

R^{N2} is selected from H and Me;

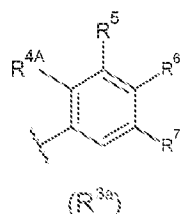
R^{N6} is selected from H and Me; and

5 R^{N12} is selected from H and Me;

and where there may be a single R^{1B} group which is selected from F and methyl;

R^2 is selected from H, methyl and CF_3 ;

R^3 is:



where R^5 , R^6 and R^7 are independently selected from H, F, methyl and CF_3 , and only one of
10 them is not H; and

R^4 is $-CH_2-C(O)NH_2$.

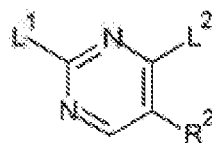
The preferences expressed in relation to compounds of formulae I and II also apply to
15 compounds of formulae Ia, Ib, Ic, IIa, IIb and IIc, where appropriate.

Embodiments of the inventions are compounds of the examples, including compounds 1 to
41. Embodiments of particular interest include compounds 5, 6, 14, 16, 24, 28, 30 and 31.

General synthesis methods

20 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 formula (II) or isomers, salts, solvates or prodrug thereof comprises reacting a compound of formula F1



F1

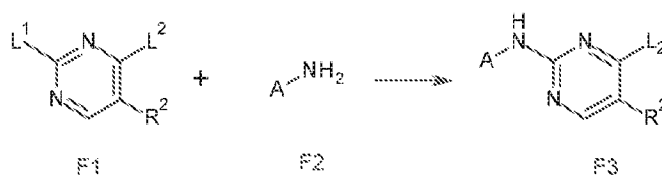
- 5 with a compound of formula $A-NH_2$ to displace the group L^1 and with a compound of formula $HCER^3$ to displace the group L^2 , or
 with a compound of formula $HCER^3$ to displace the group L^2 and with a compound of formula $A-NH_2$ to displace the group L^1 ,
 wherein A, R^2 and R^3 are as defined in formula (I) or (II) above and L^1 and L^2 are leaving
 10 groups.

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

15 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 $-SO_2R$ 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_2Me .

20 Compounds of formulae I and II, as described above, can be prepared by synthetic strategies outlined below, wherein the definitions above apply:

Scheme A

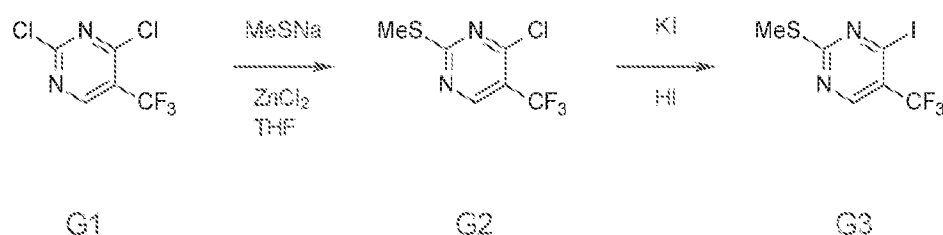


25 Compounds of formula F1 may be reacted with substituted commercial or synthetic amino substituted compounds of formula F2 (as prepared in scheme C to N) to form intermediates of formula F3 where L^1 and L^2 may be the same or different and include Cl, Br, I, SMe, SO_2Me .

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-

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

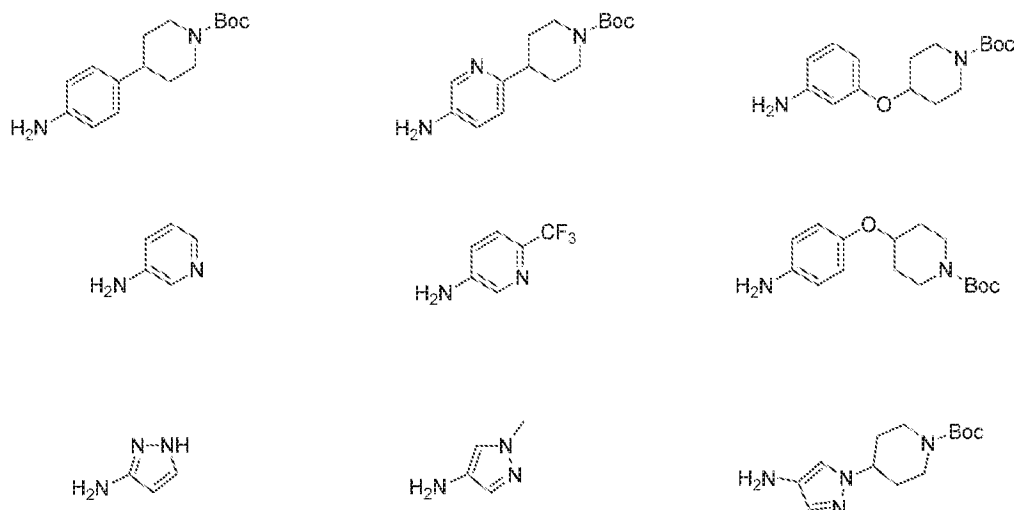


Commercially available 2,4-dichloro-5-(trifluoromethyl)pyrimidine (G1) can be selectively reacted with sodium thiomethoxide in the presence of zinc(II) chloride to give 2-thiomethyl-4-chloro-5-(trifluoromethyl)pyrimidine (G2). 2-Thiomethyl-4-chloro-5-(trifluoromethyl)pyrimidine (G2) can be further reacted,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

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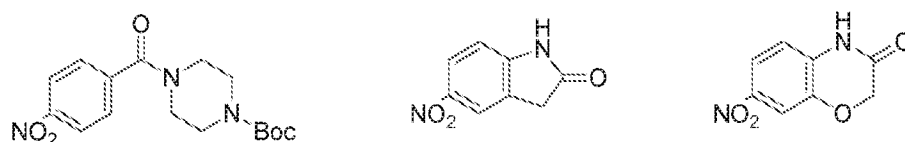
Table 1



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 including, but not limited to those depicted in table 2.

Table 2

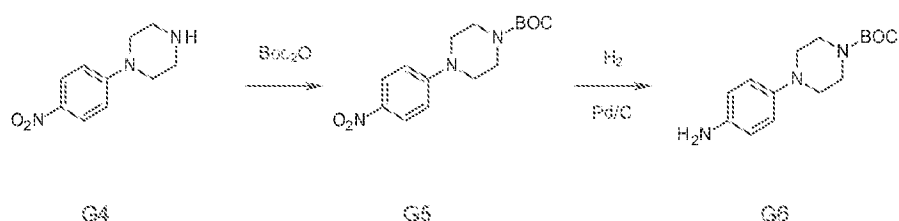


It will be appreciated that such compounds can be reduced under suitable conditions, for example in the presence of palladium under an atmosphere of hydrogen, to give amino compounds of the formula F2.

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 phenyl containing starting materials with suitable heteroaromatic systems.

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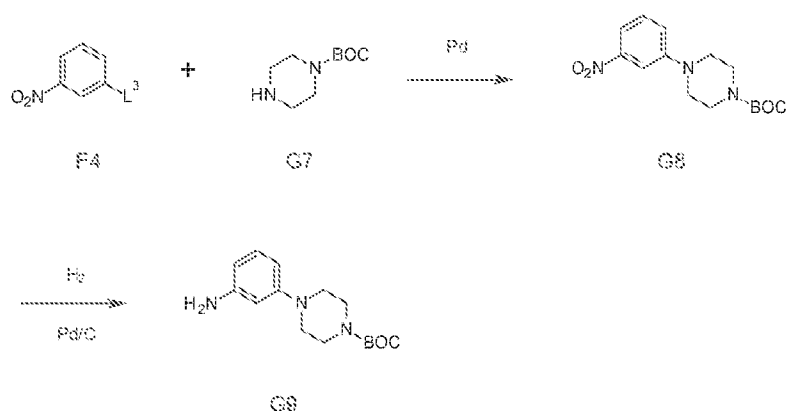
Scheme C



Commercially available 1-(4-nitrophenyl)piperazine (G4), or a salt thereof, can be reacted with Boc anhydride to give *tert*-butyl 4-(4-nitrophenyl)piperazine-1-carboxylate (G5).

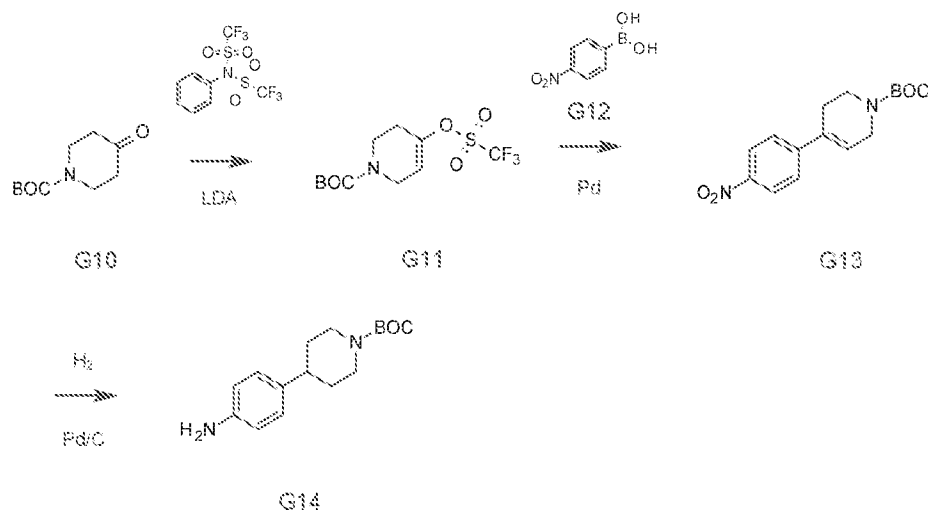
- 5 Subsequent reduction *via* hydrogenation in the presence of a catalyst, for example palladium on charcoal, gives the corresponding aniline, *tert*-butyl 4-(4-aminophenyl)piperazine-1-carboxylate (G6).

Scheme D



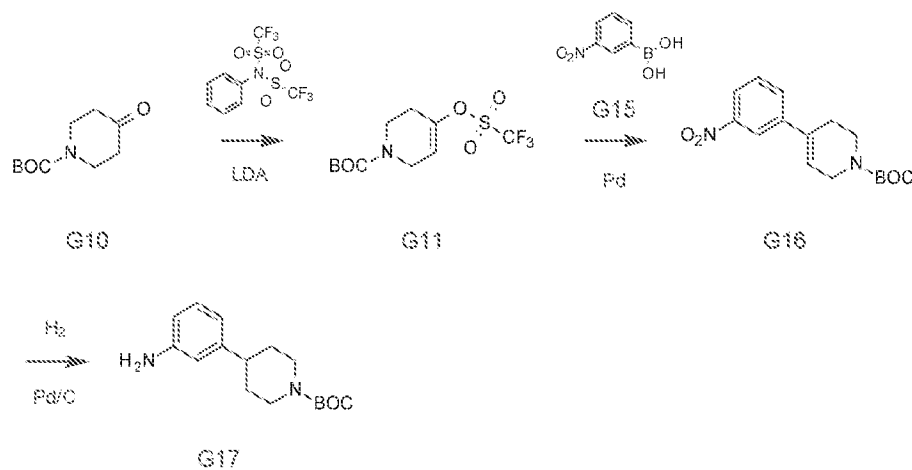
- 10 *tert*-Butyl 4-(3-aminophenyl)piperazine-1-carboxylate (G9) can be prepared by coupling of commercially available *tert*-butyl piperazine-1-carboxylate (G7) and compounds of the formula F4, where $\text{L}^3 = \text{I}$ or Br , in a Buchwald type reaction to give *tert*-butyl 4-(3-nitrophenyl)piperazine-1-carboxylate (G8). Reduction with hydrogen in the presence of a catalyst, for example palladium on charcoal, gives *tert*-butyl 4-(3-aminophenyl)piperazine-1-carboxylate (G9).
- 15

Scheme E



The corresponding 4-piperidine analogues of G6 can be prepared by a sequence of reactions starting with the conversion of commercially available *tert*-butyl 4-oxopiperidine-1-carboxylate (G10) to vinyl triflate G11. Coupling of G11 in a Suzuki type reaction with (4-nitrophenyl)boronic acid (G12) gives tetrahydropyridine G13. Subsequent reduction via hydrogenation in the presence of a catalyst, for example palladium on charcoal, gives *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (G14).

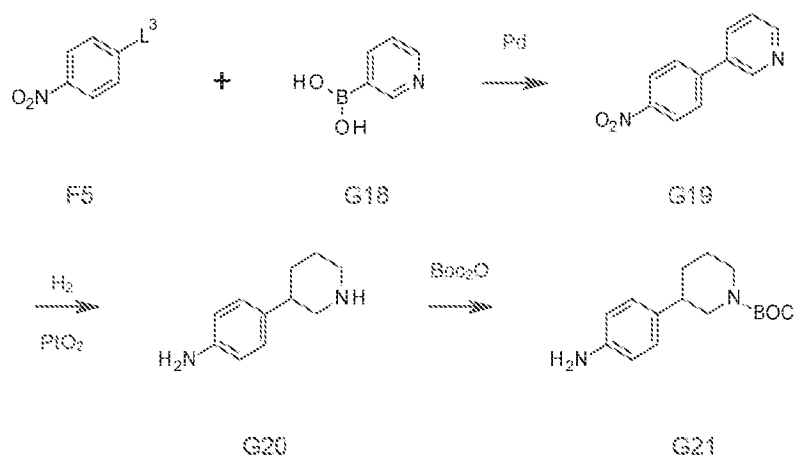
10 Scheme F



The corresponding 4-(3-aminophenyl)piperidine analogue of G9 can be prepared by a sequence of reactions starting with the conversion of commercially available *tert*-butyl 4-oxopiperidine-1-carboxylate (G10) to vinyl triflate G11. Coupling of G11 in a Suzuki type reaction with (3-nitrophenyl)boronic acid (G15) gives tetrahydropyridine G16. Subsequent

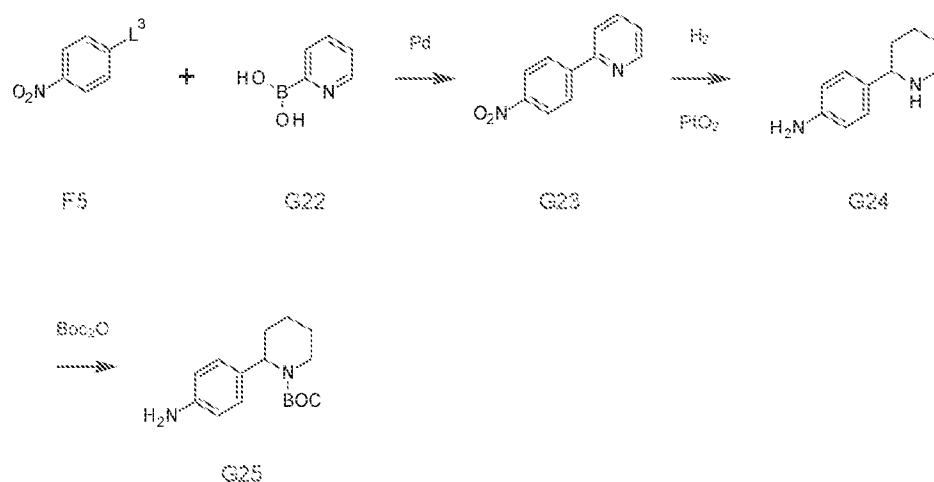
reduction via hydrogenation in the presence of a catalyst, for example palladium on charcoal, gives *tert*-butyl 4-(3-aminophenyl)piperidine-1-carboxylate (G17).

Scheme G



The 3-(4-aminophenyl)piperidine regioisomers of G14 can be prepared by reaction of commercially available compounds of the formula F5, where L³ = I or Br, with pyridin-3-ylboronic acid (G18) in a Suzuki type reaction to form 3-(4-nitrophenyl)pyridine (G19). Reduction of G19 with hydrogen in the presence of a catalyst, for example platinum oxide, gives 4-(piperidin-3-yl)aniline (G20) which may be protected using Boc anhydride to give *tert*-butyl 3-(4-aminophenyl)piperidine-1-carboxylate (G21).

Scheme H

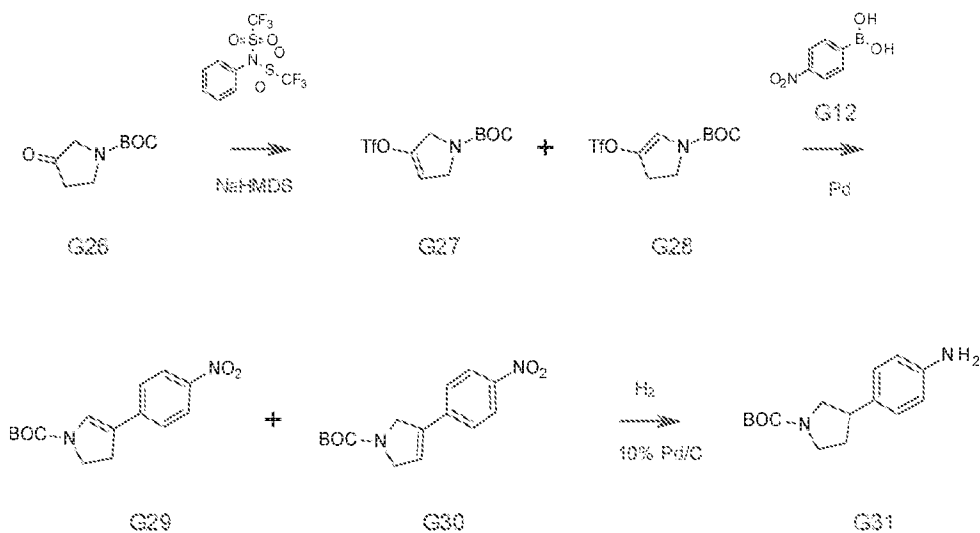


The 2-(4-aminophenyl)piperidine regioisomer of G14 can be prepared by reaction of commercially available compounds of the formula F5, where L³ = I or Br, with pyridin-2-ylboronic acid (G22) in a Suzuki type reaction to form 2-(4-nitrophenyl)pyridine (G23). Reduction of G23 with hydrogen in the presence of a catalyst, for example platinum oxide,

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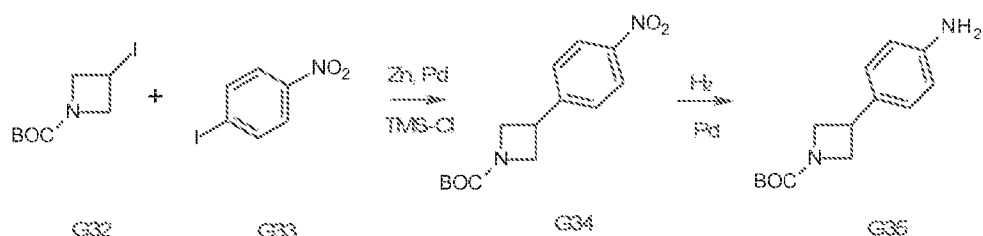
gives 4-(piperidin-2-yl)aniline (G24) which may be protected using Boc anhydride to give *tert*-butyl 2-(4-aminophenyl)piperidine-1-carboxylate (G25).

Scheme I



Commercially available *tert*-butyl 3-oxopyrrolidine-1-carboxylate (G26) can be converted to a mixture of vinyl triflates G27 and G28 in the presence of a triflamide and a suitable base, for example NaHMDS. Coupling of the mixture with (4-nitrophenyl)boronic acid (G12) under Suzuki conditions gives dihydropyrroles G29 and G30. Reduction of this mixture using hydrogen in the presence of a catalyst, for example 10% palladium on charcoal, gives *tert*-butyl 3-(4-aminophenyl)pyrrolidine-1-carboxylate (G31).

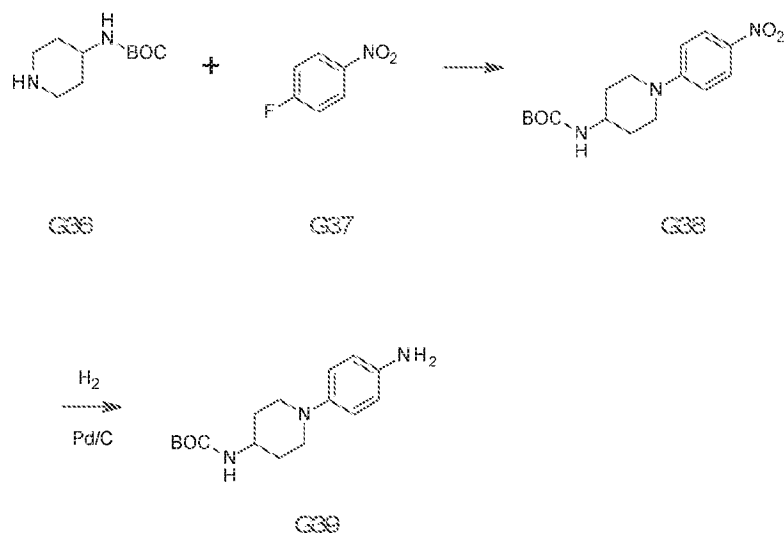
Scheme J



A metal/silyl mediated coupling of commercially available *tert*-butyl 3-iodoazetidine-1-carboxylate (G32) and 4-iodo-nitrobenzene (G33) gives *tert*-butyl 3-(4-nitrophenyl)azetidine-1-carboxylate (G34). Subsequent reduction via hydrogenation in the presence of a catalyst, for example palladium on charcoal, gives the *tert*-butyl 3-(4-aminophenyl)azetidine-1-carboxylate (G35).

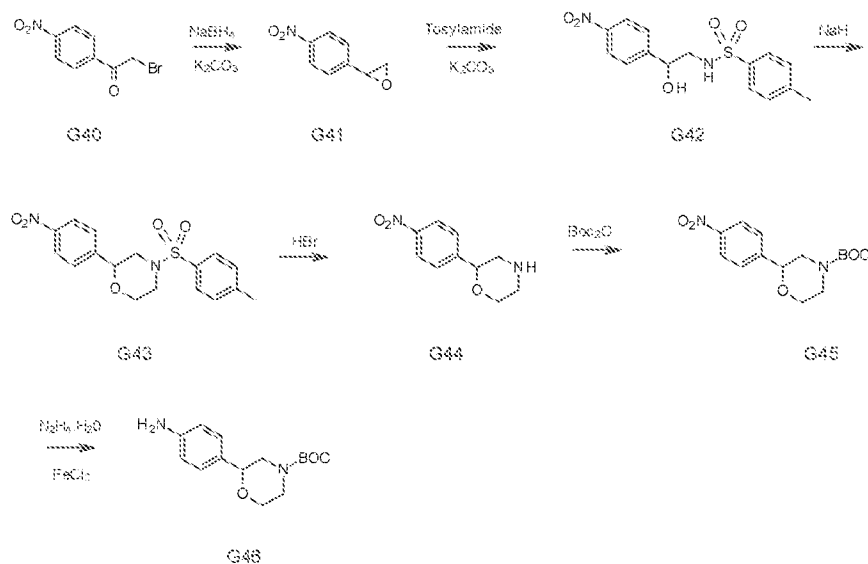
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Scheme K



tert-Butyl (1-(4-aminophenyl)piperidin-4-yl)carbamate (G39) can be prepared by nucleophilic aromatic substitution of commercially available *tert*-butyl piperidin-4-ylcarbamate (G36) and 1-fluoro-4-nitrobenzene (G37) under thermal conditions to give *tert*-butyl (1-(4-nitrophenyl)piperidin-4-yl)carbamate (G38). Reduction of G38 with hydrogen in the presence of a catalyst, for example 10% palladium on charcoal, gives *tert*-butyl (1-(4-aminophenyl)piperidin-4-yl)carbamate (G39).

10 Scheme L

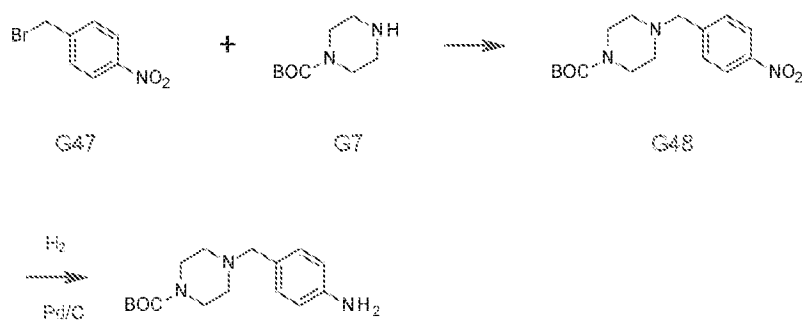


Commercially available 2-bromo-1-(4-nitrophenyl)ethanone (G40) can be reduced and cyclised to give epoxide G41. Opening of the epoxide with tosylamide followed by cyclisation with (2-bromoethyl)diphenylsulfonium trifluoromethanesulfonate gives morpholine G43. Cleavage of the sulphonamide and subsequent re-protection with Boc anhydride gives

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carbamate G45. Reduction using hydrazine in the presence of iron(III) chloride gives *tert*-butyl 2-(4-aminophenyl)morpholine-4-carboxylate (G46).

Scheme M



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G49

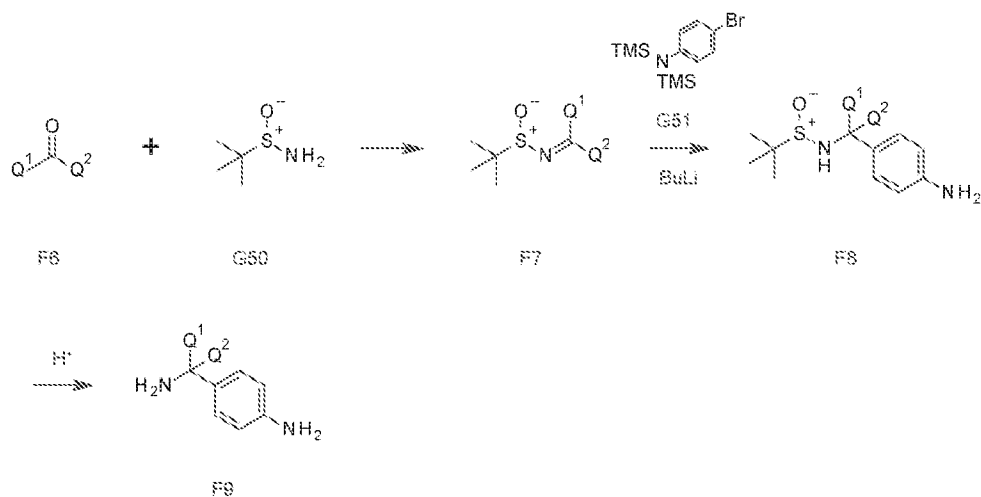
tert-Butyl 4-(4-aminobenzyl)piperazine-1-carboxylate (G49) can be prepared by the nucleophilic displacement of commercially available 1-(bromomethyl)-4-nitrobenzene (G47) with *tert*-butyl piperazine-1-carboxylate (G7) to give *tert*-butyl 4-(4-nitrobenzyl)piperazine-1-carboxylate (G48). Subsequent reduction with hydrogen in the presence of a catalyst, for example 10% palladium on charcoal, gives *tert*-butyl 4-(4-aminobenzyl)piperazine-1-carboxylate (G49).

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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 using an Ellman type procedure as outlined in scheme N.

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Scheme N

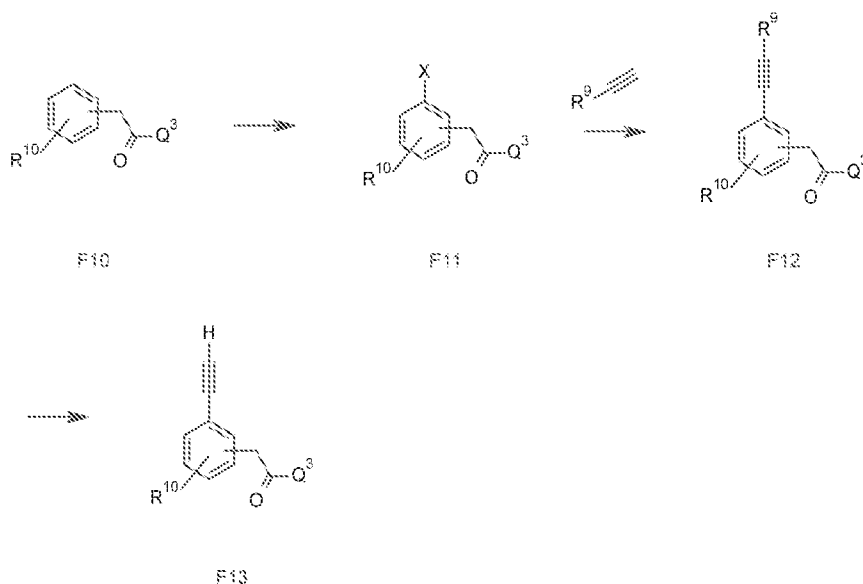


Carbonyl compounds of the formula F6 can be reacted with 2-methylpropane-2-sulfonamide (G50) to give compounds of the formula F7. Compounds of the formula F7 can be reacted with anions prepared from suitably protected amino compounds, for example *N*-(4-bromophenyl)-1,1,1-trimethyl-*N*-(trimethylsilyl)silanamine (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 Q¹ and Q² may be the same or different and may be fused together to form a ring structure, for example as in cyclobutanone –

Substituents Q¹ and Q² 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.

Where compounds are required where R³ is aryl or substituted aryl compounds of the formula F13 may be prepared as outlined in scheme O.

Scheme O

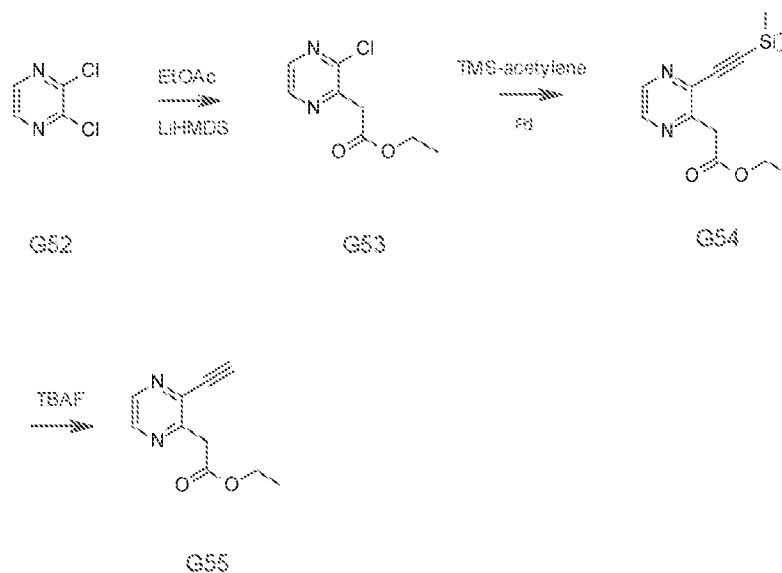


Compounds of the formulae F10 and F11 where R¹⁰ are independently H, F, Me or CF₃; Q³ may be OH, O-alkyl, NH₂ or substituted N and X= Cl, Br or I, are either commercially available or may be prepared synthetically. It will be appreciated that for compounds of the formula F10 and F11 that the nature of Q³ 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 $R^9 = \text{TMS}$, TES or $\text{C}(\text{CH}_3)_2\text{OH}$. R^9 may then be removed to generate compounds of the formula F13. When $R^9 = \text{TMS}$ or TES potassium carbonate or tetra-*n*-butyl ammonium fluoride may be employed to induce this transformation. When $R^9 = \text{C}(\text{CH}_3)_2\text{OH}$, sodium hydride in refluxing toluene may be used.

Alternatively, when compounds in which $R^3 = \text{heteroaryl}$ are desired, heteroaryl analogues of F13 may be prepared as outlined in Schemes P, Q and R.

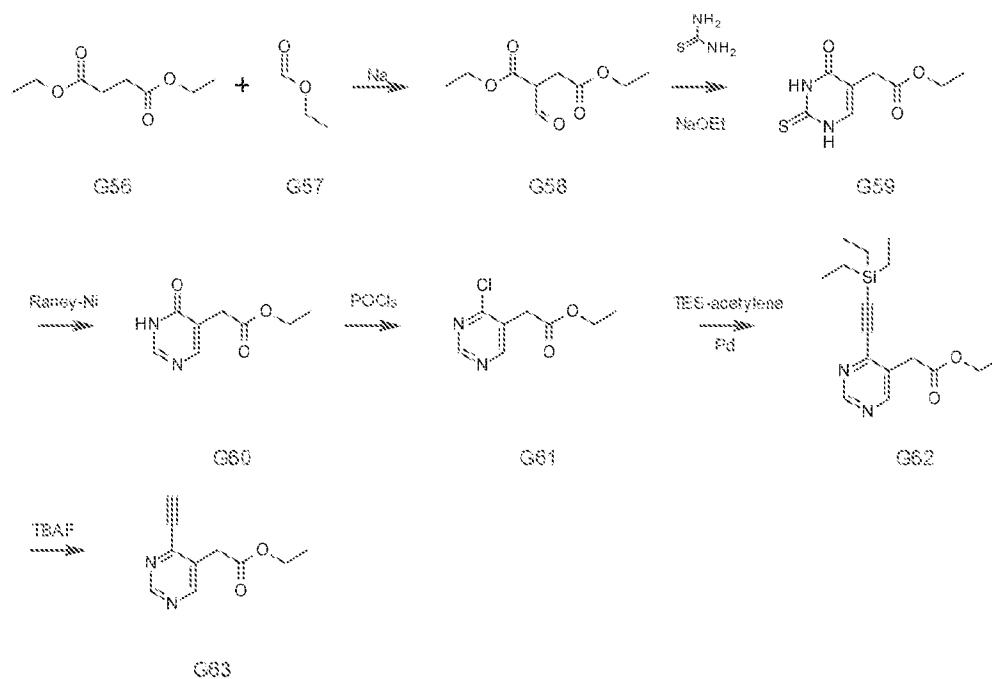
Scheme P



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).

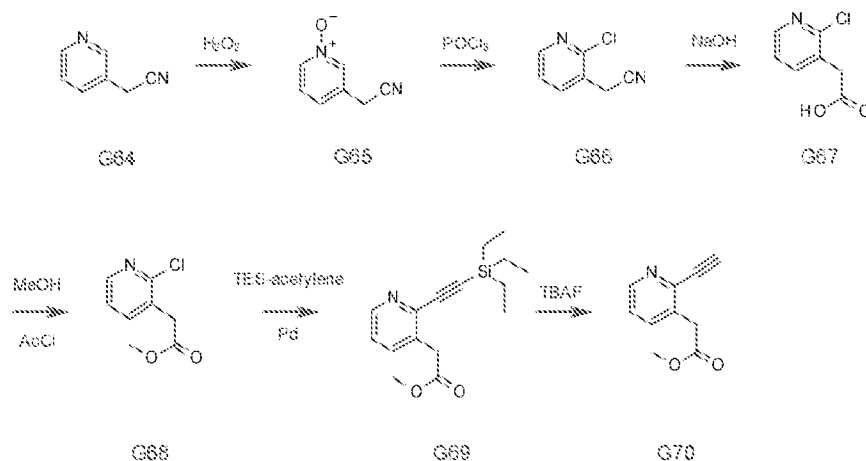
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Scheme Q



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 Sonogashira 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.

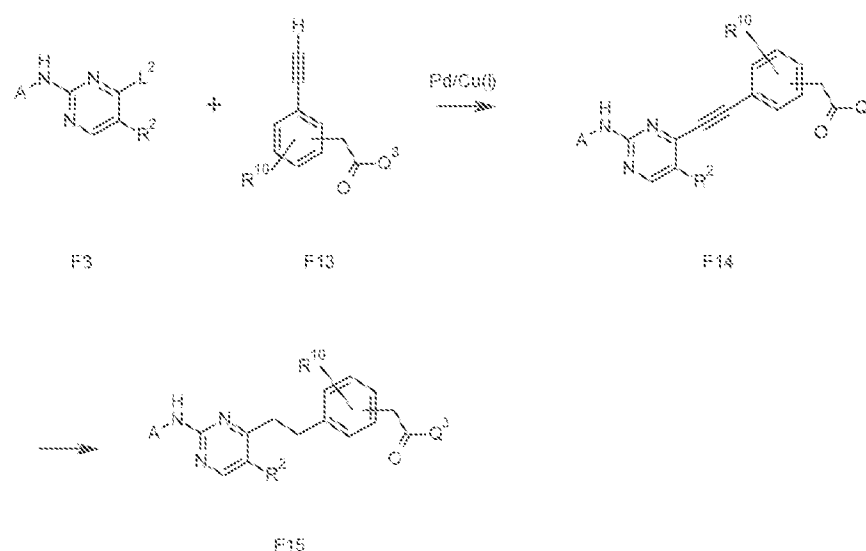
Scheme R



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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 compounds 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



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 R². For example, where R² = F, CF₃, methyl or methoxy, 10% Pd/C may be used, where R² = Cl, platinum oxide is employed. Functional group manipulation may be carried on compounds of the formula F15 if necessary. For example, compounds of the formula F15 where Q³ = O-alkyl (i.e. esters) may then be deprotected to give carboxylic acids of the formula F15 where Q³ = OH. In esters where Q³ = OMe, lithium hydroxide solutions may be employed. Where Q³ = Ot-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.

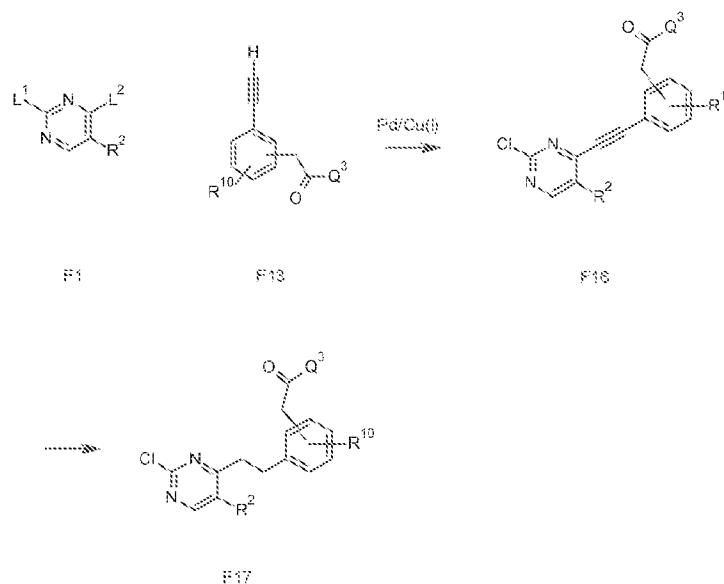
Compounds of the formula F15 where $Q^3 = OH$ may then be converted to amides and substituted amides as described in formula (1) using a suitable choice of amine in the presence of a coupling agent for example EDCI.HCl or HATU.

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 may be 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.

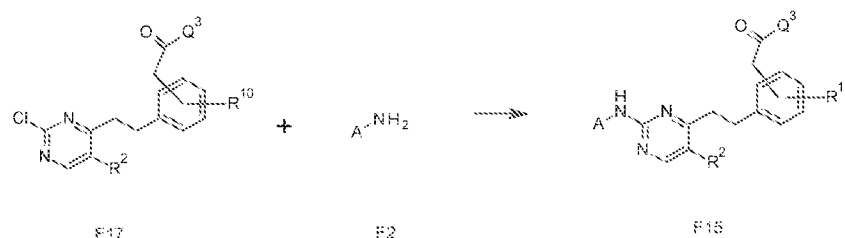
Alternatively, a complementary approach to that described scheme S can be employed, where R^2 is not CF_3 , whereby pyrimidines of the formula F1 are initially coupled to acetylenes of the formula F13 as detailed in scheme T.

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 $R^2 = \text{Me}$, 10% Pd/C may be used, where $R^2 = \text{Cl}$, platinum oxide is employed. The desired amide may already be present in compounds of the formula F13, or alternatively an ester may be used and subsequently derivatised as described above.

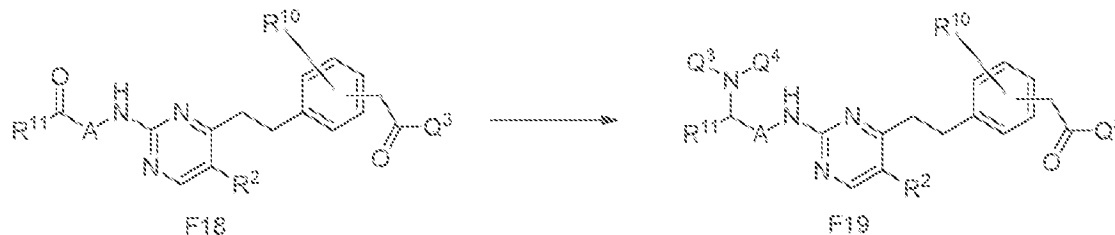
Scheme U



Compounds of the formula F17 may then be reacted with amino compounds of the formula F2, prepared as described above, to give compounds of the formula F15. Such couplings may either 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 15 may then be further elaborated as desired as described above.

Scheme W



Ketones of formula F18 where R^{11} is an alkyl group or similar may be substituted with amines to form compounds of formula F19. It will be appreciated that Q4 and Q5 may be the same such as H to form a primary amine or different such as NHMe and may also be fused

together to form a ring structure, for example but not limited to azetidine, pyrrolidine, piperazine, morpholine and piperidine.

Use of Compounds of the Invention

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

10 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.

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

20 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 activity, comprising contacting a cell with an effective amount of an active compound, whether *in vitro* or *in vivo*.

25 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.

30 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.

35 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.

5 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.

10 Cancer

The present invention provides 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.

15 The invention provides the use of the active compounds for the treatment of cancer in the human or animal body. The invention further provides 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.

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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 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, colon cancer, melanoma such as cutaneous or intraocular melanoma, haematological malignancies, Hodgkin's disease, lung cancer, 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
30 embodiments, the cancer is melanoma, breast cancer or head and neck cancer.

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, and skin.

5 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 preventing the spread of cancer and in the prevention of metastasis.

10 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 prevent the spread of cancer or prevent metastasis. There is also provided a compound of formula (I) or formula (II) or an isomer, salt, solvate or prodrug thereof for use in a method for preventing the spread of cancer or preventing of metastasis.

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

20 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 topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

30 (ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH

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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 α -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 [Herceptin^T], the anti-EGFR antibody panitumumab, the anti erbB1 antibody cetuximab [Erbix^T, 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 (Avastin^T), 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 $\alpha v \beta 3$ 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 gemcitabine, cisplatin and the camptothecin prodrug irinotecan.

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 formula (II) 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 formula (II) 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.

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.

5

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.

10

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.

15

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.

20

Formulations may be in the form of liquids, solutions, suspensions, emulsions, elixirs, syrups, tablets, lozenges, granules, powders, capsules, cachets, pills, ampoules, suppositories, pessaries, ointments, gels, pastes, creams, sprays, mists, foams, lotions, oils, boluses, electuaries, or aerosols.

25

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.

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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

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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 lozenges 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, dichloro-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*-butoxycarbonyl (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 (Et₂O), ethyl acetate (EtOAc), triethylamine (Et₃N), dichloromethane (methylene chloride, DCM), trifluoroacetic acid (TFA), trifluoroethanol (TFE), dimethylformamide (DMF), sodium sulphate (Na₂SO₄), 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 (MgSO₄), sodium hydrogen carbonate (NaHCO₃), *tert*-butanol (*t*-BuOH), 1-ethyl-3-(3-dimethylaminopropyl) carbodimide hydrochloride salt (EDCI.HCl), tetra-*n*-butylammonium fluoride (TBAF), *N,N*-diisopropylethylamine (DIPEA), 1-hydroxybenzotriazole (HOBT), *trans*-dichlorobis(triphenylphosphine)palladium(II) (PdCl₂(PPh₃)₂), tris(dibenzylideneacetone)dipalladium(0) (Pd₂(dba)₃), tri-*t*-butyl phosphonium tetrafluoroborate (*t*-Bu₃PH.BF₄), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), triphenylphosphine (PPh₃) 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.

¹HMR spectra were recorded on either a Bruker Avance DRX300 (300 MHz) or a Bruker Ultrashield plus (400 MHz). The multiplicity of a signal is designated by the following abbreviations: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; tt, triplet of triplets; td, triplet of doublets; q, quartet; br, broad; m, multiplet. All observed coupling constants, *J*, are reported in Hertz.

LC/MS data was generated using either an Agilent 6100 Series Single Quad LC/MS (LCMS-A) or Waters ZQ 3100 system (LCMS-B).

LCMS Method A (LCMS-A)

5 Instrument: Agilent 6100 Series Single Quad LC/MS
Agilent 1200 Series HPLC
Pump: 1200 Series G1311A Quaternary pump
Autosampler: 1200 Series G1329A Thermostatted Autosampler
Detector: 1200 Series G1314B Variable Wavelength Detector

10

LC conditions:

Reverse Phase HPLC analysis

Column: Luna C8(2) 5 μ 50 $\times$ 4.6 mm 100A

Column temperature: 30 °C

15

Injection Volume: 5 μ L

Solvent A: Water 0.1% Formic Acid

Solvent B: Acetonitrile 0.1% Formic Acid

Gradient: 5-100% B over 10 min

Detection: 254 nm or 214 nm

20

MS conditions:

Ion Source: Quadrupole

Ion Mode: Multimode-ES

Drying gas temp: 300 °C

25

Vaporizer temperature: 200 °C

Capillary voltage (V): 2000 (positive)

Capillary voltage (V): 4000 (negative)

Scan Range: 100-1000

Step size: 0.1 sec

30

Acquisition time: 10 min

LCMS Method B (LCMS-B)

Instrument: Waters ZQ 3100 -Mass Detector

35

Waters 2545-Pump

Waters SFO System Fluidics Organizer

Waters 2996 Diode Array Detector

Waters 2767 Sample Manager

LC conditions:

5 Reverse Phase HPLC analysis

Column: XBridge TM C18 5 μ m 4.6 $\times$ 100 mm

Injection Volume 10 μ L

Solvent A: Water 0.1% Formic Acid

Solvent B: Acetonitrile 0.1% Formic Acid

10 Gradient: 10-100% B over 10 min

Flow rate: 1.5 ml/min

Detection: 100-600 nm

MS conditions:

15 Ion Source: Single-quadrupole

Ion Mode: ES positive

Source Temp: 150 °C

Desolvation Temp: 350 °C

Detection: Ion counting

20 Capillary (KV): 3.00

Cone (V): 30

Extractor (V):3

RF Lens (V): 0.1

Scan Range: 100-1000 Amu

25 Scan Time: 0.5 sec

Acquisition time: 10 min

Gas Flow : 100 L/hr

Desolvation: 650 L/hr

30 Semi-preparative HPLC separations were achieved using a Waters ZQ 3100 system (HPLC)

Semi-preparative HPLC (HPLC)

Instrument:

35 Waters ZQ 3100--Mass Detector

Waters 2545-Pump

Waters SFO System Fluidics Organizer

Waters 2996 Diode Array Detector

Waters 2767 Sample Manager

5 LC conditions:

Reverse Phase HPLC analysis

Column: XBridge TM C18 5 μ m, 19 $\times$ 50mm

Injection Volume 500 μ L

Solvent A: Water 0.1% Formic Acid

10 Solvent B: Acetonitrile 0.1% Formic Acid

Gradient: 25-100% B over 10 min

Flow rate: 19 ml/min

Detection: 100-600 nm

15 MS conditions:

Ion Source: Single-quadrupole

Ion Mode: ES positive

Source Temp: 150 $^{\circ}$ C

Desolvation Temp: 350 $^{\circ}$ C

20 Detection: Ion counting

Capillary (KV): 3.00

Cone (V): 30

Extractor (V): 3

RF Lens (V): 0.1

25 Scan Range: 100-1000 Amu

Scan Time: 0.5 sec

Acquisition time: 10 min

Desolvation: 650 L/hr

Cone: 100 L/hr

30

LCMS Method C (LCMS-C)

Instrument: Finnigan LCG Advantage Max

Finnigan Surveyor LC Pump

Finnigan Surveyor Autosampler

35 Finnigan Surveyor PDA Detector

LC conditions:

Reverse Phase HPLC analysis

Column: Gemini 3 μ m C18 20 $\times$ 4.0 mm 110A

Injection Volume: 10 μ L

5 Solvent A: Water 0.1% Formic Acid

Solvent B: Acetonitrile 0.1% Formic Acid

Gradient: 10-100% B over 10 min

Detection: 100-600 nm

10 MS conditions

Ion Source: Ion trap

Ion Mode: ES positive

Temp: 300 °C

Detection: Ion counting

15 Scan Range: 80-1000 Amu

Scan Time: 0.2 sec

Acquisition time: 10 min

20 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 or a Biotage Isolera purification system using either Grace, RediSep® or Biotage silica cartridges. Microwave irradiation was achieved using a CEM Explorer SP

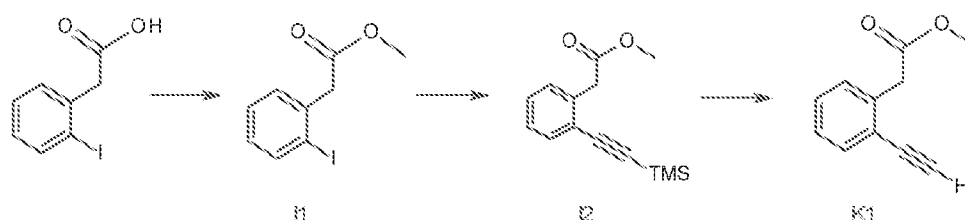
25 Microwave Reactor. All reactions carried out using microwave irradiation were stirred.

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

30

Synthesis of Key Intermediates

Key Intermediate 1: Methyl 2-(2-ethynylphenyl)acetate (*K1*)



5 (a) Methyl 2-(2-iodophenyl)acetate (*I1*)

To a solution of 2-(2-iodophenyl)acetic acid (5.00 g, 19.1 mmol) in MeOH (150 mL) was added concentrated aqueous H₂SO₄ (250 μ L) and the resulting mixture was stirred at 80 °C under nitrogen for 16 hours. The volatiles were removed by evaporation under reduced pressure and the residue was taken up in EtOAc (100 mL). The resulting solution was washed with 10% aqueous NaHCO₃ (100 mL), dried (MgSO₄) and the volatiles evaporated under reduced pressure to give the title compound *I1* as a clear liquid (5.20g, 99%); ¹H NMR (400 MHz, CDCl₃) δ 7.85 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.35-7.27 (m, 2H), 6.97 (m, 1H), 3.81 (s, 2H), 3.72 (s, 3H).

15 (b) Methyl 2-(2-((trimethylsilyl)ethynyl)phenyl)acetate (*I2*)

A mixture of methyl 2-(2-iodophenyl)acetate (*I1*) (4.65 g, 16.8 mmol), PdCl₂(PPh₃)₂ (295 mg, 421 μ mol), CuI (80.0 mg, 421 μ mol) and (trimethylsilyl)acetylene (2.80 mL, 20.2 mmol) in dry degassed THF (20 mL) and Et₃N (20 mL) was stirred at room temperature for 16 hours. The volatiles were removed under reduced pressure to give a black residue which was adsorbed onto silica gel and purified using column chromatography (0-5% EtOAc in petroleum benzine 40-60 °C) to give the title compound *I2* as a light brown liquid (4.63 g, 99%); ¹H NMR (400 MHz, CDCl₃) δ 7.48 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.32-7.14 (m, 3H), 3.84 (s, 2H), 3.71 (s, 3H), 0.26 (s, 9H). LCMS-B: rt 6.64 min.

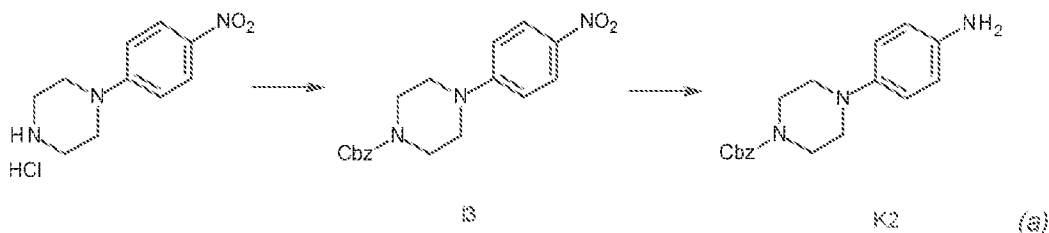
25 (c) Methyl 2-(2-ethynylphenyl)acetate (*K1*)

TBAF (1.0 M in THF; 28.5 mL, 28.5 mmol) was added to a solution of methyl 2-(2-((trimethylsilyl)ethynyl)phenyl)acetate (*I2*) (4.63 g, 19.0 mmol) in DCM (200 mL) at 0 °C. The solution was stirred at room temperature for 1 hour before washing with 10% aqueous NaHCO₃ (100 mL). The organic layer was dried (MgSO₄) before removing the volatiles *in vacuo* to give a dark brown/black residue which was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, 0-10% EtOAc in petroleum benzine 40-60 °C) to give the title compound *K1* as a red liquid (2.76 g, 83%); ¹H NMR (400 MHz, CDCl₃) δ 7.52

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(dd, $J = 7.6, 1.1$ Hz, 1H), 7.43-7.16 (m, 3H), 3.88 (d, $J = 9.6$ Hz, 2H), 3.77-3.52 (m, 3H), 3.28 (s, 1H).

Key intermediate 2: Benzyl 4-(4-aminophenyl)piperazine-1-carboxylate (K2)



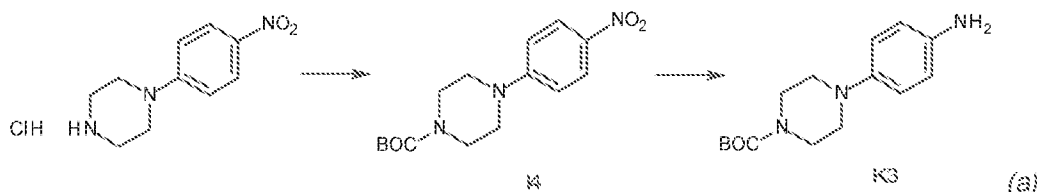
Benzyl 4-(4-nitrophenyl)piperazine-1-carboxylate (13)

Benzyl chloroformate (0.515 mL, 3.61 mmol) was added to a mixture of 1-(4-nitrophenyl)piperazine hydrochloride (0.800 g, 3.28 mmol) and Et_3N (1.14 mL, 8.21 mmol) in THF (20 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour then at room temperature for 2 hours. DCM (40 mL) was added and the organics were washed with saturated NaHCO_3 (40 mL), water (40 mL) then dried over MgSO_4 . The volatiles removed *in vacuo* to give the title compound 13 as a yellow solid (1.11 g, 99%); ^1H NMR (400 MHz, CDCl_3) δ 8.04-8.01 (m, 2H), 7.32-7.18 (m, obscured), 7.15 (s, 1H), 6.72-6.69 (m, 2H), 5.06 (s, 2H), 3.62-3.54 (m, 4H), 3.37-3.26 (m, 4H).

(b) Benzyl 4-(4-aminophenyl)piperazine-1-carboxylate (K2)

To a mixture of benzyl 4-(4-nitrophenyl)piperazine-1-carboxylate (13) (1.11 g, 3.25 mmol) and CoCl_2 (0.844 g, 6.50 mmol) in MeOH (30 mL) was added NaBH_4 (1.23 g, 32.5 mmol) portion-wise at 0 °C. Stirring was continued at 0 °C for 1 hour before aqueous 3 M HCl (10 mL) was added. The mixture was concentrated *in vacuo* to remove the MeOH and the aqueous layer was extracted twice with diethyl ether. The aqueous layer was basified with 1 M aqueous NaOH and extracted twice with EtOAc. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo*, then adsorbed onto silica gel and purified by silica gel column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 50-60% EtOAc in hexanes) to give the title compound K2 as a purple solid (397 mg, 39%); ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.29 (m, 5H), 6.83-6.78 (m, 2H), 6.68-6.62 (m, 2H), 5.16 (s, 2H), 3.70-3.61 (m, 4H), 3.46 (s, 2H), 3.10-2.86 (m, 4H). LCMS-A: rt 4.650 min; m/z 312.1 $[\text{M}+\text{H}]^+$.

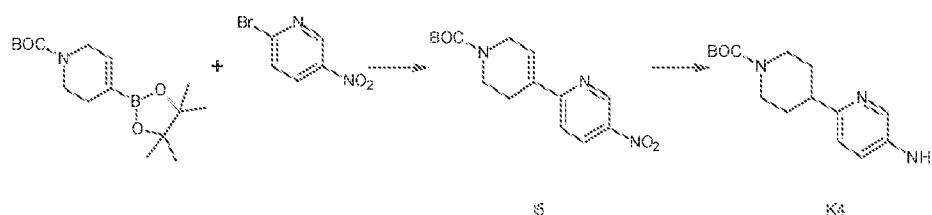
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Key intermediate 3: *tert*-Butyl 4-(4-aminophenyl)piperazine-1-carboxylate (K3)***tert*-Butyl 4-(4-nitrophenyl)piperazine-1-carboxylate (14)**

To a solution of 1-(4-nitrophenyl)piperazine hydrochloride (5.00 g, 20.5 mmol) in DCM (100 mL) was added Et₃N (7.15 mL, 51.3 mmol) and Boc anhydride (4.93 g, 22.6 mmol). The resulting solution was stirred at room temperature for 20 hours before water (100 mL) and DCM (70 mL) were added. The aqueous layer was extracted with DCM (100 mL) then the organics were combined, washed with brine (100 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give a yellow-orange residue. The residue was purified by silica gel column chromatography (Biotage Isolera, 120 g SiO₂ cartridge, 0-100% EtOAc in petroleum benzene 40-60 °C) to give the title compound 14 as a yellow solid (4.90 g, 78%); ¹H NMR (400 MHz, *d*₅-DMSO) δ 8.10-8.04 (m, 2H), 7.04-6.97 (m, 2H), 3.48 (m, 8H), 1.42 (s, 9H). LCMS-A: rt 6.13 min; *m/z* 208.2 [(M-Boc)+2H]⁺.

(b) *tert*-Butyl 4-(4-aminophenyl)piperazine-1-carboxylate (K3)

A slurry of 10% Pd/C (0.500 g) in EtOAc (10 mL) was added to a solution of *tert*-butyl 4-(4-nitrophenyl)piperazine-1-carboxylate (14) (3.24 g, 10.5 mmol) in EtOAc (90 mL) and the resulting suspension was stirred under a hydrogen atmosphere for 42 hours at room temperature. The catalyst was removed by filtration through Celite, washing with EtOAc (7 × 10 mL), then the filtrate was evaporated to dryness to give the title compound K3 as a pale pink solid (2.92 g, 99%); ¹H NMR (400 MHz, *d*₅-DMSO) δ 6.72-6.66 (m, 2H), 6.52-6.45 (m, 2H), 4.60 (s, 2H), 3.44-3.39 (m, 4H), 2.87-2.79 (m, 4H), 1.41 (s, 9H). LCMS-A: rt 4.40 min; *m/z* 278.2 [M+H]⁺.

Key intermediate 4: *tert*-Butyl 4-(5-aminopyridin-2-yl)piperidine-1-carboxylate (K4)**(a) *tert*-Butyl 5-nitro-5',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate (15)**

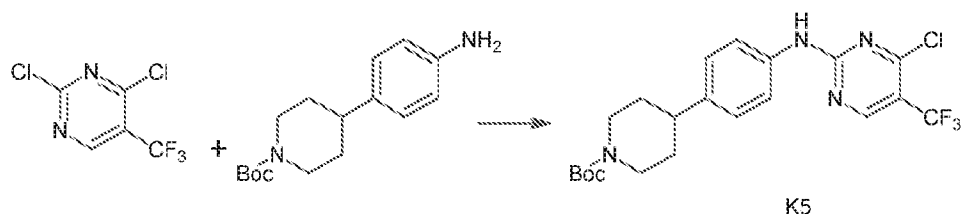
To a mixture of *N*-Boc-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (1.52 g, 4.93 mmol), 2-bromo-5-nitropyridine (1.00 g, 4.93 mmol) and PdCl₂(PPh₃)₂ (173 mg, 0.246 mmol)

) under nitrogen was added dioxane (30 mL) followed by 3 M aqueous Na_2CO_3 (4.93 mL, 14.8 mmol). The resulting mixture was degassed with a stream of nitrogen for 10 minutes then heated at reflux for 16 hours. On cooling, EtOAc (150 mL) was added and the resulting mixture was washed with water (3×50 mL) and brine (50 mL). The organics were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a brown solid that was purified by silica gel column chromatography (Biotage Isolera, 40 g SiO_2 cartridge, 0-30% EtOAc in petroleum benzine 40-60 °C) to give the title compound **15** as a yellow solid (1.43 g, 95%); ^1H NMR (400 MHz, CDCl_3) δ 9.37 (dd, $J = 2.6, 0.5$ Hz, 1H), 8.43 (dd, $J = 8.8, 2.7$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 1H), 6.95-6.83 (m, 1H), 4.20 (d, $J = 3.0$ Hz, 2H), 3.67 (t, $J = 5.6$ Hz, 2H), 2.70-2.63 (m, 2H), 1.49 (s, 9H). LCMS-A: rt 6.140 min; m/z 304 $[\text{M}-\text{H}]^-$.

(b) *tert*-Butyl 4-(5-aminopyridin-2-yl)piperidine-1-carboxylate (**K4**)

A slurry of 10% Pd/C (500 mg) in DMF (5 mL) was added to a solution of *tert*-butyl 5-nitro-5',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate (**15**) (1.40, 4.59 mmol) in DMF (45 mL). The resulting mixture was stirred under a hydrogen atmosphere for 16 hours at room temperature then EtOAc (100 mL) was added and the resulting solution filtered through a Celite pad, washing with EtOAc (150 mL). The filtrate was evaporated to dryness to give a residue that was purified by silica gel chromatography (Biotage Isolera, 40 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C and then 0-20% MeOH in EtOAc) to give the title compound **K4** as a yellow oil (1.18 g, 93%); ^1H NMR (400 MHz, CDCl_3) δ 8.03 (dd, $J = 2.4, 1.0$ Hz, 1H), 7.00-6.87 (m, 2H), 4.22 (br. s, 2H), 3.59 (br. s, 2H), 2.85-2.67 (m, 3H), 1.86 (m, 2H), 1.72-1.59 (m, 2H), 1.46 (s, 9H). LCMS-A: rt 4.416 min; m/z 278 $[\text{M}+\text{H}]^+$.

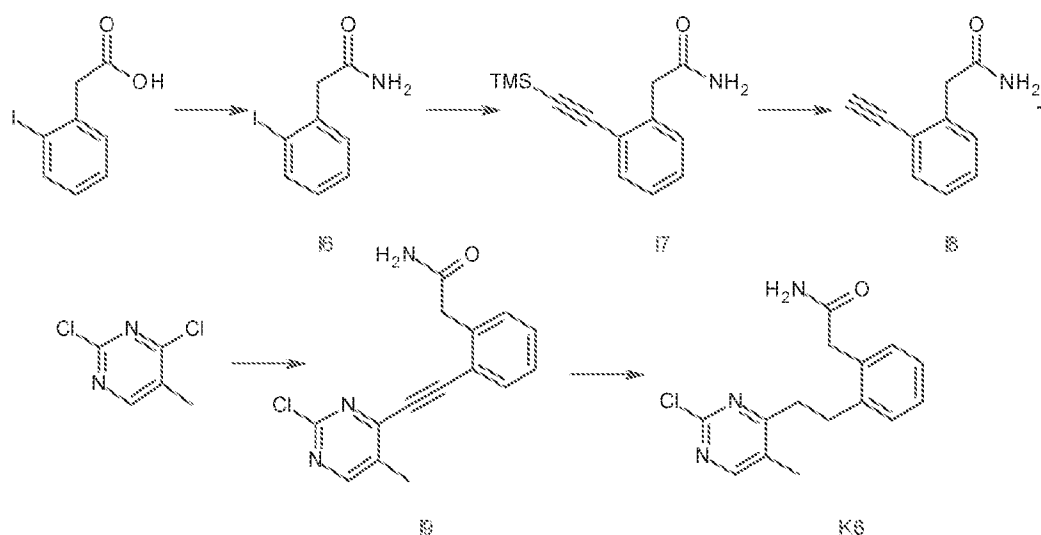
Key intermediate 5: *tert*-Butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (K5**)**



2,4-Dichloro-5-(trifluoromethyl)pyrimidine (4.12 g, 19.0 mmol) was stirred in a 1:1 *t*-BuOH:DCE mixture (400 mL) at room temperature. A 1.0 M ZnCl_2 solution in Et_2O (21.7 mL, 21.7 mmol) was added cautiously and after addition the reaction was stirred at room temperature for 10 minutes. 1-Boc-4-(4-aminophenyl)piperidine (5.00 g, 18.1 mmol) was then added followed by Et_3N (6.05 mL, 43.4 mmol) and the resulting mixture was stirred at room temperature overnight. The organic solvents were evaporated and the resulting solid was suspended in water (500 mL). The suspension was sonicated for 30 minutes and then

filtered. The filter cake was washed with water (2×100 mL) and dried under high vacuum to give the title compound **K5** as a tan solid (8.11 g, 98%); ^1H NMR (400 MHz, d_6 -DMSO) δ 10.61 (s, 1H), 8.78 (s, 1H), 7.59 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.5$ Hz, 2H), 4.07 (d, $J = 11.1$ Hz, 2H), 2.80 (s, 2H), 2.65 (t, $J = 12.0$ Hz, 1H), 1.74 (d, $J = 12.3$ Hz, 2H), 1.42 (s, 11H). LCMS-A: rt 6.834 min; m/z 457 $[\text{M}+\text{H}]^+$.

Key intermediate 6: 2-(2-(2-(2-Chloro-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (K6)



(a) 2-(2-iodophenyl)acetamide (16)

A solution of 2-iodophenylacetic acid (20.5 g, 78.2 mmol) in thionyl chloride (70 mL) was stirred at 75 °C for 3 hours. The thionyl chloride was removed *in vacuo* and the resulting residue was dissolved in DCM (100 mL). Ammonium carbonate (15.03 g, 156.5 mmol) was added and the resulting mixture was stirred at 60 °C for 20 hours. The volatiles were evaporated *in vacuo*, water (100 mL) was added and the resulting suspension was sonicated for 1 minute, before filtering and washing the filter cake with water then Et₂O. After air drying, the title compound **16** was obtained as a light cream coloured solid (12.9 g, 63%); ^1H NMR (300 MHz, d_6 -DMSO) δ 7.82 (d, $J = 8.3$ Hz, 1H), 7.41 (brs s, 1H), 7.30-7.37 (m, 2H), 6.95-7.01 (m, 2H), 3.55 (s, 2H). LCMS-B: rt 5.108 min; m/z 262 $[\text{M}+\text{H}]^+$.

(b) 2-(2-((Trimethylsilyl)ethynyl)phenyl)acetamide (17)

A mixture of 2-(2-iodophenyl)acetamide (**16**) (12.91 g, 49.52 mmol), Et₃N (26 mL), ethynyltrimethylsilane (9.08 mL, 64.3 mmol), PdCl₂(PPh₃)₂ (0.347 g, 0.495 mmol) and CuI (0.188 g, 0.989 mmol) in DMF (44 mL) was stirred under a nitrogen atmosphere at 50 °C for 3 hours. The volatiles were removed *in vacuo* and the resulting residue partitioned between

EtOAc (100 mL) and water. The aqueous phase was extracted with EtOAc (3 × 50 mL), then the combined organic extracts were washed with water (3 × 70 mL), brine, dried (MgSO₄), filtered and evaporated *in vacuo* to give the title compound *17* as a brown solid (11.4 g, 99%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 7.40 (d, *J* = 7.5 Hz, 1H), 7.20-7.36 (m, 4H), 6.94 (brs, 1H), 3.58 (s, 2H), 0.24 (s, 9H). LCMS-B: rt 6.884 min; *m/z* 232 [M+H]⁺.

(c) 2-(2-Ethynylphenyl)acetamide (*18*)

A 1.0 M solution of TBAF in THF (59.1 mL, 59.1 mmol) was slowly added to a cooled (5 °C water/ice bath) solution of 2-(2-((trimethylsilyl)ethynyl)phenyl)acetamide (*17*) (11.4 g, 49.3 mmol) in DCM (150 mL) and acetic acid (3.66 mL, 64.1 mmol). The mixture was stirred at 5 °C for 1 hour before 10% aqueous NaHCO₃ solution (150 mL) was added. The resulting mixture was extracted with DCM (3 × 50 mL) then the combined organics were dried (MgSO₄), filtered and evaporated *in vacuo* until approximately 15 mL of solvent remained. This solution was diluted with Et₂O (100 mL) and EtOAc (100 mL) resulting in the formation of a precipitate, which was filtered and dried to give 2.81 g of the title compound *18* as a brown solid. The remaining filtrate was adsorbed onto silica gel and purified using column chromatography (CombiFlash Rf, 80 g SiO₂ Cartridge, 0-10% MeOH in DCM). An additional 2.62 g of the title compound *18* was isolated as a brown solid (combined total 5.43 g, 69%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 7.44 (d, *J* = 7.5 Hz, 1H), 7.21-7.37 (m, 4H), 6.93 (brs, 1H), 4.32 (s, 1H), 3.59 (s, 2H). LCMS-B: rt 4.734 min; *m/z* 160 [M+H]⁺.

(d) 2-(2-((2-Chloro-5-methylpyrimidin-4-yl)ethynyl)phenyl)acetamide (*19*)

A mixture of 2-(2-ethynylphenyl)acetamide (*18*) (5.40 g, 33.9 mmol), 2,4-dichloro-5-methylpyrimidine (6.63 g, 40.7 mmol) and CuI (0.129 g, 0.678 mmol) in 1,4-dioxane (180 mL) and Et₃N (14.2 mL, 101 mmol) was placed under nitrogen. PdCl₂(PPh₃)₂ (0.238 g, 0.339 mmol) was added and the resulting mixture was stirred at 70 °C for 20 minutes, then adsorbed onto silica gel and purified by column chromatography (CombiFlash Rf, 120 g SiO₂ Cartridge, 0-5% MeOH in DCM) to give the title compound *19* as a yellow solid (5.01 g, 51%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 8.75 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.35-7.52 (m, 4H), 6.97 (brs, 1H), 3.71 (s, 2H), 2.42 (s, 3H). LCMS-B: rt 5.689 min; *m/z* 286 [M+H]⁺.

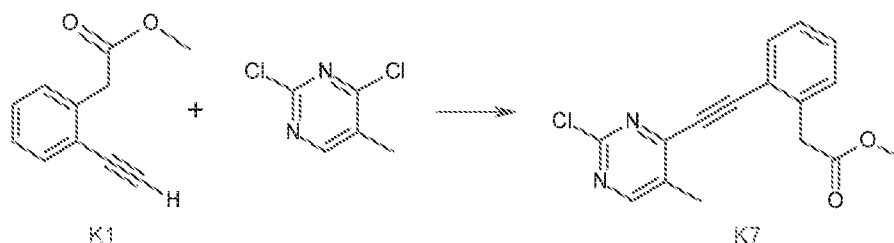
(e) 2-(2-(2-(2-Chloro-5-methylpyrimidin-4-yl)ethynyl)phenyl)acetamide (*K6*)

A suspension of 2-(2-((2-chloro-5-methylpyrimidin-4-yl)ethynyl)phenyl)acetamide (*19*) (5.01 g, 17.5 mmol) in DMF (231 mL) and MeOH (80 mL) containing platinum oxide (0.995 g, 4.38 mmol) was stirred under a hydrogen atmosphere for 40 hours. The resulting mixture was filtered through a pad of Celite and the filtrate concentrated *in vacuo*. The resulting residue

was diluted with ice water (400 mL) to give a precipitate, which was filtered and dried to give the title compound *K6* (4.23 g, 83%), ^1H NMR (300 MHz, d_6 -DMSO) δ 8.47 (s, 1H), 7.44 (brs, 1H), 7.21-7.24 (m, 1H), 7.12-7.15 (m, 3H), 6.92 (brs, 1H), 3.47 (s, 2H), 2.99 (s, 4H), 2.15 (s, 3H). LCMS-B: rt 5.528 min; m/z 290 $[\text{M}+\text{H}]^+$.

5

Key intermediate 7: Methyl 2-((2-chloro-5-methylpyrimidin-4-yl)ethynyl)phenylacetate (*K7*)



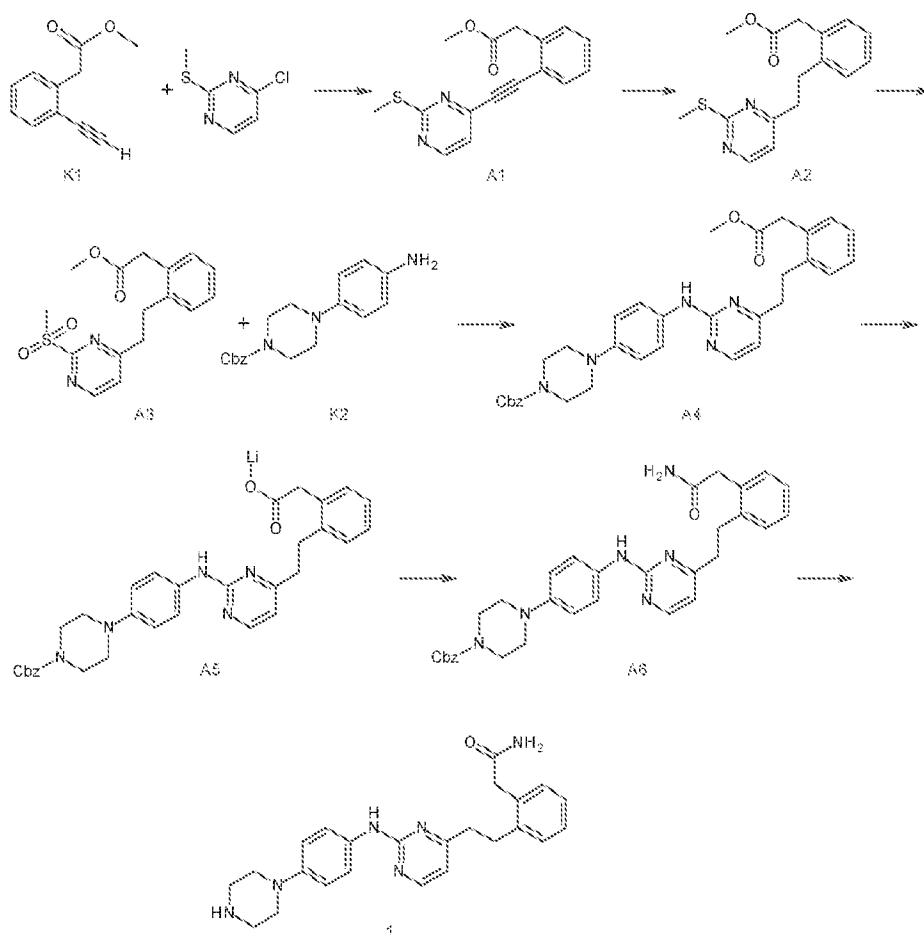
10 PPh_3 (31 mg, 0.12 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (84 mg, 0.12 mmol), Et_3N (0.67 mL, 4.8 mmol) and methyl 2-(2-ethynylphenyl)acetate (*K1*) (0.25 g, 1.4 mmol) were added to a solution of 2,4-dichloro-5-methylpyrimidine (0.20 g, 1.2 mmol) in anhydrous DMF (5.0 mL). The solution was degassed with nitrogen for 10 minutes before the addition of CuI (23 mg, 0.12 mmol). The resulting mixture was heated under microwave irradiation at 120 $^\circ\text{C}$ for 15 minutes then

15 diluted with EtOAc (30 mL) and filtered through Celite. The filtrate was evaporated under reduced pressure and the resulting residue adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, 40 g SiO_2 cartridge, 0-35% EtOAc in petroleum benzine 40-60 $^\circ\text{C}$) to give the title compound *K7* as a yellow solid (0.28 g, 78%); ^1H NMR (400 MHz, CDCl_3) δ 8.49 (s, 1H), 7.66 (d, $J = 7.7$ Hz, 1H), 7.46-7.40 (m, 1H), 7.39-7.31 (m, 2H), 3.93

20 (s, 2H), 3.71 (s, 3H), 2.45 (s, 3H). LCMS-A: rt 5.993 min; m/z 301 $[\text{M}+\text{H}]^+$.

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Example 1: Synthesis of 2-{2-[2-(2-{(4-{piperazin-1-yl}phenyl)amino)pyrimidin-4-yl)ethyl]phenyl}acetamide (1)



(a) Methyl 2-(2-((2-(methylthio)pyrimidin-4-yl)ethynyl)phenyl)acetate (A1)

- 5 A suspension of 4-chloro-2-methylthiopyrimidine (200 μ L, 1.72 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (121 mg, 0.172 mmol), CuI (33.0 mg, 0.172 mmol), PPh_3 (45.0 mg, 0.172 mmol), methyl 2-(2-ethynylphenyl)acetate (K1) (359 mg, 1.08 mmol) and Et_3N (0.938 mL) in THF (6 mL) was heated at 100 $^\circ\text{C}$ under microwave irradiation for 10 minutes. The volatiles were removed *in vacuo* and the resultant residue adsorbed onto silica gel and purified by column
- 10 chromatography (Biotage Isolera, SiO_2 cartridge, 0-40% EtOAc in petroleum benzine 40-60 $^\circ\text{C}$, then Biotage Isolera, SiO_2 cartridge, 0-40% EtOAc in DCM) to give the title compound A1 as a yellow oil (323 mg, 63%); ^1H NMR (400 MHz, CDCl_3) δ 8.50 (d, J = 5.0 Hz, 1H), 7.63 (dd, J = 7.6, 1.1 Hz, 1H), 7.44-7.29 (m, 3H), 7.12 (d, J = 5.0 Hz, 1H), 3.92 (s, 2H), 3.71 (s, 3H), 2.59 (s, 3H).

(b) Methyl 2-(2-(2-(2-(methylthio)pyrimidin-4-yl)ethyl)phenyl)acetate (A2)

A suspension of methyl 2-(2-(2-(2-(methylthio)pyrimidin-4-yl)ethynyl)phenyl)acetate (A1) (323 mg, 1.08 mmol) and 10% Pd/C (300 mg) in DMF (15 mL) was stirred under a hydrogen atmosphere at room temperature for 20 hours. The resulting mixture was filtered through Celite, washing with EtOAc (100 mL). The filtrate was evaporated *in vacuo* to yield a brown oil which was dissolved in DMF (10 mL). A slurry of 10% Pd/C (330 mg) in DMF (5 mL) was added and the resulting suspension was stirred under a hydrogen atmosphere at room temperature for a further 20 hours. The resulting mixture was filtered through Celite, washing with EtOAc (100 mL) then the filtrate was evaporated *in vacuo*. The resulting residue was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, 12 g SiO₂ cartridge, 0-20% EtOAc in petroleum benzine 40-60 °C) to yield the title compound A2 as a clear oil (170 mg, 52%); ¹H NMR (400 MHz, CDCl₃) δ 8.36 (d, *J* = 5.0 Hz, 1H), 7.25-7.14 (m, 4H), 6.75 (d, *J* = 5.1 Hz, 1H), 3.69 (m, 5H), 3.11-3.04 (m, 2H), 2.99-2.91 (m, 2H), 2.57 (s, 3H). LC-MS- A: rt 6.060 min; *m/z* 303.1 [M+H]⁺.

(c) Methyl 2-(2-(2-(2-(methylsulfonyl)pyrimidin-4-yl)ethyl)phenyl)acetate (A3)

m-CPBA (70%; 174 mg, 1.01 mmol) was added to a solution of methyl 2-(2-(2-(2-(methylthio)pyrimidin-4-yl)ethyl)phenyl)acetate (A2) (170 mg, 0.458 mmol) in DCM (50 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour, then warmed to room temperature and stirred for a further 18 hours. The temperature was reduced to 0 °C and additional *m*-CPBA (70%; 174 mg, 1.01 mmol) was added. After warming to room temperature, stirring was continued for a further 3 hours then 10% aqueous NaHCO₃ (50 mL) was added. The layers were separated and the organics were dried (MgSO₄), evaporated under reduced pressure and adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound A3 as a clear oil (150 mg, 80%); ¹H NMR (400 MHz, CDCl₃) δ 8.73 (d, *J* = 5.1 Hz, 1H), 7.31 (d, *J* = 5.1 Hz, 1H), 7.24-7.21 (m, 1H), 7.21-7.18 (m, 2H), 7.14-7.09 (m, 1H), 3.70 (s, 3H), 3.68 (s, 2H), 3.35 (s, 3H), 3.23-3.17 (m, 2H), 3.17-3.11 (m, 2H).

(d) Benzyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)pyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (A4)

A solution of methyl 2-(2-(2-(2-(methylsulfonyl)pyrimidin-4-yl)ethyl)phenyl)acetate (A3) (150 mg, 449 μmol) and benzyl 4-(4-aminophenyl)piperazine-1-carboxylate (K2) (168 mg, 538 μmol) in TFE (5 mL) containing TFA (180 μL) was heated at 100 °C under microwave irradiation for 60 minutes. Additional TFA (200 μL) was added and the resulting solution heated at 120 °C under microwave irradiation for a further 40 minutes. Additional TFA (200

μL) was again added and the mixture was heated at 150 °C under microwave irradiation for a further 20 minutes. The resulting mixture was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound A4 as a brown oil (76 mg, 30%). LCMS-A: rt 6.212 min; *m/z* 566.2 [M+H]⁺.

(e) 2-(2-(2-(2-((4-(4-((Benzyloxy)carbonyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A5)

LiOH.H₂O (40 mg, 0.93 mmol) was added to a solution of benzyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)pyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (A4) (76 mg, 0.13 mmol) in THF (7 mL), water (1.5 mL) and MeOH (1 mL) and the resulting mixture was stirred at room temperature for 16 hours. The volatiles were removed *in vacuo* and the resultant residue was diluted with EtOAc (50 mL) and saturated aqueous NaHCO₃ (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound A5 as yellow oil; LCMS-A: rt 5.803 min; *m/z* 552.1 [M+H]⁺.

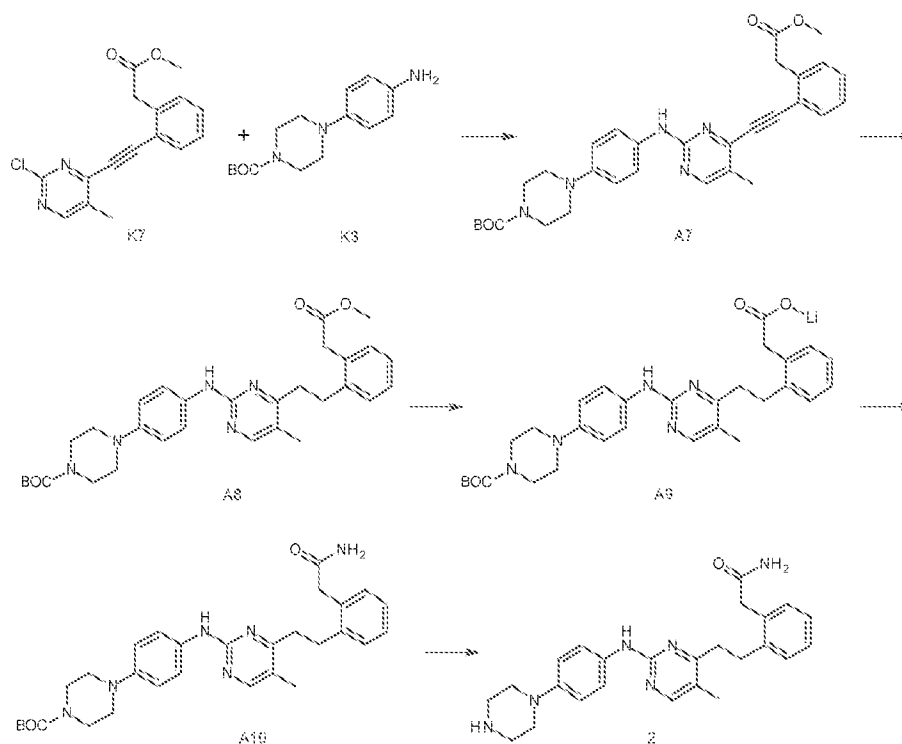
(f) Benzyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)pyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (A6)

HOBt (24 mg, 0.17 mmol), EDCI.HCl (33 mg, 0.17 mmol) and DIPEA (0.12 mL, 0.67 mmol) were added to a stirred solution of 2-(2-(2-(2-((4-(4-((benzyloxy)carbonyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A5) (74 mg, 0.13 mmol) in dry THF (5 mL) and dry DMF (2 mL) under an atmosphere of nitrogen. After 10 minutes ammonium carbonate (65 mg, 0.67 mmol) was added and stirring was continued at room temperature for 18 hours. The volatiles were removed *in vacuo* and the residue was diluted with EtOAc (65 mL) and saturated NaHCO₃ (65 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) then the combined organic layers were washed with brine (50 mL) and dried over Na₂SO₄. After filtration the solvent was removed *in vacuo* to afford a pale yellow solid which was purified by silica gel column chromatography (Biotage Isolera, SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound A6 as brown oil (70 mg, 95%); ¹H-NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 7.64 (s, 1H), 7.48 (d, *J* = 8.9 Hz, 2H), 7.37 (d, *J* = 4.3 Hz, 4H), 7.32 (m, 1H), 7.25-7.17 (m, 4H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.51 (d, *J* = 4.9 Hz, 1H), 5.77 (s, 1H), 5.51 (s, 1H), 5.16 (s, 2H), 3.69-3.64 (m, 4H), 3.64 (s, 2H), 3.11-3.06 (m, 4H), 3.05 (dd, *J* = 9.6, 6.5 Hz, 2H), 2.91-2.84 (m, peak obscured), 2.07 (t, *J* = 7.0 Hz, 1H). LCMS-A: rt 5.646 min; *m/z* 551.2 [M+H]⁺.

(g) 2-(2-(2-(2-((4-(Piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (1)

To a solution of benzyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)pyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (A6) (73 mg, 0.13 mmol) in DMF (5 mL) under nitrogen, was added a slurry of 10% Pd/C (20 mg) in DMF. The resulting mixture was stirred under an atmosphere of hydrogen at room temperature for 19 hours then filtered through a 2.0 PFTE filter. The filtrate was evaporated *in vacuo* and the residue was loaded onto a SCX (5 g) column using MeOH. The column was washed with 2 column volumes of MeOH followed by 3 column volumes of 1% MeNH₂ in MeOH. The 1% MeNH₂ in MeOH filtrate was evaporated *in vacuo* to give a pale brown oil which was taken up in DCM (0.5 mL) and cyclohexane (1 mL) and sonicated. The resulting precipitate was filtered and the filter cake dried *in vacuo* to give the title compound 1 as a white solid (1.4 mg, 90% purity). ¹H-NMR: (400 MHz, *d*₂-MeOH) δ 8.22-8.16 (m, 1H), 7.57-7.48 (m, 2H), 7.20 (m, 4H), 7.01-6.93 (m, 2H), 6.60 (dd, *J* = 5.0, 2.8 Hz, 1H), 3.63 (d, *J* = 2.3 Hz, 2H), 3.18-3.12 (m, 4H), 3.09 (dd, *J* = 9.2, 6.4 Hz, 5H), 2.93-2.83 (m, 3H). LC-MS Method A: rt 4.305 min; *m/z* 417.2 [M+H]⁺.

Example 2: Synthesis of 2-(2-(2-(5-methyl-2-((4-(piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (2)



(a) *tert*-Butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)-5-methylpyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (A7)

A mixture of *tert*-butyl 4-(4-aminophenyl)piperazine-1-carboxylate (*K3*) (0.845 g, 3.06 mmol), methyl 2-(2-((2-chloro-5-methylpyrimidin-4-yl)ethynyl)phenyl)acetate (*K7*) (0.460 g, 1.53 mmol), Pd₂(dba)₃ (0.070 g, 0.076 mmol), Xantphos (0.089 g, 0.15 mmol), and Na₂CO₃ (0.648 g, 6.12 mmol) in DME (16 mL) was degassed with nitrogen before heating under microwave irradiation for 30 minutes at 110 °C, then a further 60 minutes at 110 °C. An additional 0.1 equivalent of Pd₂(dba)₃ and 0.1 equivalent of Xantphos were added before the solution was degassed with nitrogen for 5 minutes and heated under microwave irradiation for 60 minutes at 110 °C. The resulting mixture was filtered and the filtrate evaporated *in vacuo* to give a dark brown residue which was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, 40 g SiO₂ cartridge, 0-100% MeOH in EtOAc), to yield the title compound *A7* as brown oil (66 mg, 8%); ¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.53-7.46 (m, 2H), 7.44-7.28 (m, 4H), 6.94 (dd, *J* = 7.2, 5.1 Hz, 2H), 3.96 (s, 2H), 3.70 (s, 3H), 3.58 (dd, *J* = 11.4, 6.2 Hz, 4H), 3.11-3.04 (m, 4H), 2.33 (s, 3H), 1.49 (s, 9H). LC-MS- A: rt 6.409 min; *m/z* 542 [M+H]⁺.

(b) *tert*-Butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (*A8*)

To a solution of *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (*A7*) (60 mg, 0.11 mmol) in anhydrous DMF (10 mL) was added a slurry of 10% Pd/C (30 mg) in DMF (2 mL). The resulting mixture was stirred at room temperature under an atmosphere of hydrogen for 72 hours then diluted with EtOAc (30 mL) and filtered through a plug of Celite, washing with EtOAc (50 mL). The filtrate was evaporated to dryness to give the title compound *A8* as a brown oily residue (44 mg, 73%); ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 7.52 (dt, *J* = 8.0, 2.5 Hz, 2H), 7.25-7.17 (m, 4H), 6.92 (dd, *J* = 7.2, 5.1 Hz, 2H), 6.88 (s, 1H), 3.72 (s, 2H), 3.68 (d, *J* = 3.0 Hz, 3H), 3.61-3.56 (m, 4H), 3.07 (dd, *J* = 9.3, 5.1 Hz, 6H), 2.06 (s, 3H), 1.48 (s, 9H). LC-MS- A: rt 6.260 min; *m/z* 546.2 [M+H]⁺.

(c) 2-(2-(2-(2-((4-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)ethynyl)phenyl)acetic acid (*A9*)

LiOH·H₂O (24 mg, 0.56 mmol) was added to a solution of *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (*A8*) (44 mg, 0.081 mmol) in THF (7 mL), water (1.5 mL) and MeOH (1 mL) and the resulting mixture was stirred at room temperature for 24 hours. The volatiles were removed *in vacuo* and the resulting residue was diluted with EtOAc (50 mL) and saturated aqueous NaHCO₃ (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 ×

50 mL). The organic layers were combined, washed with brine (50 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure to give the title compound A9 as brown oily residue (36 mg, 84%); LCMS-A: rt 5.737 min; m/z 532.2 $[\text{M}+\text{H}]^+$.

(d) *tert*-Butyl 4-((4-((2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (A10)

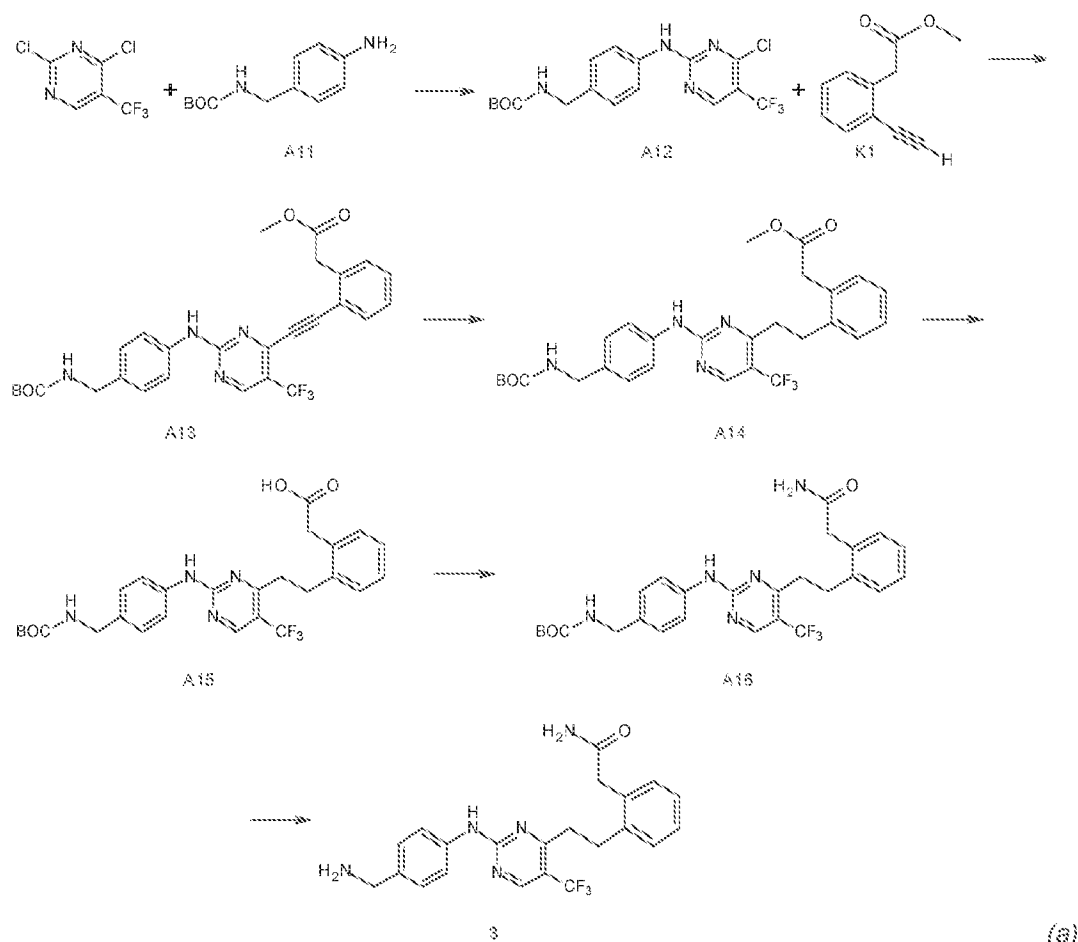
HOBt (15 mg, 0.11 mmol), EDCI.HCl (21 mg, 0.11 mmol) and DIPEA (72 μL , 0.41 mmol) were added to a solution of 2-(2-(2-(2-((4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetic acid (A9) (44 mg, 0.083 mmol) in dry DMF (10 mL) under an atmosphere of nitrogen. After 10 minutes ammonium carbonate (40 mg, 0.41 mmol) was added and the resulting mixture was stirred at room temperature for 18 hours. A solution of HOBt (15 mg, 0.11 mmol), EDCI.HCl (21 mg, 0.11 mmol) and DIPEA in DMF (3 mL) was then added and after 10 minutes ammonium carbonate (40 mg, 0.41 mmol) was added in one portion. The resulting mixture was stirred at 26 °C for a further 24 hours before the volatiles were removed *in vacuo* and the residue partitioned between EtOAc (65 mL) and saturated NaHCO_3 (65 mL). The aqueous layer was extracted with EtOAc (2 $\times$ 50 mL) then the combined organics were washed with brine (50 mL) and dried over Na_2SO_4 . After filtration the solvent was removed *in vacuo* to afford a pale yellow solid which was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C then 0-100% MeOH in EtOAc). After removing the solvent *in vacuo* the resulting residue was taken up in EtOAc, filtered through cotton wool and the filtrate evaporated to dryness to give the title compound A10 as a light brown solid (28 mg, 64%); ^1H NMR (400 MHz, CDCl_3) δ 8.05 (s, 1H), 7.47-7.41 (m, 2H), 7.25-7.17 (m, 4H), 7.13 (s, 1H), 6.93-6.88 (m, 2H), 5.59 (s, 1H), 5.53 (s, 1H), 3.65 (s, 2H), 3.61-3.55 (m, 4H), 3.10-3.01 (m, 6H), 2.92-2.88 (m, 2H), 2.08 (s, 3H), 1.48 (s, 9H). LCMS-A: rt 5.525 min; m/z 531.2 $[\text{M}+\text{H}]^+$

(e) 2-(2-(2-(5-Methyl-2-((4-(piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (2)

To a solution of *tert*-butyl 4-((4-((2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (A10) (28 mg, 0.053 mmol) in DCM (8 mL) was added TFA (2 mL) and the resulting solution was stirred at 25 °C for 24 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (10 mL) and 2 M NaOH (20 mL). The aqueous layer was extracted with EtOAc (2 $\times$ 10 mL) then the combined organic layers washed with brine (10 mL) and dried (MgSO_4). The solvent was removed *in vacuo* to give a brown solid which was taken up in MeOH and purified by SCX cartridge (5 g,

MeOH followed by 0.5 M NH_3 in MeOH). The volatiles from the ammoniacal filtrate were removed *in vacuo* and the resulting solid residue suspended in cyclohexane and sonicated. The resulting suspension was filtered and the filter cake dried to give the title compound 2 as a light brown solid (8 mg, 35%); ^1H NMR (400 MHz, d_6 -DMSO) δ 9.08 (s, 1H), 8.11 (s, 1H), 7.60 (dd, $J = 9.2, 2.2$ Hz, 2H), 7.41 (s, 1H), 7.26-7.20 (m, 1H), 7.19-7.13 (m, 3H), 6.92 (s, 1H), 6.85 (d, $J = 9.1$ Hz, 2H), 4.02 (s, 1H), 3.50 (s, 2H), 3.03 (dd, $J = 10.1, 5.7$ Hz, 2H), 2.97 (m, 2H), 2.85 (m, 4H), 2.69-2.64 (m, 2H), 2.36-2.30 (m, 2H), 2.05 (s, 3H). LCMS-A: rt 4.364 min; m/z 431.1 $[\text{M}+\text{H}]^+$.

Example 3: Synthesis of 2-{2-[2-(2-{(4-aminomethyl)phenyl)amino}-5-(trifluoromethyl)pyrimidin-4-yl]ethyl]phenyl}acetamide (3)



tert-Butyl 4-aminobenzoate (A11)

Boc anhydride (4.46 g, 20.5 mmol) was added to a stirred solution of 4-aminobenzylamine (2.50 g, 20.5 mmol) and Et_3N (5.70 mL, 40.9 mmol) in DCM (100 mL) at room temperature. The resulting mixture was stirred overnight before the volatiles were removed *in vacuo*. The

residue was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to yield the title compound A11 as a yellow solid (4.28 g, 94%); ¹H NMR (400 MHz, CDCl₃) δ 7.09 (d, *J* = 8.2 Hz, 2H), 6.69-6.64 (m, 2H), 4.73 (s, 1H), 4.21 (d, *J* = 5.4 Hz, 2H), 3.66 (s, 2H), 1.48 (s, 9H). LCMS-A: rt 4.363 min.

(b) *tert*-Butyl 4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzylcarbamate (A12)

A 1.0 M ZnCl₂ solution in Et₂O (5.40 mL, 5.40 mmol) was added cautiously to a stirred suspension of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (1.03 g, 4.72 mmol) in 1:1 *t*-BuOH:DCE (200 mL) at room temperature. After stirring for 20 minutes, *tert*-butyl 4-aminobenzylcarbamate (A11) (1.00 g, 4.50 mmol) was added followed by Et₃N (752 μL, 5.40 mmol) and the resulting mixture stirred at room temperature overnight. The volatiles were removed *in vacuo* and the resulting tan solid was suspended in water (500 mL). The suspension was sonicated for 10 minutes, filtered and the filter cake was washed with water (2 × 100 mL) then dried under high vacuum to give the title compound A12 as a tan solid (1.77 g, 97%); ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.63 (s, 1H), 8.79 (s, 1H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.10 (d, *J* = 6.0 Hz, 2H), 1.40 (s, 9H). LCMS-A: rt 6.356 min; *m/z* 401 [M-1].

(c) Methyl 2-(2-((2-((4-((*tert*-butoxycarbonyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethynyl)phenyl)acetate (A13)

A suspension of *tert*-butyl 4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzylcarbamate (A12) (500 mg, 1.24 mmol), CuI (12 mg, 0.06 mmol), PPh₃ (16 mg, 0.06 mmol), and Et₃N (346 μL, 2.28 mmol) in DMF (3 mL) was sonicated for 5 minutes before the addition of PdCl₂(PPh₃)₂ (44 mg, 0.06 mmol) and methyl 2-(2-ethynylphenyl)acetate (K1) (324 mg, 1.86 mmol). The resulting mixture was heated under microwave irradiation at 120 °C for 20 minutes then adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to yield a yellow solid. The solid was suspended in toluene and the resulting suspension sonicated for 10 minutes. The resulting suspension was filtered and the filter cake dried to give the title compound A13 as a yellow solid (412 mg, 61%); ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.44 (s, 1H), 8.82 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.58-7.52 (m, 1H), 7.50-7.40 (m, 2H), 7.36 (t, *J* = 6.0 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 4.10 (d, *J* = 6.0 Hz, 2H), 3.96 (s, 2H), 3.62 (s, 3H), 1.40 (s, 9H). LCMS-A: rt 6.497 min; *m/z* 539 [M-1].

(d) Methyl 2-(2-(2-(2-((4-(((tert-butoxycarbonyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetate (A14)

A suspension of 10% Pd/C (200 mg) and methyl 2-(2-(2-(2-((4-(((tert-butoxycarbonyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetate (A13) (412 mg, 0.762 mmol) in DMF (5 mL) and Et₃N (1 mL) was stirred under a hydrogen atmosphere at room temperature for 16 h. The resulting mixture was filtered through Celite, washing with EtOAc (200 mL) then the combined filtrates were evaporated *in vacuo* to give the title compound A14 as a white solid (306 mg, 74%); ¹H NMR (400 MHz, d₆-DMSO) δ 10.19 (s, 1H), 8.68 (s, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.34 (t, J = 6.0 Hz, 1H), 7.27-7.16 (m, 6H), 4.09 (d, J = 6.0 Hz, 2H), 3.76 (s, 2H), 3.59 (s, 3H), 3.11-2.95 (m, 4H), 1.40 (s, 9H). LCMS-A: rt 6.637 min; m/z 545 [M+H]⁺.

(e) 2-(2-(2-(2-((4-(((tert-Butoxycarbonyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A15)

LiOH·H₂O (94 mg, 2.2 mmol) was added to a solution of methyl 2-(2-(2-(2-((4-(((tert-butoxycarbonyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetate (A14) (306 mg, 0.562 mmol) in MeOH (1 mL), water (1 mL) and THF (10 mL) and the resulting mixture was stirred at room temperature overnight. The volatiles were removed *in vacuo* and the resultant oil partitioned between EtOAc (150 mL) and 2 M aqueous NaOH (100 mL). The organic layer was separated, washed with water (2 × 100 mL), brine (50 mL) and dried over MgSO₄. The volatiles were removed *in vacuo* to yield the title compound A15 as a yellow oil (0.25 g, 83%); LCMS-A: rt 6.267 min; m/z 531 [M+H]⁺.

(f) tert-Butyl 4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzylcarbamate (A16)

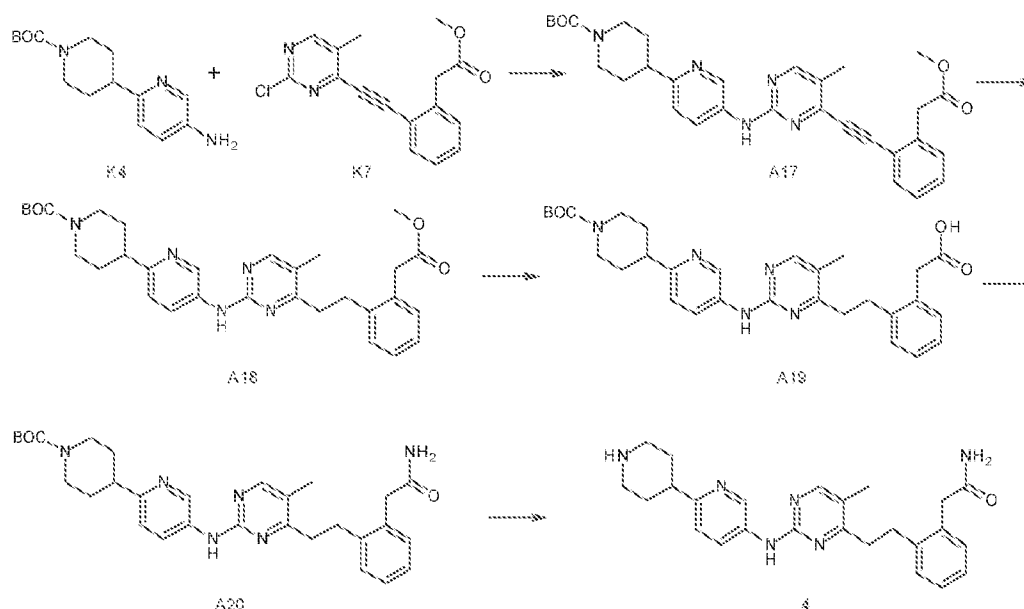
HOBt (76 mg, 0.56 mmol) and EDCI·HCl (108 mg, 0.561 mmol) were added to a solution of 2-(2-(2-(2-((4-(((tert-butoxycarbonyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A15) (251 mg, 0.468 mmol) and DIPEA (326 μL, 1.87 mmol) in DMF (2 mL) and THF (10 mL). The resulting mixture was stirred at room temperature overnight then the volatiles were removed *in vacuo* and the residue partitioned between EtOAc (150 mL) and saturated aqueous NaHCO₃ (100 mL). The layers were separated and the organic layer was washed with water (100 mL), brine (50 mL) and dried over MgSO₄. The volatiles were removed *in vacuo* and the residue adsorbed onto silica gel and purified by silica gel column chromatography (Biotage Isolera, SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound A16 as a tan solid (0.22 g, 89%); ¹H NMR (400 MHz, d₆-DMSO) δ 10.18 (s, 1H), 8.67 (s, 1H), 7.68 (d, J = 8.5

Hz, 2H), 7.43 (s, 1H), 7.33 (t, $J = 6.0$ Hz, 1H), 7.27-7.10 (m, 6H), 6.91 (s, 1H), 3.50 (s, 2H), 3.18 (d, $J = 5.3$ Hz, 2H), 3.14-2.99 (m, 4H), 1.40 (s, 9H). LCMS-A: rt 6.086 min; m/z 530 $[M+H]^+$.

5 (g) 2-(2-(2-(2-((4-(Aminomethyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (3)

TFA (954 μ L, 12.5 mmol) was added to a solution of *tert*-butyl 4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzylcarbamate (A16) (220 mg, 0.415 mmol) in DCM (10 mL) and the resulting mixture stirred for 20 hours at room
 10 temperature. The volatiles were removed *in vacuo* and the resulting residue partitioned between EtOAc (100 mL) and 2 M aqueous NaOH (100 mL). The layers were separated and the organic layer washed with water (100 mL), brine (50 mL), dried ($MgSO_4$) then evaporated *in vacuo* to yield a white solid. The solid was taken up in DCM (10 mL) and sonicated for 2 minutes then petroleum benzene 40-60 °C (100 mL) was added and
 15 sonication continued for a further 10 minutes. The resulting suspension was filtered and the filler cake dried to give the title compound 3 as a white solid (135 mg, 76%); 1H NMR (400 MHz, d_2 -MeOH) δ 8.57 (s, 1H), 7.68 (d, $J = 8.6$ Hz, 2H), 7.33 (d, $J = 8.8$ Hz, 2H), 7.31-7.17 (m, 4H), 3.81 (s, 2H), 3.69 (s, 2H), 3.22-3.06 (m, 4H). LCMS-A: rt 4.722 min; m/z 428 $[M-1]^+$.

20 **Example 4: Synthesis of 2-(2-(2-(5-methyl-2-((6-(piperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (4)**



(a) *tert*-Butyl 4-(5-((4-((2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)-5-methylpyrimidin-2-yl)amino)pyridin-2-yl)piperidine-1-carboxylate (A17)

To a solution of methyl 2-(2-((2-chloro-5-methylpyrimidin-4-yl)ethynyl)phenyl)acetate (K7) (100 mg, 0.333 mmol) in 1,4-dioxane (8 mL) was added *tert*-butyl 4-(5-aminopyridin-2-yl)piperidine-1-carboxylate (K4) (92.2 mg, 0.333 mmol), Cs₂CO₃ (433 mg, 1.33 mmol), Pd₂(dba)₃ (30 mg, 0.033 mmol) and Xantphos (58 mg, 0.10 mmol). The resulting mixture was degassed with nitrogen for 5 minutes before heating under microwave irradiation for 30 minutes at 120 °C. The resulting mixture was diluted with EtOAc (100 mL) then washed with water (2 × 25 mL), brine (25 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Biotage Isolera, 40 g SiO₂ cartridge, 0-100% EtOAc in hexanes) to give the title compound A17 as a yellow foam (112 mg, 62%); ¹H NMR (400 MHz, CDCl₃) δ 8.62 (d, *J* = 2.4 Hz, 1H), 8.32 (d, *J* = 0.6 Hz, 1H), 8.16 (dd, *J* = 8.5, 2.7 Hz, 1H), 7.66 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.43-7.30 (m, 3H), 7.14 (d, *J* = 8.5 Hz, 1H), 7.10 (s, 1H), 4.25 (br. s, 2H), 3.95 (s, 2H), 3.70 (s, 3H), 2.86-2.78 (m, 3H), 2.35 (d, *J* = 0.4 Hz, 3H), 1.91 (d, *J* = 13.3 Hz, 2H), 1.75-1.63 (m, 2H), 1.47 (s, 9H). LCMS-A: rt 5.462 min; *m/z* 542 [M+H]⁺.

(b) *tert*-Butyl 4-(5-((4-((2-(2-methoxy-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)pyridin-2-yl)piperidine-1-carboxylate (A18)

A suspension of 10% Pd/C (53% water; 30 mg) and *tert*-butyl 4-(5-((4-((2-(2-methoxy-2-oxoethyl)phenethyl)ethynyl)-5-methylpyrimidin-2-yl)amino)pyridin-2-yl)piperidine-1-carboxylate (A17) (125 mg, 0.231 mmol) in DMF (5 mL) and Et₃N (1 mL) was stirred under a hydrogen atmosphere at room temperature for 44 hours. The resulting mixture was filtered through Celite, washing with EtOAc (200 mL). The combined filtrates were evaporated *in vacuo* and the resulting oil purified by silica gel chromatography (Biotage Isolera, 12 g SiO₂ cartridge, 0-100% EtOAc in hexanes) to give the title compound A18 as a yellow foam (115 mg, 91%); ¹H NMR (400 MHz, CDCl₃) δ 8.62 (d, *J* = 2.5 Hz, 1H), 8.16 (dd, *J* = 8.5, 2.7 Hz, 1H), 8.11 (d, *J* = 0.5 Hz, 1H), 7.25-7.16 (m, 5H), 7.11 (d, *J* = 8.5 Hz, 1H), 4.25 (br. s, 2H), 3.71 (s, 2H), 3.67 (s, 3H), 3.09 (dd, *J* = 9.6, 6.1 Hz, 2H), 2.93 (dd, *J* = 9.4, 6.0 Hz, 2H), 2.88-2.76 (m, 3H), 2.08 (s, 3H), 1.91 (d, *J* = 11.8 Hz, 2H), 1.75-1.61 (m, 2H), 1.47 (s, 9H). LCMS-A: rt 5.401 min; *m/z* 546 [M+H]⁺.

(c) 2-(2-(2-(2-((6-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)pyridin-3-yl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetic acid (A19)

LiOH·H₂O (442 mg, 10.5 mmol) was added to a stirred solution of *tert*-butyl 4-(5-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)pyridin-2-yl)piperidine-1-

carboxylate (A18) (115 mg, 0.211 mmol) in water (4 mL) and THF (40 mL) and the resulting mixture heated at 40 °C for 18 hours. On cooling the volatiles were removed *in vacuo* and the residue taken up in EtOAc (100 mL). The resulting solution was washed with water (100 mL), brine (50 mL) and dried over MgSO₄. The volatiles were removed *in vacuo* to give the title compound A19 as a clear oil (96 mg, 86%); LCMS-A: rt 5.137 min; *m/z* 532 [M+H]⁺.

(d) *tert*-Butyl 4-(5-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)pyridin-2-yl)piperidine-1-carboxylate (A20)

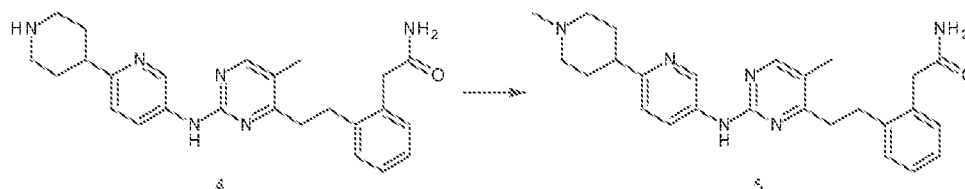
HOBt (71 mg, 0.52 mmol), EDCI.HCl (0.11 g, 0.59 mmol) and DIPEA (0.16 mL, 0.90 mmol) were added to a stirred solution of 2-(2-(2-(2-((6-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)pyridin-3-yl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetic acid (A19) (96 mg, 0.18 mmol) in dry DMF (5 mL) under an atmosphere of nitrogen. After 10 minutes ammonium carbonate (174 mg, 1.81 mmol) was added in one portion and the resulting mixture was stirred for 18 hours at room temperature. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (10 mL) and saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) then the combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄. The volatiles were removed *in vacuo* and the residue adsorbed onto silica gel and purified by chromatography (Biolage Isolera, 40 g SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C followed by 0-25% MeOH in DCM) to give the title compound A20 as a clear oil (72 mg, 75%). ¹H NMR (400 MHz, CDCl₃) δ 8.82 (d, *J* = 2.4 Hz, 1H), 8.14-8.06 (m, 1H), 7.93 (dd, *J* = 8.5, 2.7 Hz, 1H), 7.37 (s, 1H), 7.26-7.22 (m, 4H), 7.10 (d, *J* = 8.5 Hz, 1H), 5.91 (s, 1H), 5.73 (s, 1H), 4.24 (s, 2H), 3.69 (s, 2H), 3.09 (dd, *J* = 9.7, 6.0 Hz, 2H), 2.97-2.90 (m, 2H), 2.86-2.72 (m, 3H), 2.12 (s, 3H), 1.90 (d, *J* = 12.8 Hz, 2H), 1.68 (m, 2H), 1.47 (s, 9H). LCMS-A: rt 5.018 min; *m/z* 531 [M+H]⁺.

(e) 2-(2-(2-(5-Methyl-2-((6-(piperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (4)

TFA (0.5 mL) was added to a solution of *tert*-butyl 4-(5-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)pyridin-2-yl)piperidine-1-carboxylate (A20) (70 mg, 0.13 mmol) in DCM (5 mL) and the resulting mixture stirred for 18 hours at room temperature. The volatiles were removed *in vacuo* and the residue partitioned between 2 M aqueous NaOH (10 mL) and EtOAc (25 mL). The organic layer was separated then washed with water (25 mL), brine (25 mL), dried (Na₂SO₄) and concentrated under reduced pressure to give the title compound 4 as an off white solid (45 mg, 79%); ¹H NMR (400 MHz, *d*₄-MeOH) δ 8.79 (dd, *J* = 2.6, 0.5 Hz, 1H), 8.15 (dd, *J* = 8.6, 2.7 Hz, 1H), 8.13 (d, *J* = 0.6 Hz,

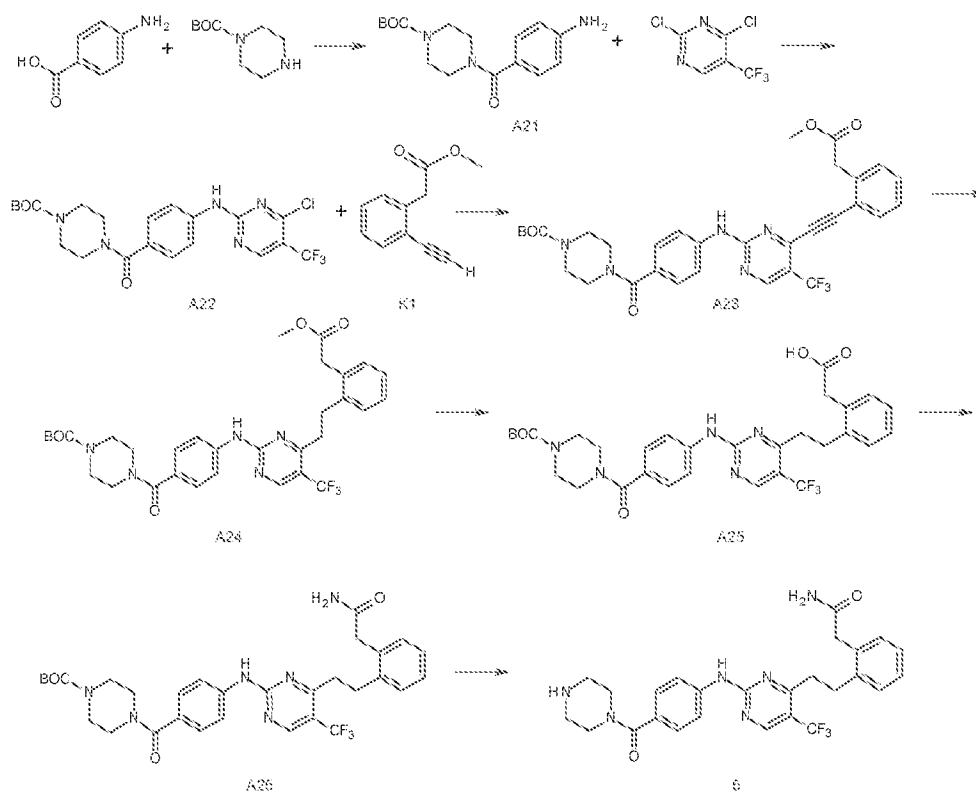
1H), 7.28-7.22 (m, 2H), 7.21-7.14 (m, 3H), 3.64 (s, 2H), 3.20-3.10 (m, 4H), 3.02-2.95 (m, 2H), 2.88-2.68 (m, 3H), 2.11 (s, 3H), 1.95-1.84 (m, 2H), 1.71 (qd, $J = 12.7, 4.0$ Hz, 2H). LCMS-A: rt 4.241 min; m/z 431 $[M+H]^+$.

5 **Example 5: Synthesis of 2-(2-(2-(5-methyl-2-((6-(1-methylpiperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (5)**



Formaldehyde (37% wt. in H_2O ; 0.017 mL, 0.22 mmol) was added to a solution of 2-(2-(2-(5-methyl-2-((6-(piperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (4) (32 mg, 0.07 mmol) in MeOH (4 mL) under an atmosphere of nitrogen. The resulting solution was stirred for 15 minutes at room temperature then sodium triacetoxyborohydride (63 mg, 0.30 mmol) was added in one portion. After stirring at room temperature for 18 hours a further portion of formaldehyde (37 wt. % in H_2O ; 0.017 mL, 0.22 mmol) was added and after 15 minutes sodium triacetoxyborohydride (63 mg, 0.30 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 20 hours then the volatiles were removed *in vacuo* and the residue partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×25 mL). The combined organic layers were washed with water (25 mL), brine (25 mL) and dried over Na_2SO_4 . The volatiles were removed under reduced pressure to give the title compound 5 as an off white solid (20 mg, 61%); 1H NMR (400 MHz, d_4 -MeOH) δ 8.79 (d, $J = 2.2$ Hz, 1H), 8.15 (dd, $J = 8.6, 2.7$ Hz, 1H), 8.12 (d, $J = 0.6$ Hz, 1H), 7.27-7.23 (m, 2H), 7.20-7.15 (m, 3H), 3.64 (s, 2H), 3.16-3.06 (m, 4H), 2.98 (dd, $J = 9.2, 6.0$ Hz, 2H), 2.72 (tt, $J = 12.0, 3.9$ Hz, 1H), 2.40 (s, 3H), 2.32 (td, $J = 12.0, 2.4$ Hz, 2H), 2.11 (s, 3H), 1.97 (d, $J = 11.9$ Hz, 2H), 1.92-1.80 (m, 2H). LCMS-A: rt 4.237 min; m/z 445 $[M+H]^+$.

Example 6: Synthesis of 2-{2-[2-{2-[(4-{piperazine-1-carbonyl}phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl]acetamide (6)



(a) *tert*-Butyl 4-(4-aminobenzoyl)piperazine-1-carboxylate (A21)

To a solution of 4-aminobenzoic acid (0.411 g, 3.00 mmol) in DMF (5.0 mL) at room temperature was added EDCI.HCl (0.862 g, 4.50 mmol), HOBT (0.608 g, 4.50 mmol), Et₃N (0.835 mL, 6.00 mmol) and *N*-Boc piperazine (0.671 g, 3.60 mmol). The resulting mixture was stirred at room temperature for 21 hours then 2 M aqueous NaOH was added to adjust the pH to >10. EtOAc was added then the layers separated and the organic layer dried over MgSO₄. The volatiles were removed under reduced pressure and the residue was purified by silica gel chromatography (Biotage Isolera, 40 g SiO₂ cartridge, 50-90% EtOAc in petroleum benzene 40-60 °C) to give the title compound A21 as a white solid (0.530 g, 56%); LCMS-A: rt 5.079 min; *m/z* 250.1 [(M-*t*-Bu)+H]⁺, 206.1 [(M-Boc)+H]⁺.

(b) *tert*-Butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzoyl)piperazine-1-carboxylate (A22)

Zinc(II) chloride (1.0 M in Et₂O; 2.00 mL, 2.00 mmol) was added to a solution of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (0.399 g, 1.84 mmol) in 1:1 DCE/*t*-BuOH (15 mL) at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 1 hour at 0 °C and then *tert*-

butyl 4-((4-aminobenzoyl)piperazine-1-carboxylate (A21) (0.510 g, 1.67 mmol) in 1:1 DCE/*t*-BuOH (15 mL) was added. A solution of Et₃N (0.256 mL, 1.84 mmol) in 1:1 DCE/*t*-BuOH (15 mL) was added dropwise at 0 °C and the resulting mixture was vigorously stirred for a further 30 minutes at 0 °C then at room temperature for 16 hours. The volatiles were removed *in vacuo* to afford a brown residue which was purified by silica gel column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-100% EtOAc in petroleum benzene 40-60 °C) to yield a pale yellow solid. The solid was suspended in MeOH (15 mL) and water (15 mL) and the resulting suspension filtered to give the title compound A22 as a white solid (0.561 g, 69%); ¹H NMR (400 MHz, CDCl₃) δ 8.61 (s, 1H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.64 (s, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 3.87-3.30 (m, 8H), 1.47 (s, 9H). LCMS-A: rt 6.206 min; *m/z* 484.1 [M-H]⁺.

(c) *tert*-Butyl 4-((4-((2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzoyl)piperazine-1-carboxylate (A23)

A solution of methyl 2-(2-ethynylphenyl)acetate (K1) (0.129 g, 0.741 mmol) in DMF (3 mL) and Et₃N (344 μL, 2.47 mmol) was added to a mixture of *tert*-butyl 4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzoyl)piperazine-1-carboxylate (A22) (0.300 g, 0.617 mmol), PdCl₂(PPh₃)₂ (0.065 g, 0.093 mmol), CuI (0.018 g, 0.093 mmol) and PPh₃ (0.016 g, 0.062 mmol) in DMF (3 mL). The resulting mixture was heated under microwave irradiation at 120 °C for 15 minutes, diluted with EtOAc and passed through a plug of Celite, washing with EtOAc (60 mL). The filtrates were combined and the volatiles were removed *in vacuo* to give a residue that was purified by silica gel column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-80% EtOAc in petroleum benzene 40-60 °C) to give the title compound A23 as a yellow oil (0.337 g, 88%); ¹H NMR (400 MHz, CDCl₃) δ 8.67 (s, 1H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.68 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.61 (s, 1H), 7.48-7.41 (m, 3H), 7.40-7.31 (m, 2H), 3.96 (s, 2H), 3.71 (s, 3H), 3.67-3.37 (m, 8H), 1.47 (s, 9H). LCMS-A: rt 6.393 min; *m/z* 624.1 [M+H]⁺.

(d) *tert*-Butyl 4-((4-((2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzoyl)piperazine-1-carboxylate (A24)

A suspension of 10% Pd/C (53% water; 0.660 g), *tert*-butyl 4-((4-((2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzoyl)piperazine-1-carboxylate (A23) (0.337 g, 0.540 mmol) and Et₃N (1 mL) was stirred at room temperature for 16 hours under an atmosphere of hydrogen. The mixture was filtered through a pad of Celite, washing with EtOAc (80 mL). The filtrates were evaporated *in vacuo* affording a yellow oil which was purified by silica gel column chromatography (Biotage Isolera, 40 g

SiO₂ cartridge, 0-80% EtOAc in petroleum benzine 40-60 °C) to yield the title compound A24 as a pale yellow oil (0.245 g, 72%); ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 8.19 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.25-7.13 (m, 4H), 3.73 (s, 2H), 3.65 (s, 3H), 3.84-3.30 (m, 8H), 3.18-3.00 (m, 4H), 1.46 (s, 9H). LCMS-A: rt 6.500 min; *m/z* 628 [M+H]⁺.

(e) *tert*-Butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzoyl)piperazine-1-carboxylate (A25)

LiOH·H₂O (0.050 g, 1.2 mmol) was added to a solution of *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzoyl)piperazine-1-carboxylate (A24) (0.25 g, 0.39 mmol) in THF (7 mL), water (1.5 mL) and MeOH (1 mL) and the resulting mixture was stirred at room temperature for 18 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (50 mL) and saturated aqueous NaHCO₃ (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄ and the volatiles removed *in vacuo* to give the title compound A25 as a white solid (0.24 g, 99%). LCMS-A: rt 6.281 min; *m/z* 558 [(M-*t*-Bu)+H]⁺, 514 [(M-Boc)+H]⁺.

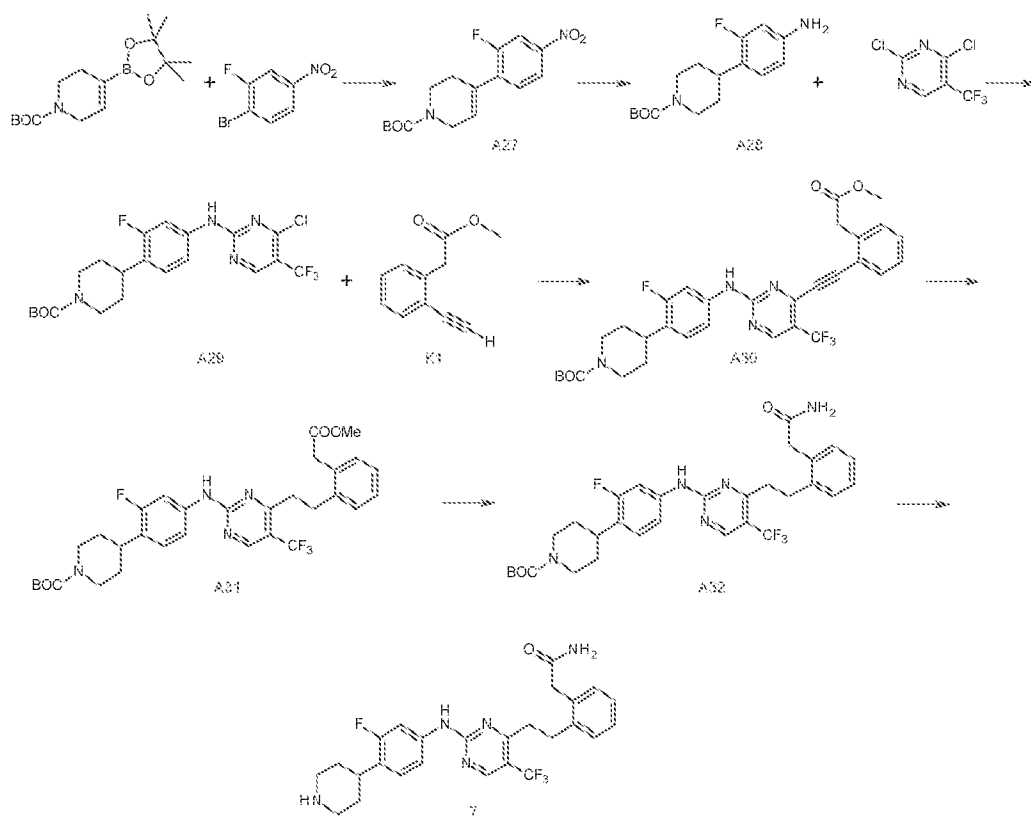
(f) *tert*-Butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzoyl)piperazine-1-carboxylate (A26)

HOBt (0.068 g, 0.50 mmol), EDCI·HCl (0.096 g, 0.50 mmol) and DIPEA (0.34 mL, 1.9 mmol) were added to a stirred solution of *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzoyl)piperazine-1-carboxylate (A25) (0.28 g, 0.39 mmol) in dry THF (6 mL) and dry DMF (1 mL) under an atmosphere of nitrogen. After 10 minutes ammonium carbonate (0.19 g, 1.9 mmol) was added in one portion and the resulting solution was stirred at room temperature for 17 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (65 mL) and saturated aqueous NaHCO₃ (65 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) then the combined organic layers were washed with brine (50 mL) and dried over MgSO₄. The volatiles were removed *in vacuo* and the residue was purified by silica gel column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C then 0-20% MeOH in EtOAc) to give the title compound A26 as a white solid (0.18 g, 77%); ¹H NMR (400 MHz, CDCl₃) δ 8.58 (s, 1H), 7.91 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.31-7.21 (m, obscured), 5.43 (br. s, 2H), 3.74 (s, 2H), 3.71-3.35 (m, 8H), 3.18-3.03 (m, 4H), 1.47 (s, 9H). LCMS-A: rt 6.120 min; *m/z* 613.3 [M+H]⁺.

(g) 2-(2-(2-(2-((4-(Piperazine-1-carbonyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (6)

To a solution of *tert*-butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzoyl)piperazine-1-carboxylate (A26) (0.182 g, 0.297 mmol) in DCM (4 mL) was added TFA (1 mL) and the resulting mixture was stirred at room temperature for 16 hours. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc (10 mL) and 2 M aqueous NaOH (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) then the combined organic fractions were washed with water (10 mL), brine (10 mL) and dried over MgSO₄. The volatiles were removed *in vacuo* to give a yellow solid, which was suspended in cyclohexane and then filtered to give the title compound 6 as a white solid (0.132 g, 87%); ¹H NMR (400 MHz, *d*₂-MeOH) δ 8.62 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 6.3 Hz, 1H), 7.23-7.15 (m, 3H), 3.68 (s, 2H), 3.82-3.46 (m, 4H), 3.23-3.15 (m, 2H), 3.12 (dd, *J* = 9.8, 5.4 Hz, 2H), 3.02-2.71 (m, 4H). LCMS-A: rt 4.676 min; *m/z* 513.3 [M+H]⁺.

Example 7: Synthesis of 2-(2-(2-(2-((3-fluoro-4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (7)



(a)

tert-Butyl 4-(2-fluoro-4-nitrophenyl)-5,6-dihydropyridine-1(2H)-carboxylate (A27)

To a mixture of 3,6-dihydro-2H-pyridine-1-*tert*-butoxycarbonyl-4-boronic acid pinacol ester (0.555 g, 1.80 mmol), 4-bromo-3-fluoronitrobenzene (0.294 g, 1.33 mmol) and PdCl₂(PPh₃)₂ (0.051 g, 0.072 mmol) under nitrogen was added 1,4-dioxane (5.0 mL) and 3 M aqueous Na₂CO₃ (1.4 mL, 4.2 mmol). The resulting solution was degassed with a stream of nitrogen for 10 minutes then heated at reflux for 16 hours. The volatiles were evaporated under reduced pressure and the residue purified using silica gel column chromatography (Biotage Isolera, SiO₂ cartridge, 0-25% EtOAc in petroleum benzine 40-60 °C) to give the title compound A27 (0.391 g, 91%); ¹H NMR (400 MHz, CDCl₃) δ 8.01 (m, 1H), 7.93 (dd, *J* = 10.6, 2.2 Hz, 1H), 7.42 (dd, *J* = 8.5, 7.6 Hz, 1H), 6.11 (s, 1H), 4.12 (m, 2H), 3.64 (t, *J* = 5.6 Hz, 2H), 2.52 (brs, 2H), 1.50 (s, 9H).

(b) tert-Butyl 4-(4-amino-2-fluorophenyl)piperidine-1-carboxylate (A28)

To a solution of *tert*-butyl 4-(2-fluoro-4-nitrophenyl)-5,6-dihydropyridine-1(2H)-carboxylate (A27) (0.391 g, 1.20 mmol) in EtOAc (10 mL) was added 10% Pd/C (0.118 g) in EtOAc (1 mL) and the resulting suspension was stirred at 30 °C under a hydrogen atmosphere for 16 hours. The resulting mixture was filtered through Celite and the filtrate concentrated under reduced pressure to give the title compound A28 (0.339 g, 96%); ¹H NMR (400 MHz, CDCl₃) δ 6.94 (dd, *J* = 8.3 Hz, 1H), 6.41 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.36 (dd, *J* = 12.1, 2.3 Hz, 1H), 4.21 (brs, 2H), 3.65 (s, 2H), 2.84 (m, 3H), 1.75 (bd, *J* = 13.3 Hz, 2H), 1.47 (s, 9H).

(c) tert-Butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluorophenyl)piperidine-1-carboxylate (A29)

Zinc(II) chloride (1.0 M in Et₂O; 1.08 mL, 1.08 mmol) was added to a solution of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (0.216 g, 0.994 mmol) in 1:1 DCE/*t*-BuOH (8 mL) at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 1 hour at 0 °C then *tert*-butyl 4-(4-amino-2-fluorophenyl)piperidine-1-carboxylate (A28) (0.266 g, 0.904 mmol) in 1:1 DCE/*t*-BuOH (8 mL) was added. A solution of Et₃N (0.139 mL, 0.994 mmol) in 1:1 DCE/*t*-BuOH (5 mL) was then added dropwise at 0 °C and the resulting mixture was vigorously stirred for a further 30 minutes at 0 °C, then at room temperature for 18 hours. The volatiles removed *in vacuo* to afford a brown residue which was purified by silica gel column chromatography (Biotage Isolera, 25 g SiO₂ Cartridge, 0-20% EtOAc in petroleum benzine 40-60 °C) to yield a pale yellow solid. The solid was suspended in MeOH (15 mL) and water (15 mL) and the resulting suspension filtered to afford the title compound A29 as a white solid (0.363 g, 85%); ¹H NMR (400 MHz, CDCl₃) δ 8.59 (s, 1H), 7.59-7.47 (m, 2H), 7.20-7.14 (m, 1H), 4.37-4.14 (m, 2H), 2.98 (tt, *J* = 12.1, 3.4 Hz, 1H), 2.83 (t, *J* = 11.7 Hz, 2H), 1.80 (d, *J* = 12.8 Hz, 2H), 1.71-1.55 (m, 3H), 1.48 (s, 9H). LCMS-A: rt 6.902 min; *m/z* 473.1 [M-H].

(d) *tert*-Butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluorophenyl)piperidine-1-carboxylate (A30)

A solution of methyl 2-(2-ethynylphenyl)acetate (*K1*) (0.15 g, 0.87 mmol) in DMF (3 mL) and Et₃N (0.40 mL, 2.9 mmol) were added to a mixture of *tert*-butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluorophenyl)piperidine-1-carboxylate (A29) (0.34 g, 0.72 mmol), PdCl₂(PPh₃)₂ (0.076 g, 0.11 mmol), CuI (0.021 g, 0.072 mmol) and PPh₃ (0.019 g, 0.072 mmol) in DMF (3 mL). The resulting mixture was heated under microwave irradiation at 120 °C for 15 minutes then diluted with EtOAc and passed through a plug of Celite, washing with EtOAc (60 mL). The filtrates were combined and the volatiles were removed *in vacuo* to give a brown residue. The residue was purified by silica gel column chromatography (Biotage Isolera, 40 g SiO₂ cartridge, 0-40% EtOAc in petroleum benzine 40-60 °C) to give the title compound A30 as a yellow oil (0.40 g, 90%); ¹H NMR (400 MHz, CDCl₃) δ 8.65 (s, 1H), 7.70-7.60 (m, 2H), 7.50 (s, 1H), 7.47-7.41 (m, 1H), 7.40-7.31 (m, 2H), 7.22-7.12 (m, 2H), 4.36-4.18 (m, 2H), 3.96 (s, 2H), 3.71 (s, 3H), 2.98 (tt, *J* = 12.1, 3.4 Hz, 1H), 2.83 (t, *J* = 12.0 Hz, 2H), 1.81 (d, *J* = 12.4 Hz, 2H), 1.70-1.55 (m, obscured), 1.49 (s, 9H). LCMS-A: rt 7.010 min; *m/z* 613.1 [M+H]⁺.

(e) *tert*-Butyl 4-(2-fluoro-4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A31)

To a solution of *tert*-butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluorophenyl)piperidine-1-carboxylate (A30) (0.399 g, 0.651 mmol) in DMF (6 mL) and Et₃N (1 mL) was added a slurry of 10% Pd/C (53% water; 0.500 g) in DMF (3 mL). The resulting mixture was stirred at room temperature for 21 hours under an atmosphere of hydrogen then filtered through a pad of Celite, washing with EtOAc (80 mL). The filtrates were concentrated *in vacuo* and the residue purified by silica gel chromatography (Biotage Isolera, 25 g SiO₂ cartridges, 0-40% EtOAc in petroleum benzine 40-60 °C) to yield the title compound A31 as a pale yellow solid (0.312 g, 78%); ¹H NMR (400 MHz, CDCl₃) δ 8.56 (s, 1H), 7.66 (dd, *J* = 12.7, 2.0 Hz, 1H), 7.45 (s, 1H), 7.29-7.12 (m, obscured by solvent), 4.41-4.16 (m, 2H), 3.77 (s, 2H), 3.68 (s, 3H), 3.18-3.06 (m, 4H), 2.97 (tt, *J* = 11.9, 3.3 Hz, 1H), 2.83 (t, *J* = 12.8 Hz, 2H), 1.81 (d, *J* = 12.1 Hz, 2H), 1.71-1.52 (m, obscured), 1.49 (s, 9H). LCMS-A: rt 7.221 min; *m/z* 617.1 [M+H]⁺.

(f) *tert*-Butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluorophenyl)piperidine-1-carboxylate (A32)

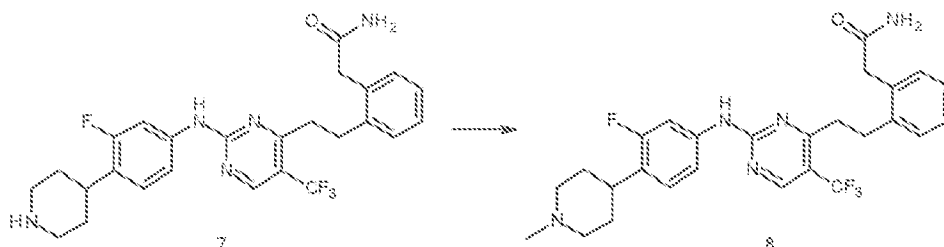
LiOH H₂O (0.063 g, 1.5 mmol) was added to a solution of *tert*-butyl 4-(2-fluoro-4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A31) (0.30 g, 0.49 mmol) in THF (10 mL), water (2 mL) and MeOH (1.5 mL) and the resulting mixture was stirred at room temperature for 18 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (50 mL) and saturated aqueous NaHCO₃ (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO₄) and the volatiles removed *in vacuo* to give a white solid. The solid was dissolved in dry THF (12 mL) and dry DMF (2 mL) under an atmosphere of nitrogen and HOBt (0.086 g, 0.64 mmol), EDCI.HCl (0.12 g, 0.64 mmol) and DIPEA (0.43 mL, 2.4 mmol) were added. After 10 minutes ammonium carbonate (0.24 g, 2.4 mmol) was added in one portion and the resulting mixture was stirred at room temperature for 18 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (65 mL) and saturated aqueous NaHCO₃ (65 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) then the combined organic layers were washed with brine (50 mL) and dried over MgSO₄. The volatiles were removed *in vacuo* to afford a pale yellow oil which was purified by silica gel column chromatography (Biotage Isolera, SiO₂ cartridge, 0-80% EtOAc in petroleum benzine 40-60 °C) to give the title compound A32 as a white solid (0.209 g, 69%); ¹H NMR (400 MHz, CDCl₃) δ 8.50 (s, 1H), 8.44 (s, 1H), 7.61 (dd, *J* = 12.8, 2.2 Hz, 1H), 7.30-7.18 (m, 5H), 7.09 (t, *J* = 8.4 Hz, 1H), 6.31 (s, 1H), 5.69 (s, 1H), 4.39-4.16 (m, 2H), 3.72 (s, 2H), 3.14-3.00 (m, 4H), 2.94 (tt, *J* = 12.1, 3.3 Hz, 1H), 2.81 (t, *J* = 11.4 Hz, 2H), 1.78 (d, *J* = 12.2 Hz, 2H), 1.69-1.53 (m, 2H), 1.49 (s, 9H). LCMS-A: rt 6.710 min; *m/z* 602.3 [M+H]⁺.

(g) 2-(2-(2-(2-((3-Fluoro-4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (7)

To a solution of *tert*-butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluorophenyl)piperidine-1-carboxylate (A32) (0.209 g, 0.347 mmol) in DCM (4 mL) was added TFA (1.0 mL) and the resulting mixture was stirred at room temperature for 16 hours. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc (10 mL) and 2 M aqueous NaOH (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) then the combined organic layers washed with water (10 mL), brine (10 mL) and dried over MgSO₄. The volatiles were removed *in vacuo* to give a yellow solid which was suspended in DCM/cyclohexane and the resulting suspension filtered to give the title compound 7 as a white solid (0.107 g, 61%); ¹H NMR (400 MHz, *d*₄-MeOH) δ 8.59 (s, 1H), 7.66 (dd, *J* = 13.2, 2.1 Hz, 1H), 7.39 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.28-7.15 (m, 5H), 3.68 (s, 2H), 3.23-3.14 (m, 4H), 3.10 (dd, *J* = 10.6, 5.4 Hz, 2H), 2.99 (tt, *J* = 11.7, 3.8

Hz, 1H), 2.80 (td, $J = 12.4, 2.9$ Hz, 2H), 1.87-1.68 (m, 4H). LCMS-A: rt 4.851 min; m/z 502.2 $[M+H]^+$.

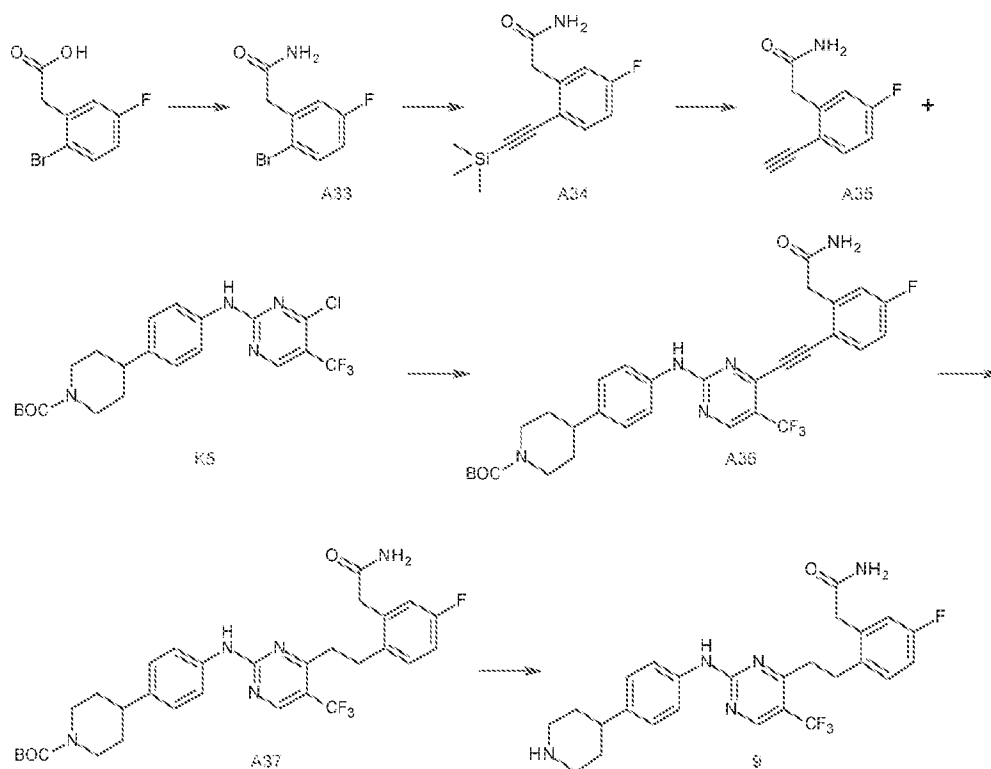
Example 8: Synthesis of 2-(2-(2-(2-((3-fluoro-4-(1-methylpiperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (8)



Formaldehyde (37 wt. % in H_2O ; 0.041 mL, 0.50 mmol) was added to a suspension of 2-(2-(2-((3-fluoro-4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (7) (0.046 g, 0.092 mmol) in anhydrous MeOH (5 mL) under an atmosphere of nitrogen. Sodium triacetoxyborohydride (0.19 g, 0.10 mmol) was then added in one portion and the resulting mixture stirred at room temperature for 3 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). Solid $NaHCO_3$ was added until the formation of gas ceased, then the layers were separated and the aqueous layer was extracted with EtOAc (2×100 mL). The organic layers were combined, washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4 . The volatiles were removed under reduced pressure to yield the title compound 8 as a white solid (0.043 g, 92%); 1H NMR (400 MHz, d_4 -MeOH) δ 8.58 (s, 1H), 7.66 (dd, $J = 13.2, 2.0$ Hz, 1H), 7.37 (dd, $J = 8.5, 2.0$ Hz, 1H), 7.28-7.14 (m, 5H), 3.68 (s, 2H), 3.20-3.12 (m, 2H), 3.13-3.04 (m, 2H), 3.01 (d, $J = 12.0$ Hz, 2H), 2.90-2.76 (m, 1H), 2.34 (s, 3H), 2.24-2.12 (m, 2H), 1.90-1.77 (m, 4H). LCMS-A rt 4.888 min; m/z 516.3 $[M+H]^+$.

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Example 9: Synthesis of 2-{5-fluoro-2-[2-(2-{(4-{piperidin-4-yl}phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl]phenyl}acetamide (9)



(a) 2-(2-Bromo-5-fluorophenyl)acetamide (A33)

5 HOBT (0.435 g, 3.22 mmol), EDCI.HCl (0.617 g, 3.22 mmol) and DIPEA (1.87 mL, 10.7 mmol) were added to a stirred solution of 2-(2-bromo-5-phenyl)acetic acid (0.500 g, 2.15 mmol) in dry THF (6 mL) and dry DMF (1 mL) under an atmosphere of nitrogen. After 10 minutes ammonium carbonate (1.03 g, 10.7 mmol) was added in one portion and the resulting mixture stirred at room temperature for 16 hours. The volatiles were removed *in*

10 *vacuo* and the residue was partitioned between DCM (50 mL) and saturated aqueous NaHCO₃ (50 mL). The aqueous phase was extracted with DCM (2 × 50 mL) then the combined organics washed with brine and dried over MgSO₄. The volatiles were removed under reduced pressure, then the residue purified by silica gel column chromatography (Biotage Isolera, SiO₂ cartridge, 20-100% EtOAc in petroleum benzine 40-60 °C) to give the

15 title compound A33 as a white solid (0.250 g, 50%); ¹H NMR (400 MHz, d₆-DMSO) δ 7.61 (dd, *J* = 8.8, 5.5 Hz, 1H), 7.48 (s, 1H), 7.25 (dd, *J* = 9.8, 3.1 Hz, 1H), 7.07 (td, *J* = 8.6, 3.2 Hz, 1H), 7.02 (s, 1H), 3.58 (s, 2H).

(b) 2-(5-Fluoro-2-((trimethylsilyl)ethynyl)phenyl)acetamide (A34)

20 Under inert conditions a suspension of 2-(2-bromo-5-fluorophenyl)acetamide (A33) (0.242 g, 1.04 mmol), PdCl₂(PPh₃)₂ (0.037 g, 0.052 mmol), *t*-Bu₃PH.BF₄ (0.015 g, 0.052 mmol), CuI

(0.010 g, 0.052 mmol) and (trimethylsilyl)acetylene (0.177 mL, 1.25 mmol) in anhydrous DMF (9 mL) was degassed with nitrogen for 10 minutes. Et₃N (3 mL) was added and the resulting mixture was stirred at 65 °C under nitrogen for 16 hours. The volatiles were removed under reduced pressure, then the residue adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-50% EtOAc in petroleum benzine 40-60 °C) to give the title compound A34 as a tan coloured solid (0.242 g, 93%); ¹H NMR (400 MHz, *d*₆-DMSO) δ 7.46 (dd, *J* = 8.6, 5.9 Hz, 1H), 7.38 (s, 1H), 7.15 (dd, *J* = 10.0, 2.7 Hz, 1H), 7.08 (td, *J* = 8.6, 2.7 Hz, 1H), 6.99 (s, 1H), 3.60 (s, 2H), 0.23 (s, 9H).

(c) 2-(2-Ethynyl-5-fluorophenyl)acetamide (A35)

To a solution of 2-(5-fluoro-2-((trimethylsilyl)ethynyl)phenyl)acetamide (A34) (0.239 g, 0.958 mmol) in DCM (10 mL) at 0 °C was added TBAF (1.0 M in THF; 1.44 mL, 1.44 mmol). The resulting mixture was stirred at 0 °C for 10 minutes, then poured into water (50 mL). The organic phase was separated and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine, dried (MgSO₄) and the volatiles removed *in vacuo*. The residue was adsorbed onto silica gel then purified by column chromatography (Biotage Isolera, SiO₂, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound A35 as a white solid (0.114 g, 67%); ¹H NMR (400 MHz, *d*₆-DMSO) δ 7.50 (dd, *J* = 8.6, 5.9 Hz, 1H), 7.44 (s, 1H), 7.17 (dd, *J* = 10.0, 2.7 Hz, 1H), 7.10 (td, *J* = 8.6, 2.8 Hz, 1H), 6.99 (s, 1H), 4.32 (s, 1H), 3.61 (s, 2H). LCMS-A: rt 4.843 min; *m/z* 178 [M+H]⁺.

(d) *tert*-Butyl 4-(4-((4-((2-(2-amino-2-oxoethyl)-4-fluorophenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A36)

A suspension of 2-(2-ethynyl-5-fluorophenyl)acetamide (A35) (0.114 g, 0.643 mmol), *tert*-butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (K5) (0.267 g, 0.585 mmol), PdCl₂(PPh₃)₂ (0.021 g, 0.029 mmol), *t*-Bu₃PH.BF₄ (8 mg, 0.03 mmol) and CuI (6 mg, 0.03 mmol) in anhydrous DMF (4 mL) was degassed with nitrogen for 10 minutes. Et₃N (1 mL) was added and the resulting mixture was heated under microwave irradiation at 120 °C for 20 minutes. The volatiles were removed under reduced pressure, then the residue adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound A36 as a yellow solid (0.198 g, 57%); ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.41 (s, 1H), 8.81 (s, 1H), 7.69-7.62 (m, 3H), 7.47 (s, 1H), 7.31-7.19 (m, 4H), 7.07 (s, 1H), 4.05 (s, 2H), 3.72 (s, 2H), 2.80 (s, 2H), 2.69-2.59 (m, 1H), 1.74 (d, *J* = 13.5 Hz, 2H), 1.55-1.44 (m, 2H), 1.42 (s, 9H). LCMS-A: rt 6.554 min; *m/z* 596 [M-H]⁺.

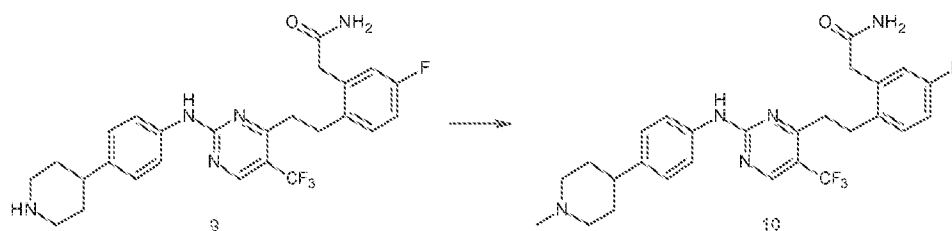
(e) *tert*-Butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)-4-fluorophenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A37)

A suspension of 10% Pd/C (0.175 g) and *tert*-butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)-4-fluorophenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A36) (0.191 g, 0.320 mmol) in DMF (10 mL) and Et₃N (1 mL) was stirred under an atmosphere of hydrogen for 16 hours. The resulting mixture was diluted with EtOAc (60 mL), filtered through Celite and the volatiles were removed under reduced pressure. The residue was adsorbed onto silica gel, then purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound A37 as a yellow solid (0.168 g, 87%); ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.14 (s, 1H), 8.65 (s, 1H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.48 (s, 1H), 7.23-7.15 (m, 3H), 7.08 (dd, *J* = 10.2, 2.8 Hz, 1H), 7.00 (td, *J* = 8.4, 2.7 Hz, 2H), 4.07 (d, *J* = 11.8 Hz, 2H), 3.50 (s, 2H), 3.13-3.04 (m, 2H), 3.04-2.95 (m, 2H), 2.79 (brs, 2H), 2.69-2.57 (m, 1H), 1.74 (d, *J* = 12.9 Hz, 2H), 1.54-1.43 (m, 2H), 1.42 (s, 9H). LCMS-A: rt 6.612 min; *m/z* 602 [M+H]⁺.

(f) 2-(5-Fluoro-2-(2-((4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (9)

TFA (0.825 mL, 10.8 mmol) was added to a solution of *tert*-butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)-4-fluorophenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A37) (0.162 g, 0.269 mmol) in DCM (20 mL) under nitrogen and the resulting solution stirred for 24 hours at room temperature. The volatiles were removed *in vacuo* and the residue was taken up in MeOH and loaded onto an SCX cartridge (10 g). The column was eluted with 5 column volumes of MeOH and then 6 column volumes of 5% v/v aqueous ammonia in MeOH. The volatiles from the ammoniacal eluent were evaporated under reduced pressure to give the title compound 9 as a yellow solid (0.117 g, 87%); ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.12 (s, 1H), 8.65 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.48 (s, 1H), 7.23-7.13 (m, 3H), 7.08 (dd, *J* = 10.2, 2.8 Hz, 1H), 7.04-6.95 (m, 2H), 3.50 (s, 2H), 3.14-2.95 (m, 6H), 2.63-2.52 (m, 3H), 1.67 (d, *J* = 10.8 Hz, 2H), 1.49 (qd, *J* = 12.4, 3.9 Hz, 2H). LCMS-A: rt 4.853 min; *m/z* 502 [M+H]⁺.

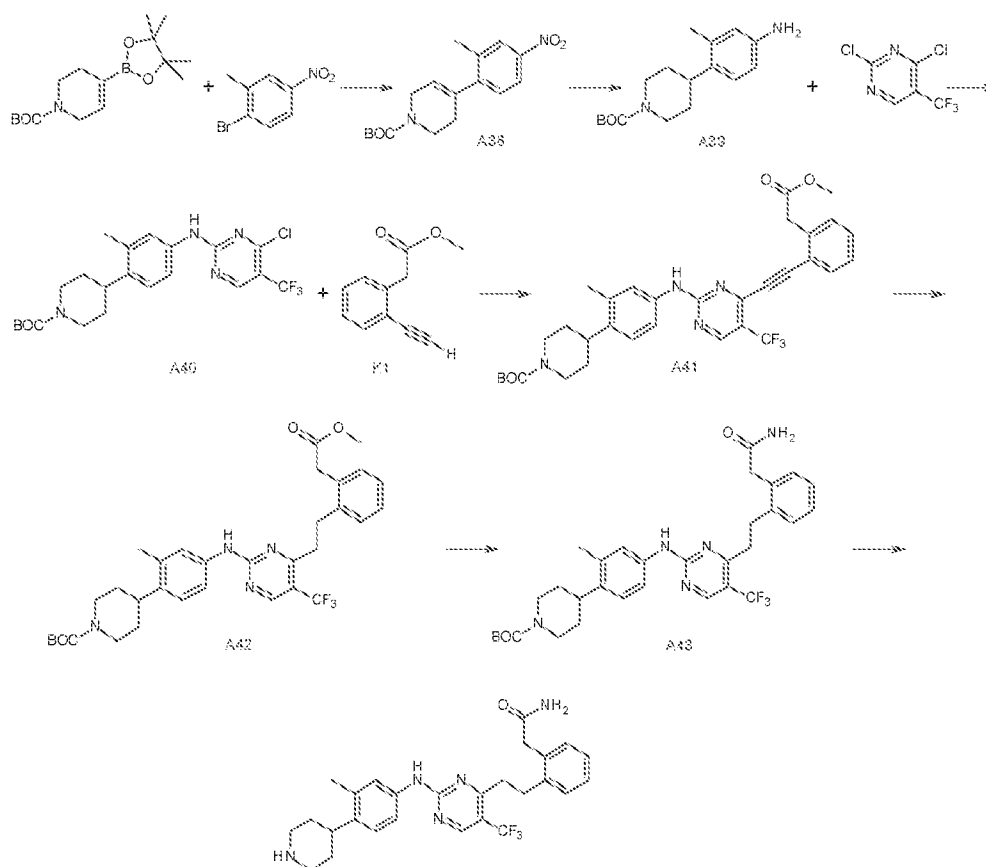
Example 10: Synthesis of 2-(5-fluoro-2-(2-(2-((4-(1-methylpiperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (10)



Formaldehyde (37 wt. % in H₂O; 29 μ L, 0.39 mmol) was added to a suspension of 2-(5-fluoro-2-(2-(2-((4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (9) (0.065 g, 0.13 mmol) in MeOH (8 mL) under an atmosphere of nitrogen. The resulting mixture was stirred for 10 minutes at room temperature then sodium triacetoxyborohydride (0.110 g, 0.518 mmol) was added in one portion and stirring continued for 3 hours. The volatiles were removed *in vacuo*, then the residue was partitioned between EtOAc (20 mL) and saturated aqueous NaHCO₃ (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 $\times$ 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na₂SO₄. The volatiles were removed under reduced pressure to yield the title compound 10 as an off-white solid (58 mg, 87%); ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.13 (s, 1H), 8.65 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.49 (s, 1H), 7.22-7.16 (m, 3H), 7.08 (dd, *J* = 10.2, 2.8 Hz, 1H), 7.04-6.95 (m, 2H), 3.50 (s, 2H), 3.12-3.04 (m, 2H), 3.04-2.95 (m, 2H), 2.87 (d, *J* = 11.3 Hz, 2H), 2.46-2.36 (m, 1H), 2.20 (s, 3H), 2.02-1.92 (m, 2H), 1.76-1.58 (m, 4H). LCMS-A: rt 4.867 min; *m/z* 516 [M+H]⁺.

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Example 11: Synthesis of 2-{2-[2-(2-[(3-methyl-4-(piperidin-4-yl)phenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl)ethyl]phenyl}acetamide (11)



11

(a) *tert*-Butyl 4-(2-methyl-4-nitrophenyl)-5,6-dihydropyridine-1(2H)-carboxylate (A38)

A suspension of *N*-Boc-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (0.29 g, 0.93 mmol), 1-bromo-2-methyl-4-nitrobenzene (0.20 g, 0.93 mmol), PdCl₂(PPh₃)₂ (0.03 g, 0.05 mmol) and 3 M aqueous Na₂CO₃ (0.93 mL, 2.8 mmol) in 1,4-dioxane (10 mL) was degassed with nitrogen for 10 minutes then heated at reflux for 16 hours. The resulting mixture was concentrated under reduced pressure and purified using silica gel column chromatography (Biotage Isolera, SiO₂ cartridge, 0-30% EtOAc in petroleum benzine 40-60 °C) to give the title compound A38 (0.25 g, 83%); ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J* = 2.4 Hz, 1H), 8.03-7.98 (m, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 5.63 (s, 1H), 4.09-4.04 (m, 2H), 3.64 (t, *J* = 5.6 Hz, 2H), 2.38 (s, 3H), 2.35 (s, 2H), 1.51 (s, 9H).

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(b) *tert*-Butyl 4-(4-amino-2-methylphenyl)piperidine-1-carboxylate (A39)

To a solution of *tert*-butyl 4-(2-methyl-4-nitrophenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (A38) (211 mg, 0.663 mmol) in DMF (7.5 mL) was added a slurry of 10% Pd/C (100 mg) in DMF (0.5 mL) and the resulting mixture was stirred for 16 hours under a hydrogen atmosphere at room temperature. The resulting mixture was filtered through Celite then the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography (Biotage Isolera, SiO₂ cartridge, 0-60% EtOAc in petroleum benzine 40-60 °C) to give the title compound A39 as a pale orange solid (185 mg, 96%); ¹H NMR (400 MHz, CDCl₃) δ 6.95 (d, *J* = 8.0 Hz, 1H), 6.56-6.48 (m, 2H), 3.51 (s, 2H), 2.88-2.65 (m, 3H), 2.26 (s, 3H), 1.74-1.66 (m, 2H), 1.63-1.51 (m, obscured by solvent), 1.48 (s, 9H).

(c) *tert*-Butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-methylphenyl)piperidine-1-carboxylate (A40)

Zinc(II) chloride (1.0 M in Et₂O; 0.661 mL, 0.661 mmol) was added to a solution of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (0.132 g, 0.606 mmol) in 1:1 DCE/*t*-BuOH (5 mL) at 0 °C under nitrogen. The resulting mixture was stirred for 1 hour at 0 °C then *tert*-butyl 4-(4-amino-2-methylphenyl)piperidine-1-carboxylate (A39) (0.160 g, 0.551 mmol) in 1:1 DCE/*t*-BuOH (5 mL) was added. A solution of Et₃N (840 µL, 0.606 mmol) in 1:1 DCE/*t*-BuOH (5 mL) at 0 °C was then added and the resulting mixture was vigorously stirred for a further 30 minutes at 0 °C then at room temperature for 16 hours. The volatiles were removed *in vacuo* to afford a brown residue which was purified by silica gel column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-50% EtOAc in petroleum benzine 40-60 °C) to yield a pale yellow solid. The solid was suspended in MeOH (10 mL) and water (10 mL) and the resulting suspension filtered to give the title compound A40 as a white solid (0.231 g, 89%); ¹H NMR (400 MHz, CDCl₃) δ 8.48 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.27 (brs, 1H), 7.24 (d, *J* = 2.3 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 4.32-4.04 (m, 2H), 2.79-2.73 (m, 3H), 2.30 (s, 3H), 1.67 (d, *J* = 13.0 Hz, 2H), 1.62-1.45 (m, obscured), 1.42 (s, 9H). LCMS-A: rt 6.895 min; *m/z* 469.1 [M-H]⁺.

(d) *tert*-Butyl 4-(4-((2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-methylphenyl)piperidine-1-carboxylate (A41)

A solution of methyl 2-(2-ethynylphenyl)acetate (K1) (0.103 g, 0.589 mmol) in DMF (1.5 mL) and Et₃N (0.273 mL, 1.96 mmol) were added to a suspension of *tert*-butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-methylphenyl)piperidine-1-carboxylate (A40) (0.231 g, 0.491 mmol), PdCl₂(PPh₃)₂ (0.052 g, 0.074 mmol), CuI (0.014 g, 0.074 mmol) and PPh₃ (0.013 g, 0.049 mmol) in DMF (2 mL). The resulting mixture was heated under microwave irradiation at 120 °C for 15 minutes, then diluted with EtOAc and passed through

a plug of Celite, washing with EtOAc (60 mL). The filtrate was washed with water (50 mL) and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organics were washed with water (50 mL), brine (50 mL) and dried (Na₂SO₄). The volatiles were removed *in vacuo* and the residue was purified by silica gel column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-40% EtOAc in petroleum benzine 40-60 °C) to give the title compound A41 as a yellow oil (0.248 g, 83%); ¹H NMR (400 MHz, CDCl₃) δ 8.62 (s, 1H), 7.68 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.45-7.40 (m, 1H), 7.39-7.29 (m, 4H), 7.18 (d, *J* = 8.4 Hz, 1H), 4.38-4.21 (m, 2H), 3.96 (s, 2H), 3.70 (s, 3H), 2.92-2.71 (m, 3H), 2.38 (s, 3H), 1.75 (d, *J* = 12.7 Hz, 2H), 1.69-1.54 (m, peak obscured), 1.49 (s, 9H). LCMS-A: rt 6.992 min; *m/z* 609.1 [M+H]⁺.

(e) *tert*-Butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-methylphenyl)piperidine-1-carboxylate (A42)

A solution of *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-methylphenyl)piperidine-1-carboxylate (A41) (0.248 g, 0.407 mmol) in EtOH (10 mL) was added to a solution of 10% Pd/C (53% water; 0.680 g) in DMF (6 mL). The resulting mixture was stirred at room temperature for 16 hours under an atmosphere of hydrogen then filtered through a pad of Celite, washing with EtOAc (80 mL). The volatiles were removed *in vacuo* to afford a yellow oil which was purified by silica gel column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-40% EtOAc in petroleum benzine 40-60 °C) to yield the title compound A42 as a clear oil (0.196 g, 79%); ¹H NMR (400 MHz, CDCl₃) δ 8.53 (s, 1H), 7.61 (s, 1H), 7.51 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.39 (d, *J* = 2.2 Hz, 1H), 7.29-7.19 (m, obscured by solvent), 7.17 (d, *J* = 8.4 Hz, 1H), 4.42-4.18 (m, 2H), 3.75 (s, 2H), 3.67 (s, 3H), 3.19-3.03 (m, 4H), 2.90-2.73 (m, 3H), 2.37 (s, 3H), 1.75 (d, *J* = 12.6 Hz, 2H), 1.62 (m, 2H), 1.50 (s, 9H). LCMS-A: rt 7.094 min; *m/z* 613.2 [M+H]⁺.

(f) *tert*-Butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-methylphenyl)piperidine-1-carboxylate (A43)

LiOH·H₂O (41.0 mg, 0.960 mmol) was added to a solution of *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-methylphenyl)piperidine-1-carboxylate (A42) (0.196 g, 0.320 mmol) in THF (7 mL), water (1.5 mL) and MeOH (1 mL) and the resulting mixture stirred at room temperature for 19 hours. The volatiles were removed *in vacuo*, then the residue was partitioned between EtOAc (50 mL) and saturated aqueous NaHCO₃ (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄ and the volatiles removed under reduced

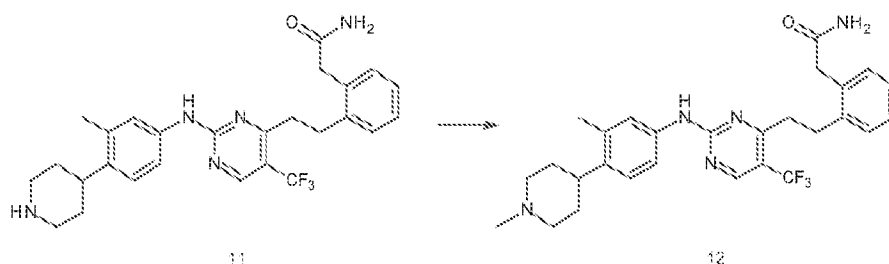
pressure. The residue was dissolved in dry THF (6 mL) and dry DMF (1 mL) under an atmosphere of nitrogen then HOBT (0.056 g, 0.41 mmol), EDCI.HCl (0.079 g, 0.41 mmol) and DIPEA (0.28 mL, 1.3 mmol) were added. After 10 minutes ammonium carbonate (0.15 g, 1.6 mmol) was added in one portion and the resulting mixture stirred at room temperature for 19 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (65 mL) and saturated NaHCO₃ (65 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) then the combined organic layers were washed with brine (50 mL) and dried over MgSO₄. The solvent was removed *in vacuo* and the residue purified by silica gel column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-80% EtOAc in petroleum benzine 40-60 °C) to give the title compound A43 as a white solid (0.16 g, 84%); ¹H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1H), 8.20 (s, 1H), 7.46 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.37 (d, *J* = 1.9 Hz, 1H), 7.28-7.18 (m, obscured by solvent), 7.13 (d, *J* = 8.4 Hz, 1H), 6.33 (s, 1H), 5.68 (s, 1H), 4.40-4.16 (m, 2H), 3.68 (s, 2H), 3.17-2.95 (m, 4H), 2.91-2.68 (m, 3H), 2.34 (s, 3H), 1.73 (d, *J* = 12.3 Hz, 2H), 1.68-1.53 (m, 2H), 1.50 (s, 9H). LCMS-A: rt 6.670 min; *m/z* 598.1 [M+H]⁺.

(g) 2-(2-(2-(2-((3-methyl-4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (11)

TFA (1 mL) was added to a stirred solution of tert-butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-methylphenyl)piperidine-1-carboxylate (A43) (0.16 g, 0.27 mmol) in DCM (4 mL) and the resulting solution was stirred at room temperature for 16 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (10 mL) and 2 M aqueous NaOH (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) then and the combined organic layers were washed with water (10 mL), brine (10 mL) and dried over MgSO₄. The volatiles were removed *in vacuo* to give a pale yellow solid. The solid was suspended in cyclohexane and the resulting suspension filtered to give the title compound 11 as a white solid (0.085 g, 64%); ¹H NMR (400 MHz, *d*₂-MeOH) δ 8.52 (s, 1H), 7.54 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 7.29-7.23 (m, 1H), 7.23-7.15 (m, 4H), 3.67 (s, 2H), 3.23-3.11 (m, 4H), 3.10-3.01 (m, 2H), 2.91 (tt, *J* = 11.7, 3.8 Hz, 1H), 2.80 (td, *J* = 12.3, 2.8 Hz, 2H), 2.35 (s, 3H), 1.84-1.59 (m, 4H). LCMS-A: rt 4.962 min; *m/z* 498.3 [M+H]⁺.

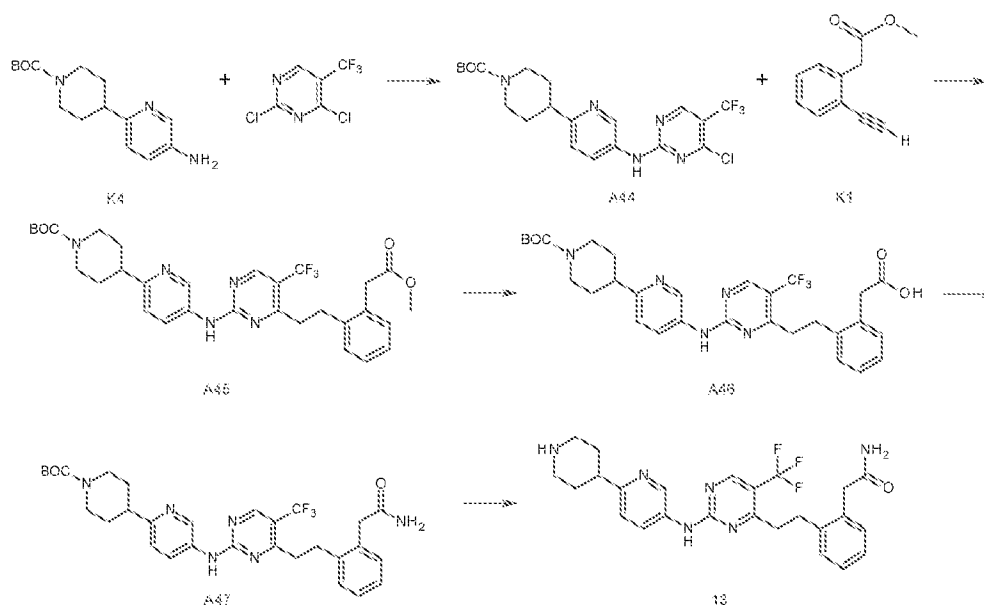
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Example 12: Synthesis of 2-(2-(2-(2-((3-methyl-4-(1-methylpiperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (12)



Formaldehyde (37 wt. % in H₂O; 0.040 mL, 0.50 mmol) was added to a suspension of 2-(2-(2-(2-((3-methyl-4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (**11**) (0.035 g, 0.070 mmol) in MeOH (5 mL) under an atmosphere of nitrogen. Sodium triacetoxyborohydride (0.19 g, 0.10 mmol) was added in one portion and the resulting mixture stirred at room temperature for 3 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (10 mL) and saturated aqueous NaHCO₃ (10 mL). Solid NaHCO₃ was added until the formation of gas ceased then the layers were separated and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with water (10 mL), brine (10 mL) and dried over Na₂SO₄. The volatiles were removed under reduced pressure to yield the title compound **12** as a white solid (0.032 g, 89%); ¹H NMR (400 MHz, *d*₇-MeOH) δ 8.52 (s, 1H), 7.53 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.44 (d, *J* = 2.2 Hz, 1H), 7.28-7.22 (m, 1H), 7.24-7.15 (m, 4H), 3.67 (s, 2H), 3.20-3.11 (m, 2H), 3.11-2.95 (m, 4H), 2.81-2.70 (m, 1H), 2.35 (s, 3H), 2.34 (s, 3H), 2.28-2.13 (m, 2H), 1.87-1.70 (m, 4H). LCMS-A: rt 4.908 min; *m/z* 512.3 [M+H]⁺.

Example 13: Synthesis of 2-{2-[2-(2-[(6-(piperidin-4-yl)pyridin-3-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl)ethyl]phenyl}acetamide (13)



(a) *tert*-Butyl 4-{5-[(4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino]pyridin-2-yl}piperidine-1-carboxylate (A44)

A 1.0 M ZnCl_2 solution in Et_2O (2.16 mL, 2.16 mmol) was added cautiously to a solution of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (411 mg, 1.89 mmol) in 1:1 *t*-BuOH:DCE (100 mL) at room temperature, and the resulting mixture stirred at room temperature for 20 minutes. *tert*-Butyl 4-(5-aminopyridin-2-yl)piperidine-1-carboxylate (K4) (500 mg, 1.80 mmol) was added followed by Et_3N (0.30 mL, 2.16 mmol) then stirring was continued for 44 hours at room temperature. The volatiles were removed *in vacuo* and the residue was suspended in water (250 mL). The resulting suspension was sonicated for 10 minutes then filtered, washing the filter cake with water (2×100 mL). The filter cake was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, 40 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound A44 as an off white solid (346 mg, 42%); ^1H NMR (400 MHz, d_6 -DMSO) δ 10.74 (s, 1H), 8.81 (s, 1H), 8.73 (d, $J = 2.4$ Hz, 1H), 8.00 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.30 (d, $J = 8.5$ Hz, 1H), 4.05 (d, $J = 11.8$ Hz, 2H), 2.82 (m, 3H), 1.81 (d, $J = 11.1$ Hz, 2H), 1.55 (m, 2H), 1.41 (s, 9H). LCMS-A: rt 5.949 min; m/z 458 $[\text{M}+\text{H}]^+$.

(b) *tert*-Butyl 4-{5-[(2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl]amino}pyridin-2-yl}piperidine-1-carboxylate (A45)

A suspension of *tert*-butyl 4-{5-[(4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino]pyridin-2-yl}piperidine-1-carboxylate (A44) (340 mg, 0.74 mmol), CuI (7 mg, 0.04 mmol), PPh_3 (10 mg,

0.04 mmol) and Et_3N (207 μL , 1.49 mmol) in DMF (2.5 mL) was sonicated for 5 minutes. $\text{PdCl}_2(\text{PPh}_3)_2$ (26 mg, 0.04 mmol) and methyl 2-(2-ethynylphenyl)acetate (*K1*) (194 mg, 1.11 mmol) in DMF (1 mL) were added and the resulting mixture degassed with nitrogen for 5 minutes before heating under microwave irradiation at 120°C for 20 minutes. The resulting mixture was adsorbed on silica gel and purified by column chromatography (Biotage Isolera, 40 g SiO_2 cartridge, 0-100% EtOAc in hexanes) to give a brown oil that was taken up in DMF (25 mL) and Et_3N (2 mL) before 10% Pd/C (53% water; 75 mg) was added. The resulting mixture was stirred at room temperature for 44 hours under a hydrogen atmosphere then filtered through Celite, washing with EtOAc (200 mL). Activated charcoal (ca. 2.5 g) was added to the filtrate and the resulting suspension stirred at room temperature for 4 hours before filtration through Celite, washing with EtOAc (100 mL). The filtrate was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a brown oil. A suspension of 10% Pd/C (53% water; 200 mg) in DMF (100 mL) and Et_3N (10 mL) was added and the resulting mixture stirred under a hydrogen atmosphere at room temperature for 4.5 days. The resulting mixture was filtered through Celite, washing with EtOAc (250 mL) then the combined filtrates were washed with water (3 x 100 mL) then brine (3 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Biotage Isolera, 40 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound **A45** as a yellow oil (96 mg, 21%); ^1H NMR (400 MHz, CDCl_3) δ 8.65 (d, J = 2.4 Hz, 1H), 8.55 (d, J = 0.5 Hz, 1H), 8.14 (dd, J = 8.5, 2.7 Hz, 1H), 7.55 (s, 1H), 7.25-7.18 (m, 4H), 7.16 (d, J = 8.5 Hz, 1H), 4.26 (s, 2H), 3.74 (s, 2H), 3.68 (s, 3H), 3.11 (s, 4H), 2.88-2.79 (m, 3H), 1.92 (d, J = 12.0 Hz, 2H), 1.77-1.64 (m, 2H), 1.47 (s, 9H). LCMS-A: rt 6.137 min; m/z 600 $[\text{M}+\text{H}]^+$.

(c) 2-(2-(2-(2-((6-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (**A46**)

$\text{LiOH}\cdot\text{H}_2\text{O}$ (297 mg, 7.1 mmol) was added to a stirred solution of *tert*-butyl 4-(5-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyridin-2-yl)piperidine-1-carboxylate (**A45**) (85 mg, 0.14 mmol) in H_2O (2 mL) and THF (20 mL) and the resulting mixture heated at 40 °C for 18 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (100 mL) and aqueous 2 M HCl (50 mL). The layers were separated and the organics washed with water (100 mL), brine (50 mL) and dried over MgSO_4 . The volatiles were removed *in vacuo* to give the title compound **A46** as an orange foam (74 mg, 89%); ^1H NMR (400 MHz, d_4 -MeOH) δ 9.00 (d, J = 1.8 Hz, 1H), 8.66 (s, 1H), 8.36 (dd, J = 8.7, 2.6 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.28-7.10 (m, 4H), 4.25

(d, $J = 13.4$ Hz, 2H), 3.72 (s, 2H), 3.19-3.09 (m, 4H), 3.07-2.83 (m, 3H), 1.94 (d, $J = 12.7$ Hz, 2H), 1.72 (m, 2H), 1.48 (s, 9H). LCMS-A: rt 5.707 min; m/z 586 $[M+H]^+$.

(d) *tert*-Butyl 4-(5-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyridin-2-yl)piperidine-1-carboxylate (A47)

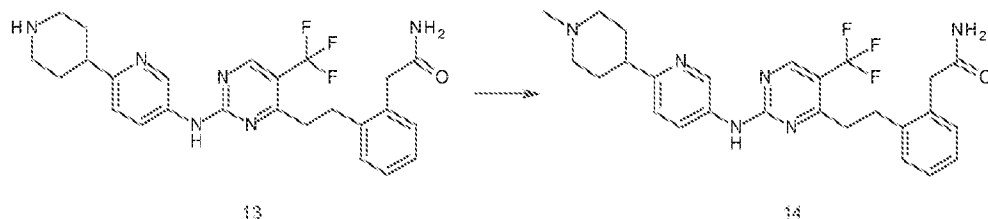
HOBt (50 mg, 0.37 mmol), EDCI.HCl (78 mg, 0.41 mmol) and DIPEA (0.11 mL, 0.63 mmol) were added to a stirred solution of 2-(2-(2-(2-((6-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A46) (74 mg, 0.13 mmol) in dry DMF (5 mL) under an atmosphere of nitrogen. After 10 minutes ammonium carbonate (121 mg, 1.26 mmol) was added in one portion and the resulting mixture was stirred for 18 hours at room temperature. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (10 mL) and saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) then the combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄. The volatiles were removed *in vacuo* and the residue purified by silica gel column chromatography (Biotage Isolera, 40 g SiO₂ cartridges, 0-100% EtOAc in petroleum benzine 40-60 °C followed by 0-25% MeOH in EtOAc) to give the title compound A47 as clear oil (58 mg, 78%); ¹H NMR (400 MHz, CDCl₃) δ 8.83 (s, 1H), 8.54 (s, 1H), 7.97 (s, 1H), 7.80 (s, 1H), 7.30-7.22 (m, 4H), 7.17 (d, $J = 8.5$ Hz, 1H), 5.78 (s, 1H), 5.62 (s, 1H), 4.25 (s, 2H), 3.74 (s, 2H), 3.11 (s, 4H), 2.83 (m, 3H), 1.92 (d, $J = 12.3$ Hz, 2H), 1.79-1.60 (m, 2H, peak obscured), 1.48 (s, 9H). LCMS-A: rt 5.549 min; m/z 585 $[M+H]^+$.

(e) 2-(2-(2-(2-((6-(Piperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (13)

TFA (0.5 mL) was added to a solution of *tert*-butyl 4-(5-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyridin-2-yl)piperidine-1-carboxylate (A47) (58 mg, 0.099 mmol) in DCM (5 mL) and the resulting solution stirred for 18 hours at room temperature. The volatiles were evaporated under reduced pressure and the residue partitioned between 2 M aqueous NaOH (10 mL) and EtOAc (25 mL). The organic layer was separated and washed with water (25 mL), brine (25 mL), dried (Na₂SO₄) and concentrated under reduced pressure to give the title compound 13 as a white solid (41 mg, 85%); ¹H NMR (400 MHz, *d*₇-MeOH) δ 8.78 (d, $J = 2.1$ Hz, 1H), 8.61 (d, $J = 0.6$ Hz, 1H), 8.19 (dd, $J = 8.6, 2.6$ Hz, 1H), 7.31 (d, $J = 8.5$ Hz, 1H), 7.26 (d, $J = 6.3$ Hz, 1H), 7.24-7.15 (m, 3H), 3.67 (s, 2H), 3.22-3.15 (m, 4H), 3.14-3.05 (m, 2H), 2.90-2.70 (m, 3H), 1.93 (d, $J = 13.9$ Hz, 2H), 1.75 (m, 2H). LCMS-A: rt 4.552 min; m/z 485 $[M+H]^+$.

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Example 14: Synthesis of 2-(2-(2-(2-((6-(1-methylpiperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (14)

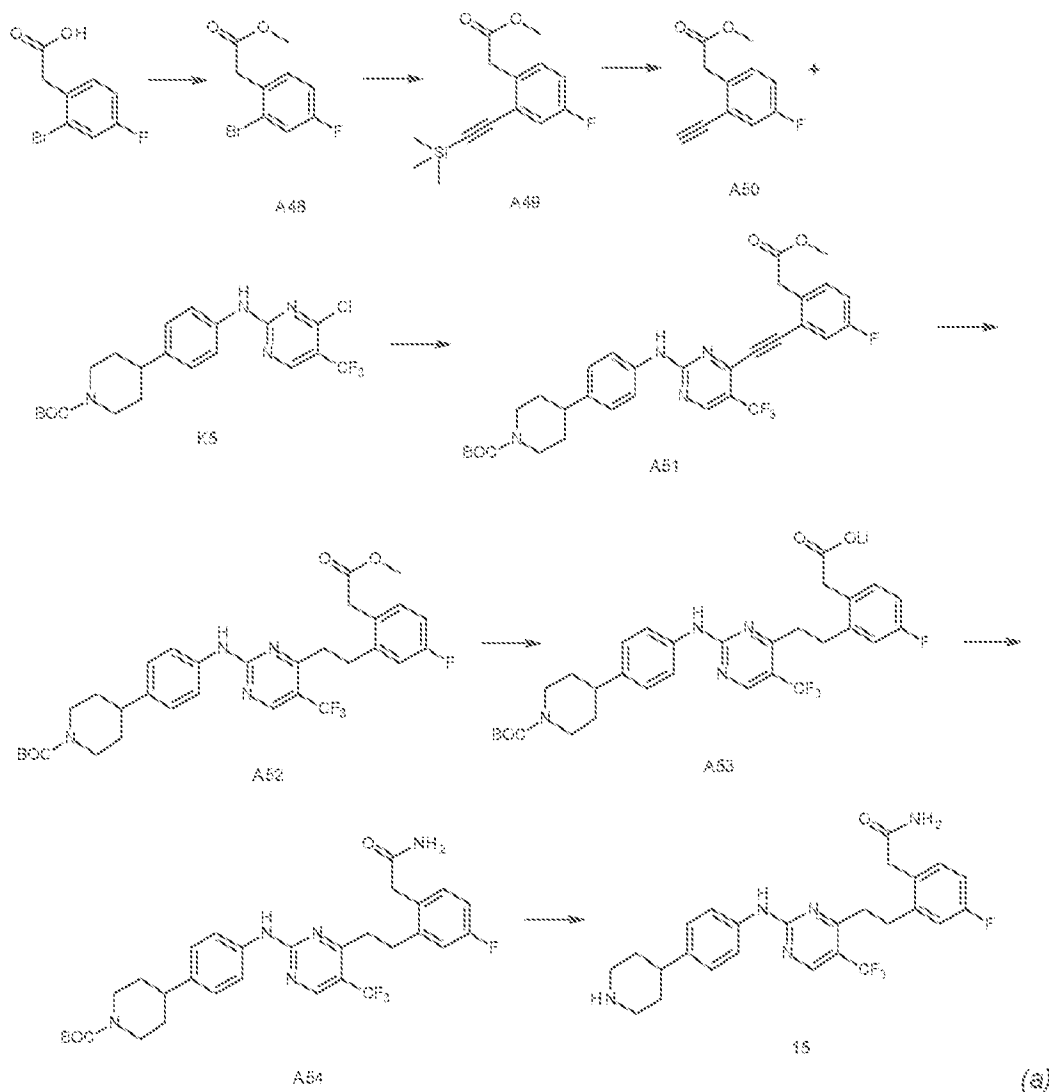


Formaldehyde (37 wt. % in H₂O; 0.012 mL, 0.17 mmol) was added to a solution of 2-(2-(2-(2-((6-(piperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (13) (27 mg, 0.056 mmol) in MeOH (2 mL) under an atmosphere of nitrogen. The resulting mixture was stirred for 15 minutes at room temperature before sodium triacetoxyborohydride (47 mg, 0.22 mmol) was added in one portion and stirring was continued at room temperature for 18 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (50 mL) and saturated aqueous NaHCO₃ (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with water (25 mL), brine (25 mL) then dried over Na₂SO₄. The solvent was removed under reduced pressure to give the title compound 14 as a white solid (25 mg, 90%); ¹H NMR (400 MHz, d₂-MeOH) δ 8.77 (d, *J* = 2.4 Hz, 1H), 8.60 (s, 1H), 8.18 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 6.3 Hz, 1H), 7.21-7.15 (m, 3H), 3.67 (s, 2H), 3.20-3.14 (m, 2H), 3.14-3.08 (m, 2H), 3.04 (d, *J* = 11.7 Hz, 2H), 2.71 (tt, *J* = 11.9, 3.9 Hz, 1H), 2.35 (s, 3H), 2.21 (td, *J* = 12.0, 2.5 Hz, 2H), 1.96 (d, *J* = 11.0 Hz, 2H), 1.92-1.80 (m, 2H). LCMS-A: rt 4.635 min; *m/z* 499 [M+H]⁺.

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Example 15: Synthesis of 2-(4-fluoro-2-(2-(2-(4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (15)



Methyl 2-(2-bromo-4-fluorophenyl)acetate (A48)

Sulfuric acid (1.50 mL) was added cautiously to a solution of 2-bromo-4-fluorophenylacetic acid (1.00 g, 4.29 mmol) in MeOH (25 mL) and the resulting mixture stirred overnight at room temperature. Saturated aqueous Na_2CO_3 solution was added until the pH of the mixture was 14, then the aqueous layer was extracted with DCM (2×100 mL). The combined organics were dried over MgSO_4 , then the volatiles were removed *in vacuo* to yield the title compound A48 as a clear oil (1.00 g, 94%); ^1H NMR (400 MHz, CDCl_3) δ 7.34 (dd, $J = 8.2, 2.6$ Hz, 1H), 7.29 (dd, $J = 8.5, 6.0$ Hz, 1H), 7.03 (td, $J = 8.3, 2.6$ Hz, 1H), 3.79 (s, 2H), 3.74 (s, 3H). LCMS-A: rt 5.911 min.

(b) Methyl 2-(4-fluoro-2-((trimethylsilyl)ethynyl)phenyl)acetate (A49)

A suspension of (trimethylsilyl)acetylene (0.696 g, 7.08 mmol), methyl 2-(2-bromo-4-fluorophenyl)acetate (A48) (0.500 g, 2.02 mmol), PPh_3 (0.053 g, 0.202 mmol), CuI (39 mg, 0.202 mmol), Et_3N (1.41 mL, 10.1 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.142 g, 0.202 mmol) in THF (25 mL) was heated at 35 °C for 16 hours. The resulting mixture was adsorbed onto silica gel and purified using column chromatography (Biotage Isolera, 40g SiO_2 cartridge, 0-40% EtOAc in petroleum benzine 40-60 °C) to yield the title compound A49 as a clear oil (0.212 g, 40%); LCMS-A: rt 5.830 min.

(c) Methyl 2-(2-ethynyl-4-fluorophenyl)acetate (A50)

A solution of TBAF (1.0 M in THF; 2.0 mL, 2.0 mmol) was added to a stirred solution of methyl 2-(4-fluoro-2-((trimethylsilyl)ethynyl)phenyl)acetate (A49) (0.212 g, 0.802 mmol) in DCM (5 mL). After 2 minutes the resulting mixture was diluted with water (100 mL) and DCM (50 mL). The organic fraction was separated and adsorbed onto silica gel then purified using column chromatography (Biotage Isolera, 12 g SiO_2 Cartridge, 0-20% EtOAc in petroleum benzine 40-60 °C) to give the title compound A50 as a brown oil (0.106 g, 69%); ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.26 (m, 1H), 7.23 (dd, J = 9.0, 2.8 Hz, 1H), 7.06 (m, 1H), 3.84 (s, 2H), 3.73 (s, 3H), 3.33 (s, 1H). LCMS-A: rt 5.838 min; m/z 193 $[\text{M}+\text{H}]^+$.

(d) tert-Butyl 4-(4-((5-fluoro-2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A51)

A suspension of *tert*-butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (K5) (0.252 g, 0.552 mmol), methyl 2-(2-ethynyl-4-fluorophenyl)acetate (A50) (0.106 g, 0.552 mmol), PPh_3 (0.007 g, 0.03 mmol), CuI (0.005 g, 0.03 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.019 g, 0.028 mmol) in DMF (3 mL) and Et_3N (1.0 mL) was heated under microwave irradiation for 20 minutes at 120 °C. The resulting mixture was diluted with EtOAc (100 mL) then washed with water (100 mL), brine (25 mL) and dried over MgSO_4 . The volatiles were evaporated *in vacuo* and the residue was adsorbed onto silica gel and purified using column chromatography (Biotage Isolera, 40g SiO_2 cartridge, 0-80% EtOAc in petroleum benzine 40-60 °C) to give the title compound A51 as a yellow solid (0.158 g, 47%); ^1H NMR (400 MHz, CDCl_3) δ 8.64 (d, J = 1.0 Hz, 1H), 7.75 (s, 1H), 7.62-7.55 (m, 2H), 7.38-7.27 (m, 2H), 7.25-7.19 (m, 2H), 7.14 (td, J = 8.3, 2.7 Hz, 1H), 4.36-4.20 (m, 2H), 3.92 (s, 2H), 3.72 (s, 3H), 2.82 (t, J = 12.8 Hz, 2H), 2.66 (td, J = 8.5, 4.2 Hz, 1H), 1.89-1.78 (m, 2H), 1.70-1.54 (m, 2H), 1.51 (s, 9H). LCMS-A: rt 1.852 min; m/z 613 $[\text{M}+\text{H}]^+$.

(e) *tert*-Butyl 4-((4-((5-fluoro-2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A52)

A suspension of Pd/C 10% (0.100 g) and *tert*-butyl 4-((4-((5-fluoro-2-(2-methoxy-2-oxoethyl)phenethyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A51) (0.158 g, 0.258 mmol) in EtOAc (20 mL) was stirred under a hydrogen atmosphere at room temperature overnight. The resulting mixture was filtered through a Celite plug, washing with EtOAc (100 mL) then the combined organic washings were evaporated *in vacuo* to yield the title compound A52 as a yellow oil (0.092 g, 58%); ¹H NMR (400 MHz, CDCl₃) δ 8.46 (s, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.17-7.10 (m, 3H), 6.91-6.78 (m, 2H), 4.18 (s, 2H), 3.62 (s, 2H), 3.60 (s, 3H), 3.01 (s, 4H), 2.73 (t, *J* = 11.9 Hz, 2H), 2.57 (tt, *J* = 12.0, 3.4 Hz, 1H), 1.75 (d, *J* = 12.8 Hz, 2H), 1.54 (qd, *J* = 12.8, 4.2 Hz, 2H), 1.41 (s, 9H). LCMS-A: rt 6.727/6.998 min; *m/z* 617 [M+H]⁺.

(f) Lithium 2-(2-(2-(2-((4-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-4-fluorophenyl)acetate (A53)

LiOH.H₂O (0.063 g, 1.5 mmol) was added to a stirred solution of *tert*-butyl 4-((4-((5-fluoro-2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A52) (0.092 g, 0.15 mmol) in H₂O (0.5 mL) and THF (5 mL) and the resulting mixture heated at 40 °C overnight. The volatiles were removed *in vacuo* and the residue was taken up in DCM (50 mL). The resulting solution was washed with saturated aqueous Na₂CO₃ (25 mL) then the aqueous phase was then extracted with DCM (2 × 25 mL). The organic layers were combined, dried over MgSO₄ and the volatiles were removed *in vacuo* to yield the title compound A53 (0.089 g, 98%); LCMS-A: rt 6.596 min; *m/z* 603 [(M-Li)+H]⁺.

(g) *tert*-Butyl 4-((4-((2-(2-amino-2-oxoethyl)-5-fluorophenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A54)

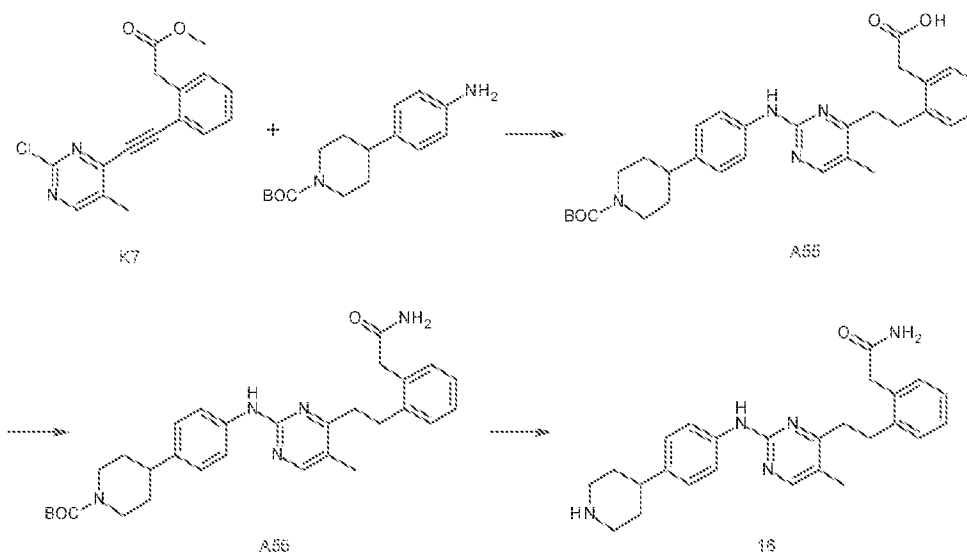
HOBt (0.024 g, 0.175 mmol) and EDCI.HCl (0.034 g, 0.175 mmol) were added to a solution of lithium 2-(2-(2-(2-((4-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-4-fluorophenyl)acetate (A53) (0.089 g, 0.146 mmol) and Et₃N (0.082 mL, 0.585 mmol) in DMF (5 mL) and the resulting mixture stirred at 40 °C overnight. Saturated aqueous NaHCO₃ (25 mL) and DCM (25 mL) were added then the layers separated and the aqueous phase extracted with CHCl₃ (3 × 25 mL). The organics were combined then the volatiles were evaporated *in vacuo*. The residue was adsorbed onto silica gel and purified using column chromatography (Biotage Isolera, 12 g SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to yield a clear oil. The oil was triturated with

water and the resulting precipitate collected by filtration to give the title compound A54 as a white solid (0.065 g, 74%); ^1H NMR (400 MHz, CDCl_3) δ 8.47 (d, J = 1.0 Hz, 1H), 7.46 (d, J = 8.2 Hz, 3H), 7.18-7.09 (m, 3H), 6.95-6.84 (m, 2H), 5.24 (d, J = 21.9 Hz, 2H), 4.18 (s, 2H), 3.60 (s, 2H), 3.02 (s, 4H), 2.74 (t, J = 10.2 Hz, 2H), 2.58 (m, 1H), 1.76 (d, J = 11.7 Hz, 2H), 1.64-1.51 (m, 2H), 1.42 (s, 9H). LCMS-A: rt 6.477 min; m/z 602 $[\text{M}+\text{H}]^+$.

(h) 2-(4-Fluoro-2-(2-(2-((4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (15)

TFA (0.5 mL) was added to a solution of *tert*-butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)-5-fluorophenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A54) (0.065 g, 0.108 mmol) in DCM (5.0 mL) and the resulting mixture stirred at room temperature overnight. The volatiles were removed *in vacuo* to yield an orange oil to which 2 M aqueous NaOH (25 mL) was cautiously added. The resulting suspension was sonicated for 10 minutes then filtered. The white filter cake was washed with water (50 mL), petroleum benzine 40-60 °C (50 mL) then air dried to yield the title compound 15 as a white solid (0.036 g, 66%); ^1H NMR (400 MHz, d_6 -DMSO) δ 10.13 (s, 1H), 8.66 (s, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.45 (s, 1H), 7.26 (dd, J = 8.3, 6.2 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 7.06-6.96 (m, 2H), 6.94 (s, 1H), 3.47 (s, 2H), 3.17-2.95 (m, 6H), 2.56 (m, 3H), 1.67 (d, J = 13.6 Hz, 2H), 1.49 (qd, J = 12.1, 2.8 Hz, 2H). LCMS-A: rt 4.687 min; m/z 502 $[\text{M}+\text{H}]^+$.

Example 16: Synthesis of 2-(2-(2-(5-methyl-2-((4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (16)



(a) 2-(2-(2-(2-((4-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)phenyl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetic acid (A55)

To a suspension of methyl 2-(2-((2-chloro-5-methylpyrimidin-4-yl)ethynyl)phenyl)acetate (*K7*) (110 mg, 0.366 mmol) in 1,4-dioxane (5 mL) was added *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (101 mg, 0.366 mmol), Cs₂CO₃ (477 mg, 1.46 mmol), Pd₂(dba)₃ (33 mg, 0.037 mmol) and Xantphos (63 mg, 0.11 mmol). The resulting suspension was degassed with nitrogen for 5 minutes then heated under microwave irradiation for 30 minutes at 120 °C. The volatiles were removed under reduced pressure and the residue was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-50% EtOAc in petroleum benzine 40-60 °C) to give a yellow oil. A suspension of 10% Pd/C (100 mg) in DMF (10 mL) and Et₃N (1 mL) was added and the resulting mixture stirred under an atmosphere of hydrogen for 16 hours. EtOAc (60 mL) was added and the resulting mixture filtered through Celite. The filtrate was evaporated under reduced pressure and the residue was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO₂ cartridges, 0-60% EtOAc in petroleum benzine 40-60 °C) to give a yellow oil. This was taken up in THF (7 mL), MeOH (7 mL) and H₂O (1.5 mL) to which LiOH.H₂O (115 mg, 2.74 mmol) was added. The resulting mixture was stirred at room temperature overnight then the volatiles were removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and aqueous HCl (2 M; 50 mL) then the layers were separated. The aqueous phase was extracted with EtOAc (2 × 50 mL) then the organics were combined, washed with brine and dried over MgSO₄. The volatiles were removed *in vacuo* to give the title compound **A55** as yellow oil (127 mg, 87%); LCMS-A: rt 6.272 min; *m/z* 531 [M+H]⁺.

(b) *tert*-Butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (**A56**)

HOBt (49 mg, 0.36 mmol), EDCI.HCl (69 mg, 0.36 mmol) and DIPEA (0.21 mL, 1.2 mmol) were added to a stirred solution of 2-(2-(2-(2-((4-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)phenyl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetic acid (**A55**) (127 mg, 0.239 mmol) in dry THF (6 mL) and dry DMF (1 mL) under an atmosphere of nitrogen. After 10 minutes ammonium carbonate (115 mg, 1.20 mmol) was added in one portion and the resulting mixture was stirred at room temperature for 24 hours. The volatiles were removed *in vacuo* then the residue was partitioned between EtOAc (50 mL) and saturated aqueous NaHCO₃ (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The organic extracts were combined, washed with brine and dried over MgSO₄. The volatiles were removed under reduced pressure and the residue purified by column chromatography (0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound **A56** as an off-white solid (66 mg, 52%); ¹H NMR (400 MHz, *d*₆-DMSO) δ 9.36 (s,

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1H), 8.25-8.16 (m, 1H), 7.74 (d, $J = 8.7$ Hz, 2H), 7.49 (s, 1H), 7.28 (m, 1H), 7.25-7.14 (m, 5H), 7.00 (s, 1H), 4.14 (m, 2H), 3.56 (s, 2H), 3.17-3.04 (m, 2H), 2.98-2.91 (m, 2H), 2.84 (m, 2H), 2.71-2.60 (m, 1H), 2.13 (s, 3H), 1.79 (d, $J = 11.7$ Hz, 2H), 1.59-1.43 (m, 11H). LCMS-A: rt 6.078 min; m/z 530 $[M+H]^+$.

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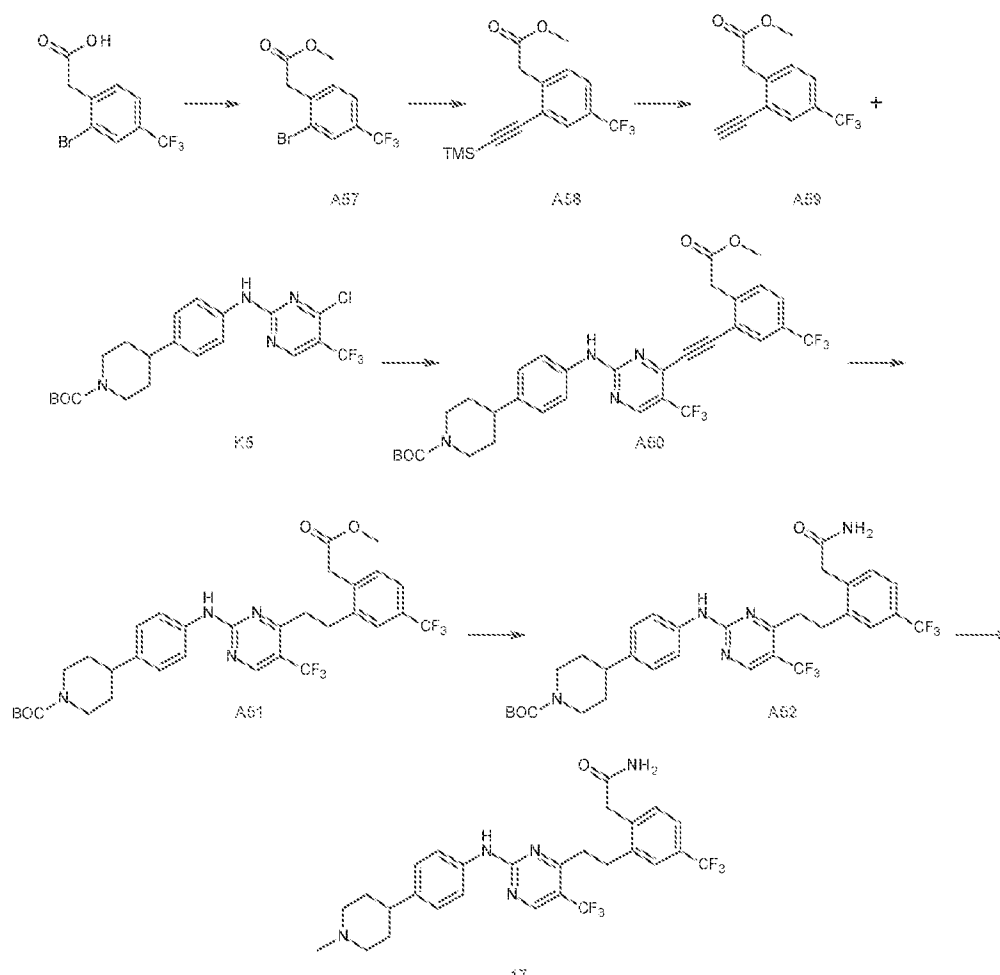
(c) 2-(2-(2-(5-Methyl-2-((4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (16)

TFA (0.37 mL, 4.8 mmol) was added to a solution of *tert*-butyl 4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A56) (64 mg, 0.12 mmol) in DCM (20 mL) under nitrogen and the resulting mixture stirred for 24 hours at room temperature. The volatiles were removed *in vacuo* and the residue was taken up in MeOH and loaded onto an SCX cartridge (10 g). The column was eluted with 5 column volumes of MeOH and then 5 column volumes of 5% v/v aqueous ammonia in MeOH. The volatiles from the ammoniacal filtrate were evaporated under reduced pressure and the resulting solid dried under high vacuum to give the title compound 16 as a white solid (36 mg, 69%). ^1H NMR (400 MHz, d_6 -DMSO) δ 9.28 (s, 1H), 8.15 (s, 1H), 7.67 (d, $J = 8.6$ Hz, 2H), 7.44 (s, 1H), 7.25-7.13 (m, 4H), 7.10 (d, $J = 8.6$ Hz, 2H), 6.93 (s, 1H), 3.50 (s, 2H), 3.10-2.98 (m, 4H), 2.94-2.82 (m, 2H), 2.65-2.53 (m, 3H), 2.06 (s, 3H), 1.67 (d, $J = 10.6$ Hz, 2H), 1.49 (qd, $J = 12.4, 3.7$ Hz, 2H). LCMS-A: rt 4.463 min; m/z 430 $[M+H]^+$.

20

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Example 17: Synthesis of 2-(2-(2-(2-((4-(1-methylpiperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-4-(trifluoromethyl)phenyl)acetamide (17)



(a) Methyl 2-(2-bromo-4-(trifluoromethyl)phenyl)acetate (A57)

- 5 A solution of 2-bromo-4-trifluoromethylphenylacetic acid (2.00 g, 7.07 mmol) and concentrated aqueous H_2SO_4 (1 mL) in MeOH (30 mL) was heated at reflux for 16 hours. The volatiles were removed under reduced pressure then the residue taken up in EtOAc. The resulting solution was washed with 10% NaHCO_3 , dried (MgSO_4) and evaporated under reduced pressure to give the title compound A57 as a clear liquid (2.07 g, 98%); ^1H NMR (400 MHz, CDCl_3) δ 7.83 (d, $J = 1.1$ Hz, 1H), 7.53 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.41 (d, $J = 8.0$ Hz, 1H), 3.84 (s, 2H), 3.72 (s, 3H). LCMS-A: rt 6.236 min; m/z 297/299 $[\text{M}+\text{H}]^+$.
- 10

(b) Methyl 2-(4-(trifluoromethyl)-2-((trimethylsilyl)ethynyl)phenyl)acetate (A58)

- A suspension of methyl 2-(2-bromo-4-(trifluoromethyl)phenyl)acetate (A57) (1.60 g, 5.38 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (189 mg, 269 μmol), $t\text{-Bu}_3\text{PH}\cdot\text{BF}_4$ (78.1 mg, 269 μmol), CuI (51.3 mg, 269 μmol) and TMS-acetylene (1.52 mL, 10.8 mmol) in Et_3N (10 mL) and anhydrous,
- 15

degassed DMF (10 mL) was stirred at 80 °C for 16 hours. The resulting mixture was adsorbed onto silica gel and purified using column chromatography (Biotage Isolera, SiO₂ cartridge, 0-10% EtOAc in petroleum benzine 40-60 °C) to give the title compound A58 as an orange liquid (1.56 g, 92%); ¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, *J* = 1.1 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 3.87 (s, 2H), 3.71 (s, 3H), 0.26 (s, 9H). LCMS-A: rt 6.979 min; *m/z* 315 [M+H]⁺.

(c) Methyl 2-(2-ethynyl-4-(trifluoromethyl)phenyl)acetate (A59)

TBAF (1.0 M in THF, 7.16 mL, 7.15 mmol) was added to a stirred solution of methyl 2-(4-(trifluoromethyl)-2-((trimethylsilyl)ethynyl)phenyl)acetate (A58) (1.50 g, 4.77 mmol) in THF (50 mL) at 0 °C. After 5 minutes the resulting mixture was diluted with EtOAc (50 mL) then washed with 10% NaHCO₃ (50 mL). The organic layer was dried (MgSO₄) and evaporated under reduced pressure. The residue was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-10% EtOAc in petroleum benzine 40-60 °C) to give the title compound A59 as a dark red liquid (956 mg, 83%); ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 1.2 Hz, 1H), 7.57 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 3.90 (s, 2H), 3.72 (s, 3H), 3.36 (s, 1H). LCMS-A: rt 6.099 min; *m/z* 243.1 [M+H]⁺.

(d) *tert*-Butyl 4-(4-((4-((2-(2-methoxy-2-oxoethyl)-5-(trifluoromethyl)phenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A60)

A stirred suspension of *tert*-butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (K5) (0.200 g, 0.438 mmol), PdCl₂(PPh₃)₂ (0.031 g, 0.044 mmol), *t*-Bu₃PH.BF₄ (0.013 mg, 0.044 mmol), CuI (0.008 g, 0.044 mmol) and methyl 2-(2-ethynyl-4-(trifluoromethyl)phenyl)acetate (A59) (0.212 g, 0.875 mmol) in anhydrous, degassed DMF (6 mL) and Et₃N (6 mL) was heated at 120 °C for 20 minutes under nitrogen. The volatiles were evaporated under reduced pressure then the residue adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound A60 as a brown solid (0.176 g, 61%); ¹H NMR (400 MHz, CDCl₃) δ 8.64 (s, 1H), 7.93 (d, *J* = 0.8 Hz, 1H), 7.67 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.51-7.49 (m, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 4.36-4.18 (m, 2H), 4.01 (s, 2H), 3.72 (s, 3H), 2.91-2.74 (m, 2H), 2.72-2.58 (m, 1H), 1.83 (d, *J* = 12.6 Hz, 2H), 1.64-1.56 (m, 2H), 1.50 (s, 9H). LCMS-A: rt 7.227 min; *m/z* 661 [M-H]⁻.

(e) *tert*-Butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)-5-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A61)

A suspension of 10% Pd/C (0.050 g) and *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)-5-(trifluoromethyl)phenethyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A60) (0.200 g, 0.302 mmol) in DMF (10 mL) and Et₃N (1 mL) was stirred at room temperature for 16 hours under an atmosphere of hydrogen. The resulting mixture was filtered through Celite, washing with MeOH. The volatiles were removed under reduced pressure then the residue was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C; repeated twice) to give the title compound A61 (170 mg, 84%); ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.49 (s, 1H), 7.47-7.45 (m, 1H), 7.41 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 4.37-4.17 (m, 2H), 3.79 (s, 2H), 3.69 (s, 3H), 3.24-3.14 (m, 2H), 3.21-3.06 (m, 2H), 2.92-2.72 (m, 2H), 2.71-2.52 (m, 1H), 1.90-1.74 (m, 2H), 1.68-1.60 (m, 2H), 1.48 (s, 9H). LCMS-A: rt 7.149 min; *m/z* 667 [M+H]⁺.

(f) *tert*-Butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)-5-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A62)

A suspension of *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)-5-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A61) (0.100 g, 0.150 mmol) and LiOH.H₂O (0.051 g, 1.21 mmol) in MeOH (2 mL), water (2 mL) and THF (2 mL) was heated at 40 °C for 16 hours. In a separate flask, a suspension of *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)-5-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A61) (0.070 g, 0.105 mmol) and LiOH.H₂O (0.036 g, 0.858 mmol) in MeOH (2 mL), water (2 mL) and THF (2 mL) was heated at 40 °C for 16 hours. The resulting mixtures were combined and the volatiles were removed under reduced pressure. The resulting solid was dissolved in dry DMF (5 mL) and dry THF (5 mL) and HOBt (0.053 g, 0.398 mmol), EDCI.HCl (0.061 g, 0.398 mmol), DIPEA (0.260 mL, 1.53 mmol) and ammonium carbonate (0.144 g, 1.53 mmol) were added. The resulting mixture was stirred at room temperature for 16 hours then HOBt (0.053 g, 0.398 mmol), EDCI.HCl (0.061 g, 0.398 mmol), DIPEA (0.260 mL, 1.53 mmol) and ammonium carbonate (0.144 g, 1.53 mmol) were added and stirring was continued overnight. The resulting mixture was diluted with EtOAc, then washed with 10% aqueous NaHCO₃. The organic layer was dried (MgSO₄) and the volatiles were removed *in vacuo*. The resulting solid was adsorbed onto silica gel then purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-50% EtOAc in petroleum benzine 40-60 °C) to give the title compound A62 as a yellow solid (0.086 g, 43%); ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 7.55-7.47 (m, 5H), 7.38 (d, *J* =

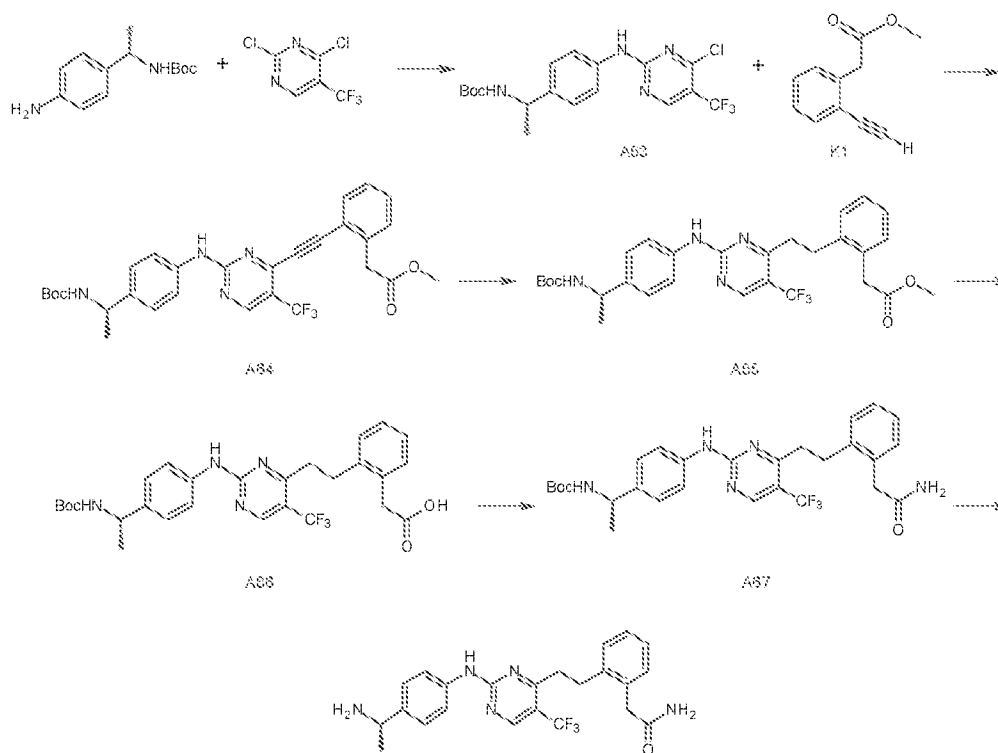
8.3 Hz, 1H), 7.21 (d, $J = 8.5$ Hz, 2H), 5.48-5.28 (m, 2H), 4.39-4.15 (m, 2H), 3.74 (s, 2H), 3.22-3.13 (m, 2H), 3.12-3.05 (m, 2H), 2.88-2.73 (m, 2H), 2.70-2.56 (m, 1H), 1.85-1.80 (m, 2H), 1.70-1.61 (m, 2H), 1.49 (s, 9H). LCMS-A: rt 6.646 min; m/z 652 $[M+H]^+$.

5 (g) 2-(2-(2-(2-((4-(1-methylpiperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-4-(trifluoromethyl)phenyl)acetamide (17)

TFA (0.1 mL) was added to a solution of *tert*-butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)-5-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A62) (0.170 g, 0.261 mmol) in DCM (4 mL) and the resulting mixture stirred for
10 24 hours at room temperature. The volatiles were evaporated under reduced pressure then the residue adsorbed onto silica gel and purified by column chromatography (SiO_2 , 0-50% MeOH in DCM). The volatiles were removed *in vacuo* and the residue dissolved in dry MeOH (5 mL). Formaldehyde (37 wt. % in H_2O ; 0.030 mL, 0.36 mmol) was added and the resulting mixture was stirred for 30 minutes at room temperature. Sodium
15 triacetoxyborohydride (0.077 g, 0.362 mmol) was added under nitrogen and the resulting mixture stirred at room temperature for 2 hours. The volatiles were evaporated under reduced pressure then the residue dissolved in EtOAc and washed with 10% $NaHCO_3$ (20 mL). The organics were dried ($MgSO_4$) and the volatiles removed under reduced pressure. The residue was adsorbed onto silica gel, then purified by silica gel column chromatography
20 (Biotage Isolera, SiO_2 cartridge, 50-100% MeOH in EtOAc then 10% NH_3 in EtOH). Further purification by semi preparative HPLC was required to give the title compound 17 as a pale cream solid (0.011 g, 26%); 1H NMR (400 MHz, d_4 -MeOH) δ 8.55 (s, 1H), 7.67-7.60 (m, 2H), 7.50-7.40 (m, 3H), 7.28-7.19 (m, 2H), 3.74 (s, 2H), 3.54-3.40 (m, 2H), 3.31-3.25 (m, 2H), 3.14-3.12 (m, 2H), 2.95 (t, $J = 11.5$ Hz, 2H), 2.80 (m, 4H), 2.08 (d, $J = 13.8$ Hz, 2H), 1.97-
25 1.92 (m, 2H). LCMS-B: rt 4.52 min; m/z 566 $[M+H]^+$.

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Example 18: Synthesis of 2-(2-(2-(2-(4-(1-aminoethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (18)



18

(a) *tert*-Butyl 1-(4-(4-chloro-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)ethylcarbamate (A63)

ZnCl₂ (1.0 M in Et₂O; 3.27 mL, 3.27 mmol) was added to a stirred solution of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (620 mg, 2.86 mmol) in a 1:1 *t*-BuOH:DCE mixture (120 mL) at room temperature. After stirring for 20 minutes *tert*-butyl 1-(4-aminophenyl)ethylcarbamate (0.643 g, 2.72 mmol) (prepared according to *Bioorganic and Medicinal Chemistry Letters*, 14(7), 1751-1755; 2004) followed by Et₃N (455 μ L, 3.27 mmol) was added and the resulting mixture stirred at room temperature overnight. The volatiles were evaporated to dryness and the resulting residue purified by silica gel column chromatography (CombiFlash Rf, SiO₂ cartridge, 0-10% EtOAc in cyclohexane) to give the title compound A63 (480 mg, 42%); ¹H NMR (300 MHz, CDCl₃) δ 8.57 (s, 1H), 7.56 (m, 1H), 7.56 (d, *J* = 8.61 Hz, 2H), 7.33 (d, *J* = 8.61 Hz, 2H), 4.81 (m, 2H), 1.46 (m, 12H). LCMS-B: rt 8.47 min; *m/z* 417 [M+H]⁺.

(b) Methyl 2-(2-((2-(4-(1-(*tert*-butoxycarbonylamino)ethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethynyl)phenyl)acetate (A64)

A suspension of *tert*-butyl 1-(4-(4-chloro-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)ethylcarbamate (A63) (487 mg, 1.17 mmol), Et₃N (760 μ L), methyl 2-(2-

ethynylphenyl)acetate (*K1*) (244 mg, 1.40 mmol), PdCl₂(PPh₃)₂ (41 mg, 0.058 mmol), CuI (22.0 mg, 0.117 mmol) and PPh₃ (36.0 mg, 0.117 mmol) in DMF (4.6 mL) was heated under microwave irradiation at 120 °C for 15 minutes. The volatiles were evaporated *in vacuo* and the residue purified by silica gel column chromatography (CombiFlash Rf, SiO₂ cartridge, 0-25% EtOAc in cyclohexane) to give the title compound A64 as a yellow solid (400 mg, 62%);
 5 ¹H NMR (300 MHz, CDCl₃) δ 8.66 (s, 1H), 7.70 (dd, *J* = 7.83, 1.17 Hz, 1H), 7.61 (d, *J* = 8.61 Hz, 2H), 7.43 (m, 3H), 7.34 (d, *J* = 8.40 Hz, 2H), 4.78 (m, 2H), 3.98 (s, 2H), 3.73 (s, 3H), 1.61 (s, 1H, peak obscured), 1.46 (m, 12H). LCMS-B: rt 8.90 min; *m/z* 555 [M+H]⁺.

10 (c) Methyl 2-(2-(2-(2-(4-(1-(*tert*-butoxycarbonylamino)ethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetate (A65)

A suspension of methyl 2-(2-(2-(2-(4-(1-(*tert*-butoxycarbonylamino)ethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetate (A64) (353 mg, 0.637 mmol) and Pd/C (10%; 250 mg) in EtOAc (13 mL) was stirred under a hydrogen atmosphere at room
 15 temperature overnight. The resulting mixture was filtered through a pad of Celite then the filtrate evaporated under reduced pressure to give the title compound A65 as an off white solid (320 mg, 90%); ¹H NMR (300 MHz, CDCl₃) δ 8.56 (s, 1H), 7.61 (d, *J* = 8.64 Hz, 2H), 7.52 (s, 1H), 7.28 (m, 5H), 4.81 (m, s, 2H), 3.77 (s, 2H), 3.70 (s, 3H), 3.13 (m, 4H), 1.66 (m, 1H, peak obscured), 1.48 (d, *J* = 6.54 Hz, 3H), 1.45 (s, 9H). LCMS-B: rt 9.07 min; *m/z* 559.5 [M+H]⁺.
 20

(d) 2-(2-(2-(2-(4-(1-(*tert*-Butoxycarbonylamino)ethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A66)

LiOH (69.0 mg, 2.86 mmol) was added to a solution of methyl 2-(2-(2-(2-(4-(1-(*tert*-butoxycarbonylamino)ethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetate (A65) (320 mg, 0.573 mmol) in THF (7.5 mL) and water (2.5 mL) and the resulting mixture stirred at room temperature overnight. The resulting mixture was evaporated *in vacuo* then the residue was partitioned between EtOAc (15 mL) and 1 M aqueous HCl. The phases were separated and the aqueous phase was extracted with
 25 EtOAc. The combined organic phases were washed with brine, dried with Na₂SO₄ and concentrated to give the title compound A66 (310 mg, 99%); LCMS-B: rt 8.30 min; *m/z* 545.4 [M+H]⁺.
 30

(e) 2-(2-(2-(2-(4-(1-(*tert*-Butoxycarbonylamino)ethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A67)

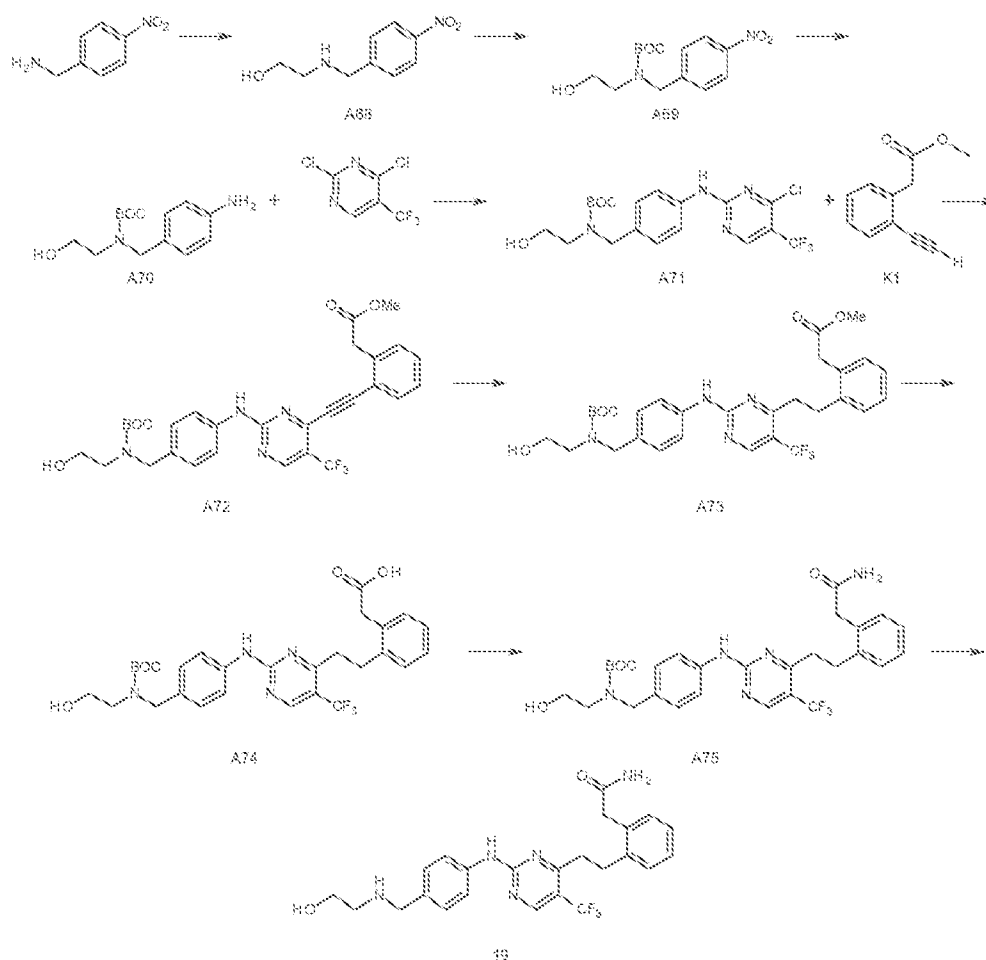
HOBt (119 mg, 0.881 mmol), EDCI.HCl (169 mg, 0.881 mmol) and DIPEA (512 μ L, 2.94 mmol) were added to a stirred solution of 2-(2-(2-(2-(4-(1-(*tert*-

5 butoxycarbonylamino)ethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A66) (320 mg, 0.588 mmol) in dry THF (7.0 mL) and dry DMF (1.5 mL) under an atmosphere of nitrogen. After 10 minutes ammonium carbonate (282 mg, 2.94 mmol) was added in one portion and the resulting mixture was stirred at 40 °C overnight. The volatiles were removed *in vacuo*, then the residue was partitioned between 10 EtOAc (50 mL) and saturated NaHCO₃ (50 mL). After separating the organic layer, the aqueous phase was extracted with EtOAc (2 $\times$ 50 mL). The combined organics were concentrated under reduced pressure then purified by silica gel column chromatography (CombiFlash Rf, SiO₂ cartridge, 0-60% EtOAc in cyclohexane) to give the title compound A67 (307 mg, 96%); ¹H NMR (300 MHz, CDCl₃) δ 8.51 (s, 1H), 7.95 (br.s, 1H), 7.56 (d, *J* = 8.52 Hz, 2H), 7.27 (m, 5H), 5.91 (m, 1H), 5.53 (br.s, 1H), 5.03 (m, 1H), 4.78 (m, 1H), 3.70 (s, 15 2H), 3.10 (m, 4H), 2.00 (br.s, 1H), 1.44 (m, 12H). LCMS-B: *rt* 7.85 min; *m/z* 544.4 [M+H]⁺.

(f) *tert*-Butyl 1-(4-(4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)ethylcarbamate (18)

20 A solution of 2-(2-(2-(2-(4-(1-(*tert*-butoxycarbonylamino)ethyl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A67) (143 mg, 0.263 mmol) and TFA (806 μ L, 1.20 mmol) in DCM (40 mL) was stirred at room temperature overnight. The volatiles were removed under reduced pressure and the residue azeotroped with toluene (x3). The residue was then dissolved in MeOH and applied to an SCX cartridge which was 25 washed with MeOH followed by ethanolic ammonia solution (5 M). The ethanolic ammonia fractions were evaporated *in vacuo* to give the title compound 18 as a light yellow solid (114 mg, 98%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 10.13 (s, 1H), 8.66 (s, 1H), 7.66 (d, *J* = 8.61 Hz, 2H), 7.44 (brs, 1H), 7.31 (d, *J* = 8.40 Hz, 2H), 7.24 (m, 1H), 7.18 (m, 3H), 6.92 (brs, 1H), 3.95 (q, *J* = 6.48 Hz, 1H), 3.51 (s, 2H), 3.33 (peak obscured), 3.11 (m, 4H), 1.24 (d, *J* = 6.60 30 Hz, 2H). LCMS-B: *rt* 5.28 min; *m/z* 444.3 [M+H]⁺.

Example 19: Synthesis of 2-{2-[2-{2-[(4-{[(2-hydroxyethyl)amino)methyl]phenyl}amino)-5-(trifluoromethyl)pyrimidin-4-yl]ethyl]phenyl]acetamide (19)



(a) 2-[(4-Nitrobenzyl)amino]ethanol (A68)

A solution of ethanolamine (10.05 mL, 166.6 mmol), DIPEA (5.08 mL, 29.2 mmol) and 4-nitrobenzyl bromide (6.00 g, 27.8 mmol) in DCM (50 mL) was stirred at room temperature for 4 hours. The volatiles were removed *in vacuo* and the resulting residue partitioned between water and EtOAc. The aqueous phase was separated and extracted with EtOAc (3 × 30 mL). The combined organic fractions were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the title compound A68 as a light yellow solid (3.34 g, 61%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 4.49 (t, *J* = 5.4 Hz, 1H), 3.84 (s, 2H), 3.47 (q, *J* = 5.6 Hz, 2H), 2.56 (t, *J* = 5.8 Hz, 2H), 2.28 (s, 1H).

(b) tert-Butyl (2-hydroxyethyl)(4-nitrobenzyl)carbamate (A69)

A solution of di-*tert*-butyl dicarbonate (1.79 g, 8.23 mmol) in DCM (17 mL) was added slowly to a solution of 2-[(4-nitrobenzyl)amino]ethanol (A68) (1.60 g, 8.15 mmol) and 2 M aqueous

sodium hydroxide (6.11 mL, 12.23 mmol) in DCM (17 mL). The resulting mixture was stirred at room temperature for 18 hours then diluted with water and DCM. The layers separated and the aqueous phase was extracted with DCM (3 × 20 mL). The combined organic fractions were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the title compound A69 as a viscous colourless oil (2.40 g, 99%); ¹H NMR (300 MHz, CDCl₃) δ 8.22 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 4.61 (s, 2H), 3.77 (m, 2H), 3.46 (s, 2H), 2.72 (t, *J* = 5.4 Hz, 1H), 1.44 (brs, 9H).

(c) *tert*-Butyl 4-aminobenzyl(2-hydroxyethyl)carbamate (A70)

A suspension of *tert*-butyl (2-hydroxyethyl)(4-nitrobenzyl)carbamate (A69) (2.40 g, 8.09 mmol) and 10% Pd/C (0.240 g) in EtOAc (12 mL) was stirred under a hydrogen atmosphere for 18 hours. The resulting mixture was filtered through a pad of Celite, washing with EtOAc and the filtrate concentrated *in vacuo*. The residue was purified using silica gel column chromatography (CombiFlash Rf, 40 g SiO₂ cartridge, 20-50% EtOAc in cyclohexane) to give the title compound A70 as a viscous light yellow oil (1.99 g, 92%); ¹H NMR (300 MHz, CDCl₃) δ 7.05 (d, *J* = 7.5 Hz, 2H), 6.66 (d, *J* = 8.0 Hz, 2H), 4.37 (s, 2H), 3.67 (m, 4H), 3.37 (s, 2H), 3.10 (s, 1H), 1.50 (s, 9H).

(d) *tert*-Butyl 4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzyl(2-hydroxyethyl)carbamate (A71)

Zinc(II) chloride (1.0 M in Et₂O; 3.30 mL, 3.30 mmol) was added to a solution of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (0.658 g, 3.03 mmol) in 1:1 DCE/*t*-BuOH (20 mL) at 0 °C under nitrogen. After stirring for 1 hour at 0 °C, a solution of *tert*-butyl 4-aminobenzyl(2-hydroxyethyl)carbamate (A70) (0.734 g, 2.75 mmol) in 1:1 DCE/*t*-BuOH (20 mL) was added followed by a solution of Et₃N (0.423 mL, 3.03 mmol) in 1:1 DCE/*t*-BuOH (5 mL) at 0 °C. The resulting mixture was vigorously stirred at 0 °C for 30 minutes, then at room temperature for 20 hours. The volatiles were evaporated *in vacuo* and the residue adsorbed onto silica gel then purified by column chromatography (CombiFlash Rf, 80 g SiO₂ cartridge, 10-40% EtOAc in cyclohexane) to give the title compound A71 as a white solid (1.06 g, 85%); ¹H NMR (300 MHz, CDCl₃) δ 8.60 (s, 1H), 7.59-7.52 (m, 3H), 7.28 (m, 2H), 4.49 (s, 2H), 3.74 (s, 2H), 3.43-3.20 (m, 3H), 1.50 (s, 9H). LCMS-B: rt 7.856 min; *m/z* 447 [M+H]⁺.

(e) Methyl 2-(2-((2-((4-(((*tert*-butoxycarbonyl)(2-hydroxyethyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethynyl)phenyl)acetate (A72)

A suspension of *tert*-butyl 4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzyl(2-hydroxyethyl)carbamate (A71) (0.518 g, 1.15 mmol), Et₃N (0.75 mL), methyl 2-(2-

ethynylphenyl)acetate (*K1*) (0.242 g, 1.39 mmol), PdCl₂(PPh₃)₂ (0.041 g, 0.058 mmol), CuI (0.022 g, 0.116 mmol) and PPh₃ (0.030 g, 0.12 mmol) in DMF (4.5 mL) was heated under microwave irradiation at 120 °C for 15 minutes. The volatiles were evaporated *in vacuo* and the residue purified using silica gel column chromatography (CombiFlash Rf, 40 g SiO₂ cartridge, 20-50% EtOAc in cyclohexane) to give the title compound A72 as an orange foam (0.589 g, 86%); ¹H NMR (300 MHz, CDCl₃) δ 8.65 (s, 1H), 7.70 (d, *J* = 7.0 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.48-7.28 (m, 6H), 4.49 (brs, 2H), 3.97 (s, 2H), 3.72 (m, 5H), 3.47 (brs, 2H), 3.01 (brs, 1H), 1.51 (s, 9H). LCMS-B: rt 8.350 min; *m/z* 585 [M+H]⁺.

(f) Methyl 2-(2-(2-(2-((4-(((*tert*-butoxycarbonyl)(2-hydroxyethyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetate (A73)

A suspension of methyl 2-(2-(2-(2-((4-(((*tert*-butoxycarbonyl)(2-hydroxyethyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetate (A72) (0.589 g, 1.00 mmol) and 10% Pd/C (0.300 g) in EtOAc (13 mL) was stirred under a hydrogen atmosphere for 18 hours. A further portion of 10% Pd/C (0.300 g) was added and the resulting mixture stirred under a hydrogen atmosphere for 20 hours. The resulting mixture was filtered through a pad of Celite, washing with EtOAc and the filtrate concentrated *in vacuo*. The residue was purified using silica gel column chromatography (CombiFlash Rf, 24 g SiO₂ Cartridge, 20-60% EtOAc in cyclohexane) to give the title compound A73 as a light yellow gum (0.443 g, 74%); ¹H NMR (300 MHz, CDCl₃) δ 8.56 (s, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.44 (s, 1H), 7.28-7.25 (m, 6H), 4.49 (brs, 2H), 3.77-3.70 (m, 7H), 3.42 (brs, 2H), 3.15-2.95 (m, 5H), 1.51 (s, 9H). LCMS-B: rt 8.469 min; *m/z* 589 [M+H]⁺.

(g) 2-(2-(2-(2-((4-(((*tert*-Butoxycarbonyl)(2-hydroxyethyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A74)

LiOH (143 mg, 5.98 mmol) was added to a solution of methyl 2-(2-(2-(2-((4-(((*tert*-butoxycarbonyl)(2-hydroxyethyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetate (A73) (0.440 g, 0.748 mmol) in THF (10 mL), MeOH (1 mL) and water (1 mL) and the resulting mixture stirred at room temperature for 20 hours. Additional LiOH (107 mg, 4.48 mmol) was added and the mixture heated to 40 °C for 24 hours. The volatiles were removed *in vacuo*. The residue was diluted with a 10% citric acid solution (20 mL) and 1 M HCl (0.5 mL) until pH 3 was obtained. The resulting precipitate was collected by filtration and dried to give the title compound A74 as a pale yellow solid (0.421 g, 98%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 10.21 (s, 1H), 8.67 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.24-

7.17 (m, 6H), 4.38 (brs, 2H), 3.64 (brs, 2H), 3.47-3.03 (m, 8H), 1.42 (s, 9H). LCMS-B: rt 7.786 min; m/z 575 $[M+H]^+$.

(h) *tert*-Butyl 4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzyl(2-hydroxyethyl)carbamate (A75)

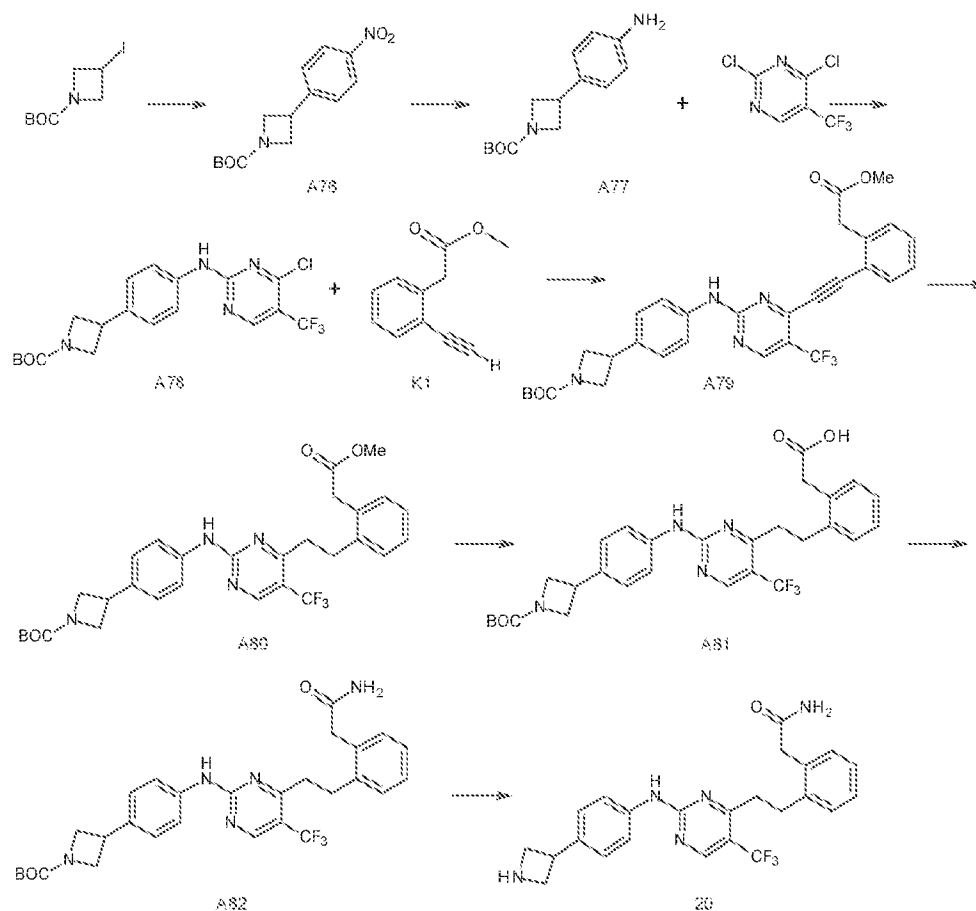
HOBt (0.119 g, 0.879 mmol) and EDCI.HCl (0.169 g, 0.879 mmol) were added to a solution of 2-(2-(2-(2-((4-(((*tert*-butoxycarbonyl)(2-hydroxyethyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A74) (0.421 g, 0.733 mmol) and Et₃N (0.408 mL, 0.297 mmol) in DMF (10 mL). After 10 minutes ammonium carbonate (1.34 g, 14.65 mmol) was added and the resulting mixture was stirred at 40 °C for 22 hours.

Saturated aqueous saturated NaHCO₃ solution (25 mL) was added the resulting mixture extracted with EtOAc (3 × 15 mL). The combined organic fractions were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was adsorbed onto silica gel then purified using column chromatography (CombiFlash Rf, 24 g SiO₂ cartridge, 40-100% EtOAc in cyclohexane) to give the title compound A75 as a white solid (0.301 g, 76%); ¹H NMR (300 MHz, CDCl₃) δ 8.56 (s, 1H), 7.61-7.58 (m, 3H), 7.30-7.26 (m, 6H), 5.48 (brs, 2H), 4.49 (brs, 2H), 3.74 (brs, 4H), 3.42 (brs, 2H), 3.15-3.12 (m, 4H), 1.50 (s, 9H). LCMS-B: rt 7.344 min; m/z 574 $[M+H]^+$.

(i) 2-(2-(2-(2-((4-(((2-Hydroxyethyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (19)

A solution of *tert*-butyl 4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzyl(2-hydroxyethyl)carbamate (A75) (0.301 g, 0.525 mmol) and trifluoroacetic acid (1.0 mL) in DCM (10 mL) was stirred at room temperature for 22 hours. The volatiles were removed *in vacuo* and 2 M aqueous sodium hydroxide solution (20 mL) added to the residue. The resulting suspension was sonicated for several minutes then filtered, washing the filter cake with water. Semi preparative HPLC of the filter cake gave the title compound 19 as a white solid (58 mg, 23%); ¹H NMR (300 MHz, *d*₂-MeOH) δ 8.61 (s, 1H), 8.53 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.29-7.19 (m, 4H), 4.19 (s, 2H), 3.82 (t, *J* = 5.2 Hz, 2H), 3.68 (s, 2H), 3.22-3.10 (m, 6H). LCMS-B: rt 5.313 min; m/z 474 $[M+H]^+$.

Example 20: Synthesis of 2-{2-[2-{2-[(4-{azetidin-3-yl})phenyl]amino)-5-(trifluoromethyl)pyrimidin-4-yl]ethyl}phenyl}acetamide (20)



(a) *tert*-Butyl 3-(4-nitrophenyl)azetidine-1-carboxylate (A76)

DCE (0.146 mL, 1.69 mmol) was added to a vigorously stirred suspension of zinc dust (0.901 g, 13.8 mmol) in THF (3.5 mL) under nitrogen. The resulting suspension was heated at 80 °C for 10 minutes then cooled to room temperature. Trimethylsilyl chloride (0.202 mL, 1.59 mmol) in THF (1.75 mL) was added and the mixture was stirred at room temperature for 4 minutes. A solution of *tert*-butyl 3-iodoazetidine-1-carboxylate (3.00 g, 10.6 mmol) in THF (3.5 mL) was added dropwise over 15 minutes and the resulting mixture stirred at room temperature for 2 hours. $\text{Pd}_2(\text{dba})_3$ (0.155 g, 0.170 mmol) and tri-2-furylphosphine (0.143 g, 0.615 mmol) were added followed by 1-iodo-4-nitrobenzene (2.90 g, 11.7 mmol) in THF (18 mL). The resulting mixture was then heated at 55 °C for 3 hours then quenched with an aqueous saturated sodium chloride solution (15 mL). After filtration through a pad of Celite, the layers were separated and the aqueous phase extracted with DCM (2 × 15 mL). The combined organic fractions were dried (MgSO_4), filtered and evaporated *in vacuo*. The residue was purified using silica gel column chromatography (CombiFlash Rf, 40 g SiO_2

cartridge, 10-40% EtOAc in cyclohexane) to give the title compound A76 as an orange oil (2.14 g, 72%); ¹H NMR (300 MHz, CDCl₃) δ 8.24 (dd, *J* = 6.8, 1.9 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 4.41 (t, *J* = 8.7 Hz, 2H), 3.98 (dd, *J* = 8.5, 5.7 Hz, 2H), 3.89-3.81 (s, 1H), 1.49 (s, 9H).

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(b) *tert*-Butyl 3-(4-aminophenyl)azetidine-1-carboxylate (A77)

A suspension of *tert*-butyl 3-(4-nitrophenyl)azetidine-1-carboxylate (A76) (2.14 g, 7.68 mmol) and 10% Pd/C (0.320 g) in EtOAc (16 mL) was stirred under a hydrogen atmosphere for 18 hours. Additional 10% Pd/C (1.00 g) was added and the mixture stirred under a hydrogen atmosphere for a further 20 hours. The resulting mixture was filtered through a pad of Celite, washing with EtOAc and the filtrate concentrated *in vacuo* to give the title compound A77 as a light yellow/cream solid (1.80 g, 94%); ¹H NMR (300 MHz, CDCl₃) δ 7.12 (d, *J* = 8.3 Hz, 2H), 6.69 (dd, *J* = 6.5, 1.9 Hz, 2H), 4.29 (t, *J* = 8.7 Hz, 2H), 3.93 (dd, *J* = 8.4, 6.1 Hz, 2H), 3.69-3.61 (s, 2H), 1.55-1.68 (m, 1H), 1.48 (s, 9H). LCMS-B: rt 4.964 min; *m/z* 249 [M+H]⁺.

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(c) *tert*-Butyl 3-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)azetidine-1-carboxylate (A78)

Zinc(II) chloride (1.0 M in Et₂O; 4.83 mL, 4.83 mmol) was added to a solution of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (0.769 g, 3.54 mmol) in DCE/*t*-BuOH (64 mL) at room temperature under nitrogen. After stirring for 10 minutes, *tert*-butyl 3-(4-aminophenyl)azetidine-1-carboxylate (A77) (0.800 g, 3.22 mmol) was added followed by Et₃N (1.08 mL, 7.73 mmol). The resulting mixture was stirred at room temperature for 20 hours then the volatiles removed *in vacuo*. Water was added to the residue and the resulting suspension sonicated for 2 minutes. The suspension was filtered and the filter cake dried then adsorbed onto silica gel and purified using column chromatography (CombiFlash Rf, 40 g SiO₂ cartridge, 10-40% EtOAc in cyclohexane) to give a white solid. The solid was suspended in MeOH (7 mL) and the resulting suspension sonicated for 30 seconds. The suspension was filtered and the filter cake washed with MeOH (3 mL), then dried to give the title compound A78 as a white solid (0.777 g, 56%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 10.6 (s, 1H), 8.79 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 4.23 (t, *J* = 7.6 Hz, 2H), 3.85-3.74 (m, 3H), 1.40 (s, 9H). LCMS-B: rt 8.810 min; *m/z* 429 [M+H]⁺.

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(d) *tert*-Butyl 3-(4-((2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)azetidine-1-carboxylate (A79)

A suspension of *tert*-butyl 3-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)azetidine-1-carboxylate (A78) (500 mg, 1.16 mmol), methyl 2-(2-

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ethynylphenyl)acetate (*K1*) (244 mg, 1.39 mmol), Et₃N (0.60 mL), PdCl₂(PPh₃)₂ (0.041 g, 0.058 mmol), CuI (0.022 g, 0.117 mmol) and PPh₃ (0.031 g, 0.117 mmol) in DMF (4 mL) were heated under microwave irradiation at 120 °C for 15 minutes. The resulting mixture was adsorbed onto silica gel and purified using column chromatography (CombiFlash Rf, 40 g SiO₂ cartridge, 0-30% EtOAc in cyclohexane) to give the title compound *A79* as a yellow foam (0.570 g, 86%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 8.65 (s, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.48-7.33 (m, 6H), 4.35 (t, *J* = 8.6 Hz, 2H), 4.01-3.96 (m, 4H), 3.75-3.72 (m, 4H), 1.49 (s, 9H). LCMS-B: rt 9.160 min; *m/z* 567 [M+H]⁺.

(e) *tert*-Butyl 3-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)azetidine-1-carboxylate (*A80*)

A suspension of *tert*-butyl 3-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)azetidine-1-carboxylate (*A79*) (570 mg, 1.00 mmol) and 10% Pd/C (0.600 g) in EtOAc (13 mL) was stirred under a hydrogen atmosphere for 18 hours. The resulting mixture was filtered through a pad of Celite, washing with EtOAc and the filtrate concentrated *in vacuo* to give the title compound *A80* as a light yellow foam (521 mg, 90%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 8.56 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.57 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.28-7.25 (m, 4H), 4.35 (t, *J* = 8.7 Hz, 2H), 3.99 (dd, *J* = 8.4, 6.7 Hz, 2H), 3.77 (m, 3H), 3.70 (brs, 3H), 3.13 (m, 4H), 1.44 (s, 9H). LCMS-B: rt 9.374 min; *m/z* 571 [M+H]⁺.

(f) 2-(2-(2-(2-((4-(1-(*tert*-Butoxycarbonyl)azetidin-3-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (*A81*)

LiOH.H₂O (0.219 g, 9.131 mmol) was added to a solution of *tert*-butyl 3-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)azetidine-1-carboxylate (*A80*) (0.521 g, 0.913 mmol) in THF (10 mL), MeOH (1 mL) and water (1 mL) and the resulting mixture stirred at 40 °C for 20 hours. Additional LiOH.H₂O (0.087 g, 3.65 mmol) was added and the mixture heated at 40 °C for a further 24 hours. The volatiles were removed *in vacuo* and the residue was diluted with 10% citric acid solution (20 mL).

Aqueous 1 M HCl (ca 0.5 mL) was then added until a pH of 3 was obtained. EtOAc was added, the layers separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine, dried (MgSO₄), filtered and evaporated *in vacuo* to give the title compound *A81* as a viscous yellow oil (0.500 g, 98%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 9.26 (brs, 1H), 8.52 (s, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.32-7.24 (m, 6H), 4.31 (t, *J* = 8.7 Hz, 2H), 3.97-3.68 (m, 5H), 3.08 (m, 4H), 1.48 (s, 9H). LCMS-B: rt 8.649 min; *m/z* 557 [M+H]⁺.

(g) *tert*-Butyl 3-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)azetidine-1-carboxylate (A82)

HOBt (146 mg, 1.07 mmol) and EDCI.HCl (207 mg, 1.07 mmol) were added to a solution of

2-(2-(2-(2-((4-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A81) (0.500 g, 0.898 mmol) and Et₃N

(455 μ L, 4.49 mmol) in DMF (13 mL). After 10 minutes ammonium carbonate (1.65 g, 18.0

mmol) was added and the resulting mixture was stirred at 40 °C for 22 hours. Additional

HOBt (0.072 g, 0.539 mmol), EDCI.HCl (0.103 g, 0.539 mmol) and ammonium carbonate

(0.413 g, 4.49 mmol) were added and the mixture stirred at 45 °C for 24 hours. The volatiles

were removed *in vacuo* and water (25 mL) added to the residue resulting in the formation of

a precipitate. The resulting suspension was sonicated for several minutes, filtered and the

filter cake dried to give a solid which was adsorbed onto silica gel and purified by column

chromatography (CombiFlash Rf, 40 g SiO₂ cartridge, 25-70% EtOAc in cyclohexane) to

give the title compound A82 as a white solid (346 mg, 69%); ¹H NMR (300 MHz, *d*₆-DMSO)

δ 10.21 (s, 1H), 8.68 (s, 1H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.42 (s, 1H), 7.30 (d, *J* = 8.6 Hz, 2H),

7.24-7.16 (m, 4H), 6.91 (s, 1H), 4.23 (t, *J* = 8.0 Hz, 2H), 3.85-3.71 (m, 3H), 3.50 (s, 2H),

3.12-3.04 (m, 4H), 1.40 (s, 9H). LCMS-B: rt 8.187 min; *m/z* 556 [M+H]⁺.

(h) 2-(2-(2-(2-((4-(azetidin-3-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (20)

A solution of *tert*-butyl 3-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-

(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)azetidine-1-carboxylate (A82) (0.346 g, 0.623

mmol) and trifluoroacetic acid (1 mL) in DCM (10 mL) was stirred at room temperature for 22

hours. The volatiles were removed *in vacuo* and 2 M aqueous NaOH (15 mL) was added to

the residue. Water (20 mL) was added and the resulting suspension sonicated for 2 minutes,

filtered and the filter cake washed with water and dried to give the title compound 20 as a

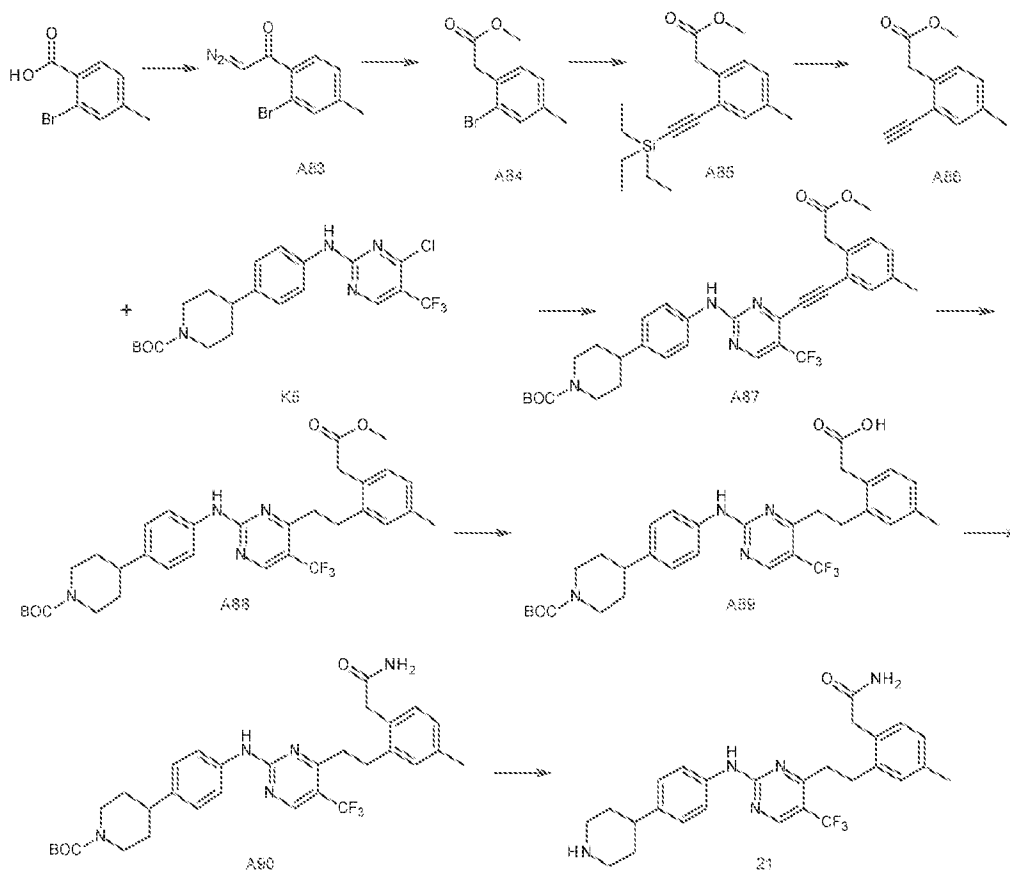
white solid (0.283 g, 99%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 10.26 (s, 1H), 8.69 (s, 1H), 7.78

(d, *J* = 8.6 Hz, 2H), 7.43 (s, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.25-7.15 (m, 4H), 6.92 (s, 1H),

4.21 (brs, 2H), 4.06-3.99 (m, 3H), 3.50 (s, 2H), 3.12-3.05 (m, 5H). LCMS-B: rt 5.442 min;

m/z 456 [M+H]⁺.

Example 21: Synthesis of 2-(4-methyl-2-(2-(2-((4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (21)



(a) 1-(2-Bromo-4-methylphenyl)-2-diazoethanone (A83)

- 5 Oxalyl chloride (0.891 mL, 10.2 mmol) was slowly added to a solution of 2-bromo-4-methylbenzoic acid (813 mg, 3.78 mmol) and DMF (0.16 mL) in THF (35 mL) under nitrogen. The resulting mixture was stirred at room temperature for 30 minutes, then the volatiles were removed *in vacuo* and the residue azeotroped with toluene (2 × 20 mL). The resulting residue was taken up in anhydrous acetonitrile (40 mL) and chilled to 0 °C under a nitrogen atmosphere. A solution of TMS-diazomethane (2.0 M in Et₂O; 4.35 mL, 8.70 mmol) was rapidly added and the resulting mixture was stirred at room temperature for 1 hour. EtOAc (30 mL) and saturated aqueous NaHCO₃ (20 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (2 × 30 mL), then the combined organic extracts were washed with water (× 2), brine, dried (MgSO₄), filtered and evaporated *in vacuo*. The residue was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 10-20% EtOAc in petroleum benzine 40-60 °C) to give the title compound A83 as a yellow oil (667 mg, 74%); ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, J = 0.6 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.15 (dd, J = 7.8, 0.7 Hz, 1H), 5.73 (s, 1H), 2.35 (s, 3H).
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(b) Methyl 2-(2-bromo-4-methylphenyl)acetate (A84)

To a solution of 1-(2-bromo-4-methylphenyl)-2-diazoethanone (A83) (667 mg, 2.79 mmol) in THF (4.3 mL) and MeOH (4.3 mL) was added a solution of silver benzoate (96 mg, 0.42 mmol) in Et₃N (1.13 mL, 11.2 mmol). The resulting mixture was stirred for 2 hours at room temperature then passed through a plug of silica gel eluting with 50% EtOAc in petroleum benzene 40-60 °C. The eluent was evaporated *in vacuo* and the residue was adsorbed onto silica gel and separated using silica gel column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-50% EtOAc in petroleum benzene 40-60 °C) to give the title compound A84 as a clear oil (678 mg, >99%); ¹H NMR (400 MHz, CDCl₃) δ 7.39 (d, *J* = 0.7 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.07 (dd, *J* = 7.7, 1.0 Hz, 1H), 3.76 (s, 2H), 3.70 (s, 3H), 2.30 (s, 3H). LCMS-A: rt 6.070 min.

(c) Methyl 2-(4-methyl-2-((triethylsilyl)ethynyl)phenyl)acetate (A85)

A solution of triethylsilyl acetylene (0.27 mL, 1.5 mmol) in degassed DMF (4 mL) and Et₃N (2.0 mL, 15 mmol) was added to a mixture of methyl 2-(2-bromo-4-methylphenyl)acetate (A84) (0.30 g, 1.2 mmol), PdCl₂(PPh₃)₂ (0.043 g, 0.062 mmol), CuI (0.012 g, 0.062 mmol) and *t*-Bu₃PH.BF₄ (0.018 g, 0.062 mmol) in degassed DMF (10 mL). The resulting mixture was heated at 70 °C for 17 hours then diluted with EtOAc and passed through a plug of Celite, washing with EtOAc (150 mL). The filtrate was concentrated under reduced pressure and adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, 40 g SiO₂ cartridge, 0-15% EtOAc in petroleum spirits) to yield the title compound A85 as a yellow oil (0.326 g, 72% purity contaminated with starting material); ¹H NMR (400 MHz, CDCl₃) δ 7.32 (s, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.12-7.08 (m, 1H), 3.82 (s, 2H), 3.68 (s, 3H), 2.31 (s, 3H), 1.05 (t, *J* = 7.9 Hz, 9H), 0.72-0.64 (m, 6H).

(d) Methyl 2-(2-ethynyl-4-methylphenyl)acetate (A86)

TBAF (1.0 M in THF; 1.16 mL, 1.16 mmol) was added to a solution of methyl 2-(4-methyl-2-((triethylsilyl)ethynyl)phenyl)acetate (A85) (0.326 g, 72% purity) in DCM (10 mL) at 0 °C and the resulting mixture stirred at room temperature for 5 minutes. Aqueous 10% NaHCO₃ was added and the layers separated. The organic layer was dried (MgSO₄) and the volatiles removed *in vacuo* to give a yellow oil which was adsorbed onto silica and purified by silica gel column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-10% EtOAc in petroleum benzene 40-60 °C) to give the title compound A86 (0.196 g, 71% pure: contaminated with methyl 2-(2-bromo-4-methylphenyl)acetate); ¹H NMR (400 MHz, CDCl₃) δ 7.33 (s, 1H), 7.19-7.12 (m, 2H), 3.82 (s, 2H), 3.70 (s, 3H), 3.25 (s, 1H), 2.31 (s, 3H). LCMS-A: rt 5.900; *m/z* 189.2 [M+H]⁺.

(e) *tert*-Butyl 4-((4-((2-(2-methoxy-2-oxoethyl)-5-methylphenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A87)

A solution of methyl 2-(2-ethynyl-4-methylphenyl)acetate (A86) (0.196 g, 71% pure) in DMF (3 mL) and Et₃N (0.309 mL, 2.22 mmol) was added to a mixture of *tert*-butyl 4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (K5) (0.371 g, 0.812 mmol), PdCl₂(PPh₃)₂ (0.078 g, 0.11 mmol), CuI (0.021 g, 0.11 mmol) and PPh₃ (0.019 g, 0.074 mmol) in DMF (3 mL). The resulting mixture was heated under microwave irradiation at 120 °C for 15 minutes then diluted with EtOAc and passed through a plug of Celite, washing with EtOAc (50 mL). The filtrate was concentrated *in vacuo* and the residue purified by silica gel column chromatography (Biotage Isolera, 40 g cartridge, 0-35% EtOAc in petroleum benzene 40-60 °C) to give the title compound A87 as a yellow oil (133 mg, 30%); ¹H NMR (400 MHz, CDCl₃) δ 8.61 (s, 1H), 7.74 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.44 (s, 1H), 7.24-7.16 (m, 4H), 4.43-4.14 (m, 2H), 3.90 (s, 2H), 3.69 (s, 3H), 2.80 (t, *J* = 11.7 Hz, 2H), 2.63 (tt, *J* = 12.0, 3.3 Hz, 1H), 2.34 (s, 3H), 1.81 (d, *J* = 12.7 Hz, 2H), 1.69-1.54 (m, 2H), 1.49 (s, 9H). LCMS-A: *t*_r 7.057 min; *m/z* 609.3 [M+H]⁺.

(f) *tert*-Butyl 4-((4-((2-(2-methoxy-2-oxoethyl)-5-methylphenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A88)

A suspension of *tert*-butyl 4-((4-((2-(2-methoxy-2-oxoethyl)-5-methylphenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A87) (0.133 g, 0.219 mmol) and 10% Pd/C (53% water; 0.133 g) in DMF (7 mL) and Et₃N (1 mL) was stirred under an atmosphere of hydrogen at room temperature for 16 hours. The resulting mixture was filtered through a pad of Celite, washing with EtOAc (50 mL). The filtrate was evaporated *in vacuo* and the residue purified by silica gel column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-35% EtOAc in petroleum benzene 40-60 °C) to yield the title compound A88 as a clear oil (0.133 g, 99%); ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.53 (s, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 1H), 7.07 (s, 1H), 7.02 (dd, *J* = 7.7, 1.2 Hz, 1H), 4.40-4.15 (m, 2H), 3.71 (s, 2H), 3.67 (s, 3H), 3.08 (m, 4H), 2.81 (t, *J* = 12.1 Hz, 2H), 2.65 (tt, *J* = 12.0, 3.4 Hz, 1H), 2.32 (s, 3H), 1.83 (d, *J* = 12.8 Hz, 2H), 1.62 (m, 2H), 1.49 (s, 9H). LCMS-A: *t*_r 7.156 min; *m/z* 613.4 [M+H]⁺.

(g) 2-(2-(2-(2-((4-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-4-methylphenyl)acetic acid (A89)

LiOH·H₂O (0.028 g, 0.65 mmol) was added to a solution of *tert*-butyl 4-((4-((2-(2-methoxy-2-oxoethyl)-5-methylphenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-

carboxylate (A88) (0.133 g, 0.217 mmol) in THF (7 mL), water (1.5 mL) and MeOH (1 mL) and the resulting mixture stirred at room temperature for 27 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (50 mL) and saturated aqueous NaHCO₃ (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄ and the volatiles removed *in vacuo* to give the title compound A89 as a white solid (0.124 g, 95%); ¹H NMR (400 MHz, *d*₄-MeOH) δ 8.49 (s, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.00 (s, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 4.18 (d, *J* = 13.1 Hz, 2H), 3.65 (s, 2H), 3.13-2.90 (m, 4H), 2.92-2.71 (m, 2H), 2.64 (tt, *J* = 12.0, 3.1 Hz, 1H), 2.26 (s, 3H), 1.78 (d, *J* = 12.5 Hz, 2H), 1.61-1.49 (m, 2H), 1.47 (s, 9H). LCMS-A: rt 6.736 min; *m/z* 599.3 [M+H]⁺.

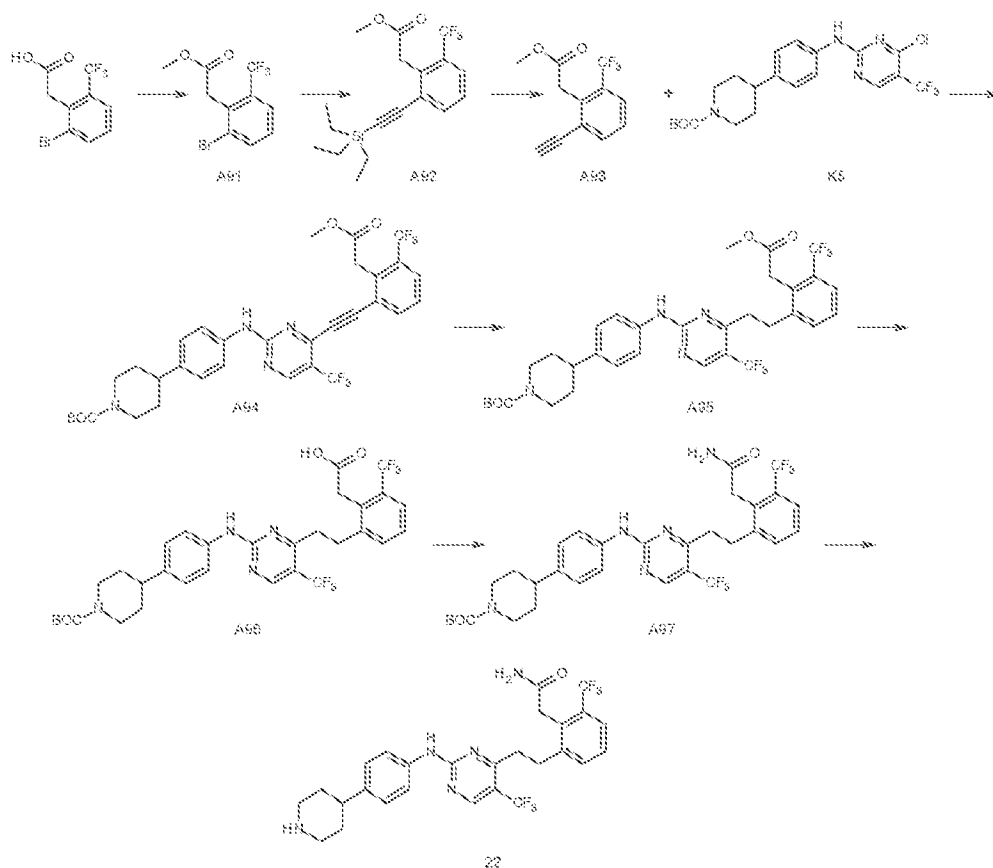
(h) *tert*-Butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)-5-methylphenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A90)

HOBt (0.036 g, 0.27 mmol), EDCI.HCl (0.052 g, 0.27 mmol) and DIPEA (0.18 mL, 1.0 mmol) were added to a solution of 2-(2-(2-(2-((4-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-4-methylphenyl)acetic acid (A89) (0.12 g, 0.21 mmol) in dry THF (6 mL) and dry DMF (1 mL) under a nitrogen atmosphere. After 10 minutes ammonium carbonate (0.10 g, 1.0 mmol) was added in one portion and the resulting mixture stirred at room temperature for 20 hours. The volatiles were removed *in vacuo* and the residue dried under high vacuum. The resulting residue was taken up in dry THF (5 mL) and dry DMF (4 mL) under a nitrogen atmosphere and HOBt (0.036 g, 0.27 mmol), EDCI.HCl (0.052 g, 0.27 mmol) and DIPEA (0.18 mL, 1.0 mmol) were added. After 10 minutes ammonium carbonate (0.10 g, 1.0 mmol) was added in one portion and the resulting mixture was stirred at 25 °C for 22 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (65 mL) and saturated aqueous NaHCO₃ (65 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄, the volatiles removed *in vacuo* and the residue absorbed onto silica gel and purified by column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound A90 as a white solid (0.106 g, 86%); ¹H NMR (400 MHz, CDCl₃) δ 8.51 (s, 1H), 7.88 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.08-7.01 (m, 2H), 5.78 (s, 1H), 5.47 (s, 1H), 4.39-4.15 (m, 2H), 3.66 (s, 2H), 3.04 (apparent s, 4H), 2.79 (t, *J* = 12.2 Hz, 2H), 2.62 (tt, *J* = 12.0, 3.3 Hz, 1H), 2.32 (s, 3H), 1.81 (d, *J* = 12.7 Hz, 2H), 1.60 (qd, *J* = 12.8, 4.2 Hz, 2H), 1.48 (s, 9H). LCMS-A: rt 6.63 min; *m/z* 598.4 [M+H]⁺.

(i) 2-(4-Methyl-2-(2-(2-((4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (21)

TFA (0.5 mL) was added to a solution of *tert*-butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)-5-methylphenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A90) (0.106 g, 0.177 mmol) in DCM (5 mL) and the resulting mixture stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (20 mL) and 2 M aqueous NaOH (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers washed with water (20 mL), brine (20 mL) and dried over MgSO₄. The volatiles were removed *in vacuo* to give a solid which was suspended in DCM and cyclohexane. The resulting suspension was filtered to give the title compound 21 as a white solid (0.085 g, 96%); ¹H NMR (400 MHz, *d*₆-MeOH) δ 8.54 (s, 1H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.06-6.98 (m, 2H), 3.62 (s, 2H), 3.28-3.21 (m, 2H), 3.15-3.08 (m, 2H), 3.08-3.01 (m, 2H), 2.86 (td, *J* = 12.6, 2.6 Hz, 2H), 2.78-2.67 (m, 1H), 2.26 (s, 3H), 1.91 (d, *J* = 12.0 Hz, 2H), 1.74 (qd, *J* = 12.9, 4.0 Hz, 2H). LCMS-A: rt 4.94 min; *m/z* 498.3 [M+H]⁺.

Example 22: Synthesis of 2-{2-[2-(2-{(4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl]ethyl]-6-(trifluoromethyl)phenyl}acetamide (22)



(a) Methyl 2-(2-bromo-6-(trifluoromethyl)phenyl)acetate (A91)

To a mixture of 2-(2-bromo-6-(trifluoromethyl)phenyl)acetic acid (0.306 g, 1.08 mmol) in 4:1 toluene/MeOH (8 mL) was added trimethylsilyldiazomethane (2.0 M in Et₂O; 0.80 mL, 1.6 mmol). The resulting mixture was stirred at room temperature for 20 hours before diluting with EtOAc (40 mL) and washing with saturated aqueous NaHCO₃ (3 × 40 mL). The organics were passed through a phase separation cartridge then concentrated under reduced pressure to give the title compound A91 (0.293 g, 91%); ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.29 (m, 1H), 4.04 (m, 2H), 3.72 (s, 3H).

(b) Methyl 2-(2-((triethylsilyl)ethynyl)-6-(trifluoromethyl)phenyl)acetate (A92)

A mixture of CuI (0.005 g, 0.03 mmol), PdCl₂(PPh₃)₂ (0.009 g, 0.01 mmol), PPh₃ (0.017 g, 0.065 mmol) and methyl 2-(2-bromo-6-(trifluoromethyl)phenyl)acetate (A91) (0.213 g, 0.717 mmol) in DMF (2.0 mL) was degassed with nitrogen for several minutes before the addition of DIPEA (2.00 mL, 11.5 mmol) and (triethylsilyl)acetylene (0.50 mL, 2.8 mmol). The resulting mixture was then degassed with nitrogen before heating under microwave irradiation at 90°C for 2 × 20 minutes. The volatiles were evaporated under reduced

pressure and the residue purified using silica gel column chromatography (0-10% EtOAc in petroleum benzine 40-60 °C) to give a mixture of product and starting material. To this material, CuI (0.013 g, 0.068 mmol), PdCl₂(PPh₃)₂ (0.013 g, 0.019 mmol), PPh₃ (0.030 g, 0.114 mmol), DMF (4.0 mL), DIPEA (2.00 mL, 11.5 mmol) and (triethylsilyl)acetylene (0.50 mL, 2.8 mmol) were added. The resulting mixture was heated at 100 °C for 30 minutes then concentrated under reduced pressure and the residue purified using silica gel column chromatography (Biotage Isolera, SiO₂ cartridge, 5-10% EtOAc in petroleum benzine 40-60 °C) to give the title compound A92 (0.175 g, 69%); ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.35 (m, 1H), 4.09 (m, 2H), 3.68 (s, 3H), 1.03 (t, J = 7.9 Hz, 9H), 0.67 (q, J = 7.9 Hz, 6H).

(c) Methyl 2-(2-ethynyl-6-(trifluoromethyl)phenyl)acetate (A93)

K₂CO₃ (0.210 g, 1.52 mmol) was added to a solution of methyl 2-(2-((triethylsilyl)ethynyl)-6-(trifluoromethyl)phenyl)acetate (A92) (0.175 g, 0.491 mmol) in MeOH (1 mL) and the mixture stirred for 10 minutes at room temperature. The resulting mixture was diluted with water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were concentrated under reduced pressure and the residue dissolved in MeOH (1 mL). K₂CO₃ (0.204 g, 1.48 mmol) was added and the mixture stirred at room temperature for 30 minutes. The resulting mixture was diluted with water (20 mL) and extracted with DCM (3 × 20 mL) then the combined organic extracts were concentrated under reduced pressure. The residue was dissolved in MeOH (2 mL) to which K₂CO₃ (0.230 g, 1.66 mmol) was added and the resulting mixture stirred at room temperature for 30 minutes. Water (20 mL) was added and the mixture extracted with DCM (3 × 20 mL). The combined organic extracts were concentrated under reduced pressure to give the title compound A93 (0.113 g, 95%); ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.38 (m, 1H), 4.08 (m, 2H), 3.70 (s, 3H), 3.35 (s, 1H).

(d) tert-Butyl 4-{4-[(2-(2-methoxy-2-oxoethyl)-3-(trifluoromethyl)phenyl)ethynyl]-5-(trifluoromethyl)pyrimidin-2-yl}amino)phenyl}piperidine-1-carboxylate (A94)

A mixture of methyl 2-(2-ethynyl-6-(trifluoromethyl)phenyl)acetate (A93) (0.113 g, 0.468 mmol), *tert*-butyl 4-{4-[(4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino]phenyl}piperidine-1-carboxylate (K5) (0.222 g, 0.487 mmol), copper(I) iodide (0.005 g, 0.03 mmol), PdCl₂(PPh₃)₂ (0.021 g, 0.030 mmol) and *t*-Bu₃PH.BF₄ (0.011 g, 0.038 mmol) in DMF (2.0 mL) was degassed with nitrogen for several minutes before the addition of DIPEA (2.0 mL, 12 mmol) then further degassed with nitrogen for several minutes. The resulting mixture was heated under microwave irradiation 110 °C for 20 minutes and then a further 30 minutes. The

volatiles were evaporated under reduced pressure and the residue purified using silica gel column chromatography (Biotage Isolera, SiO₂ cartridge, 0-30% EtOAc in petroleum benzine 40-60 °C) to give the title compound A94 (0.127 g, 41%); ¹H NMR (400 MHz, CDCl₃) δ 8.63 (s, 1H), 7.88 (d, *J* = 7.3 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.41 (s, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 4.25 (m, 2H), 4.17 (s, 2H), 3.69 (s, 3H), 2.81 (t, *J* = 12.5 Hz, 2H), 2.65 (m, 1H), 1.83 (d, *J* = 12.6 Hz, 2H), 1.63 (m, 2H), 1.49 (s, 9H). LCMS-A: rt 7.12 min; *m/z* 661.1 [M-H]⁺.

(e) *tert*-Butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)-3-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A95)

A suspension of *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)-3-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A94) (0.127 g, 0.192 mmol) and 10% Pd/C (53% water; 0.234 g) in EtOAc (4.0 mL) and triethylamine (0.2 mL) was stirred under a hydrogen atmosphere for 20 hours. The resulting mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15-30% EtOAc in petroleum benzine 40-60 °C) to give the title compound A95 (0.106 g, 83%); ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 7.56 (m, 3H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.36 (m, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 4.25 (m, 2H), 3.98 (s, 2H), 3.68 (s, 3H), 3.11 (m, 4H), 2.81 (m, 2H), 2.64 (m, 1H), 1.83 (m, 2H), 1.62 (m, 2H), 1.49 (s, 9H). LCMS-A: rt 7.19 min; *m/z* 665.1 [M-H]⁺.

(f) 2-(2-(2-(2-((4-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-6-(trifluoromethyl)phenyl)acetic acid (A96)

LiOH (31 mg, 1.3 mmol) was added to a solution of *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)-3-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A95) (0.106 g, 0.159 mmol) in THF (2.0 mL), MeOH (1.0 mL) and water (1.0 mL) and the resulting mixture was stirred at room temperature for 16 hours. Water (20 mL) was added and the mixture extracted with EtOAc (2 × 20 mL). The combined organic extracts were concentrated under reduced pressure and the residue taken up in THF (2.0 mL), MeOH (1.0 mL) and water (1.0 mL). LiOH (0.103 g, 4.30 mmol) was added and the resulting mixture stirred for 136 hours at room temperature. The mixture was diluted with water (30 mL) then extracted with EtOAc (3 × 30 mL). The combined organic extracts were passed through a phase separation cartridge then concentrated under reduced pressure to give the title compound A96 (0.104 g, 99%); ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.27 (bs, 1H), 8.65 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.25 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.19 (d, *J* = 8.6 Hz,

2H), 4.06 (m, 2H), 3.48 (s, 2H), 3.14 (m, 2H), 3.05 (m, 2H), 2.80 (m, 2H), 2.61 (m, 1H), 1.74 (m, 2H), 1.48 (m, 2H), 1.42 (s, 9H). LCMS-A: rt 6.78 min; m/z 653.3 $[M+H]^+$.

(g) *tert*-Butyl 4-((4-(2-(2-amino-2-oxoethyl)-3-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A97)

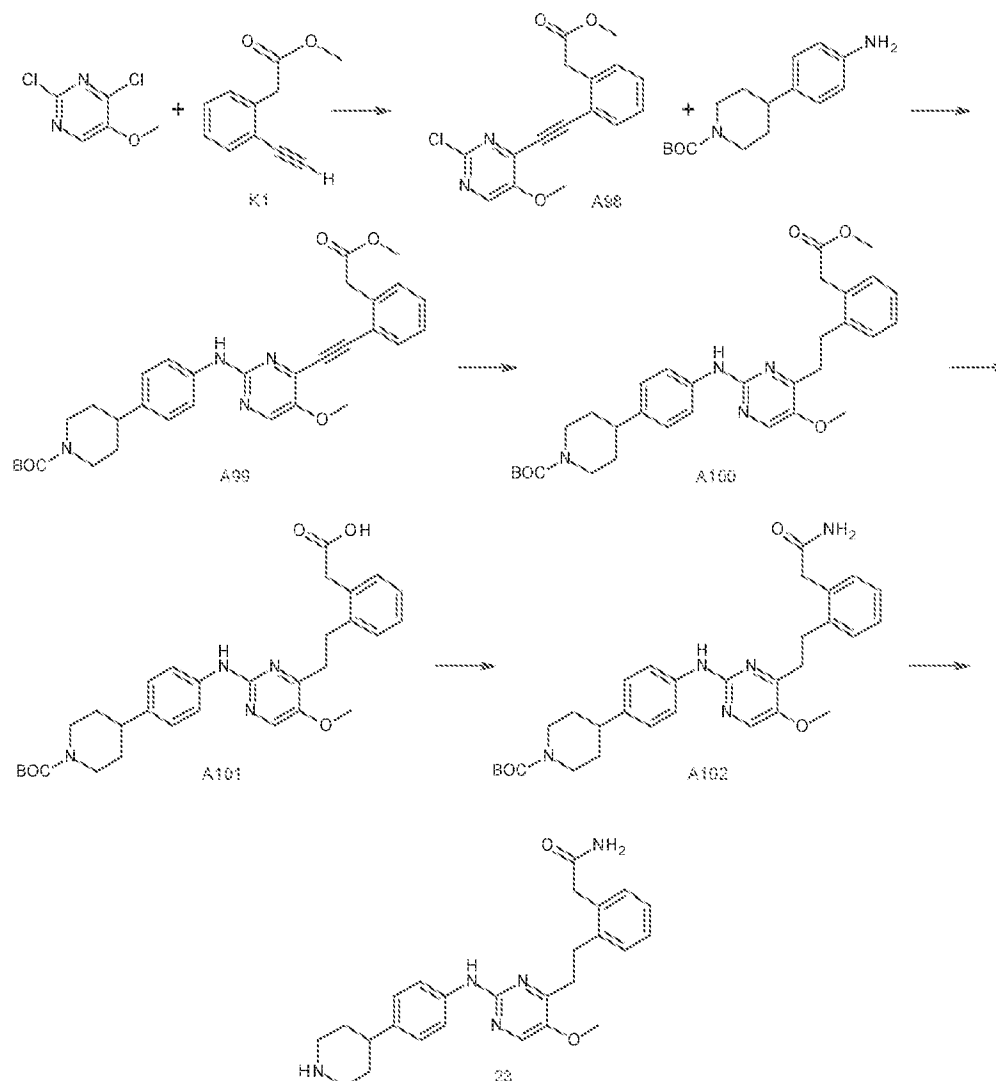
DIPEA (0.16 mL, 0.92 mmol) was added to a mixture of 2-(2-(2-(2-((4-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-6-(trifluoromethyl)phenyl)acetic acid (A96) (0.104 g, 0.160 mmol), HOBT (0.037 g, 0.27 mmol), and EDCI.HCl (0.056 g, 0.29 mmol) in DMF (5.0 mL) under a nitrogen atmosphere. After 15 minutes ammonium carbonate (0.077 g, 0.80 mmol) was added and stirring continued at room temperature for 24 hours. Additional HOBT (0.072 g, 0.53 mmol), EDCI.HCl (0.056 g, 0.29 mmol) and DIPEA (0.16 mL, 0.92 mmol) were added, then and after 15 minutes ammonium carbonate (0.121 g, 1.26 mmol) was also added and the resulting mixture stirred at room temperature for 16 hours. The resulting mixture was diluted with water (20 mL) then extracted with EtOAc (3 x 20 mL). The combined organic extracts were concentrated under reduced pressure and the residue purified using silica gel column chromatography (Biotage Isolera, SiO₂ cartridge, 0-50% EtOAc in petroleum benzine 40-60 °C) to give the title compound A97 (75 mg, 72%); ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.16 (s, 1H), 8.66 (s, 1H), 7.64 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 7.4 Hz, 1H), 7.47 (s, 1H), 7.41 (dd, J = 7.7, 7.7 Hz, 1H), 7.19 (d, J = 8.6 Hz, 2H), 6.96 (s, 1H), 4.07 (m, 2H), 3.74 (s, 2H), 3.09 (m, 4H), 2.79 (m, 2H), 2.62 (m, 1H), 1.74 (m, 2H), 1.49 (m, 2H), 1.42 (s, 9H). LCMS-A: rt 6.63 min; m/z 652.3 $[M+H]^+$.

(h) 2-(2-(2-(2-((4-(Piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-6-(trifluoromethyl)phenyl)acetamide (22)

To a solution of *tert*-butyl 4-((4-(2-(2-amino-2-oxoethyl)-3-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A97) (0.075 g, 0.12 mmol) in DCM (5 mL) was added TFA (0.20 mL, 2.6 mmol) and the resulting mixture was stirred at room temperature for 16 hours. The volatiles were evaporated under reduced pressure and the residue partitioned between water (20 mL) and EtOAc. The layers were separated and the aqueous layer extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried using a phase separation cartridge then the volatiles were removed under reduced pressure. The residue was triturated with Et₂O and the resulting precipitate collected by filtration to give the title compound 22 (56 mg, 88%); ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.22 (s, 1H), 8.67 (s, 1H), 8.29 (brs, 1H), 7.68 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.48 (s, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.19 (d, J = 8.6 Hz,

2H), 6.94 (s, 1H), 3.73 (s, 2H), 3.38 (m, 2H), 3.10 (m, 4H), 2.98 (td, $J = 12.8, 2.6$ Hz, 2H), 2.79 (tt, $J = 11.7, 2.7$ Hz, 1H), 1.93 (d, $J = 15.8$ Hz, 2H), 1.74 (qd, $J = 13.8, 4.0$ Hz, 2H).
LCMS-A: rt 4.99 min; m/z 552.3 $[M+H]^+$.

5 **Example 23: Synthesis of 2-(2-(2-(5-methoxy-2-((4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (23)**



(a) Methyl 2-(2-((2-chloro-5-methoxypyrimidin-4-yl)ethynyl)phenyl)acetate (A98)

10 A solution of methyl 2-(2-ethynylphenyl)acetate (K1) (0.35 g, 2.0 mmol) in DMF (3 mL) and Et_3N (0.70 mL, 5.0 mmol) was added to a mixture of 2,4-dichloro-5-methoxypyrimidine (0.30 g, 1.7 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.12 g, 0.17 mmol), CuI (0.032 g, 0.17 mmol) and PPh_3 (0.044 g, 0.17 mmol) in DMF (3 mL). The resulting mixture was heated under microwave irradiation at 120 °C for 15 minutes, then diluted with EtOAc and passed through a plug of Celite, washing with EtOAc (50 mL). The volatiles were removed *in vacuo* and the residue

was purified by silica gel column chromatography (Biotage Isolera, 24 g SiO₂ cartridge, 0-25% EtOAc in hexanes) to give the title compound A98 as a pale yellow solid (0.38 g, 72%); ¹H NMR (400 MHz, CDCl₃) δ 8.26 (s, 1H), 7.65 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.46-7.29 (m, 3H), 4.03 (s, 3H), 3.99 (s, 2H), 3.71 (s, 3H). LCMS-A: rt 5.92 min; *m/z* 317.1 [M+H]⁺.

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(b) *tert*-Butyl 4-(4-((5-methoxy-4-((2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A99)

To a solution of methyl 2-(2-((2-chloro-5-methoxypyrimidin-4-yl)ethynyl)phenyl)acetate (A98) (0.10 g, 0.32 mmol) in 1,4-dioxane (6 mL) was added *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (0.087 g, 0.32 mmol), Cs₂CO₃ (0.41 g, 1.3 mmol), Pd₂(dba)₃ (0.030 g, 0.032 mmol) and Xantphos (0.055 g, 0.095 mmol). The resulting mixture was degassed with nitrogen for 5 minutes, before heating under microwave irradiation for 30 minutes at 120 °C, then for 60 minutes at 120 °C. EtOAc (100 mL) was added and the mixture was washed with water (2 × 25 mL), brine (25 mL), dried (MgSO₄) and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Biotage Isolera, 40 g SiO₂ cartridge, 0-25% EtOAc in petroleum benzine 40-60 °C) to give the title compound A99 as a yellow oil (0.11 g, 64%); ¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.43-7.29 (m, 3H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.98 (s, 1H), 4.38-4.17 (m, 2H), 4.02 (s, 2H), 3.94 (s, 3H), 3.70 (s, 3H), 2.80 (t, *J* = 11.9 Hz, 2H), 2.62 (tt, *J* = 12.0, 3.3 Hz, 1H), 1.82 (d, *J* = 13.0 Hz, 2H), 1.68-1.51 (m, peak obscured), 1.49 (s, 9H). LCMS-A: rt 6.69 min; *m/z* 557.3 [M+H]⁺.

(c) *tert*-Butyl 4-(4-((5-methoxy-4-(2-(2-methoxy-2-oxoethyl)phenethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A100)

A slurry of 10% Pd/C (53% water; 0.100 g) in DMF (2 mL) was added to a solution of *tert*-butyl 4-(4-((5-methoxy-4-((2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A99) (0.112 g, 0.201 mmol) in DMF (8 mL) and TEA (1 mL), and the resulting mixture stirred under an atmosphere of hydrogen at room temperature for 16 hours. The resulting mixture was filtered through a pad of Celite, washing with EtOAc (50 mL). The solvent was removed *in vacuo* and the resultant residue purified by silica gel column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-65% EtOAc in petroleum benzine 40-60 °C) to yield the title compound A100 as a pale yellow oil (0.110 g, 98%); ¹H NMR (400 MHz, CDCl₃) δ 7.95 (s, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.24-7.14 (m, 4H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.02 (s, 1H), 4.34-4.13 (m, 2H), 3.76 (s, 3H), 3.73 (s, 2H), 3.65 (s, 3H), 3.06-2.98 (m, 2H), 2.98-2.90 (m, 2H), 2.77 (t, *J* = 12.1 Hz, 2H), 2.58 (tt, *J* = 11.9, 3.3

Hz, 1H), 1.78 (d, $J = 13.0$ Hz, 2H), 1.57 (qd, $J = 12.9, 4.5$ Hz, 2H), 1.46 (s, 9H). LCMS-A: rt 6.77 min; m/z 561.4 $[M+H]^+$.

(d) 2-(2-(2-(2-((4-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)phenyl)amino)-5-methoxypyrimidin-4-yl)ethyl)phenyl)acetic acid (A101)

LiOH.H₂O (0.025 g, 0.59 mmol) was added to a solution of *tert*-butyl 4-((5-methoxy-4-(2-(2-methoxy-2-oxoethyl)phenethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A100) (0.11 g, 0.20 mmol) in THF (7 mL), water (1.5 mL) and MeOH (1 mL) and the resulting mixture stirred at room temperature for 17 hours. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (50 mL) and saturated aqueous NaHCO₃ (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄ and the volatiles removed *in vacuo* to give the title compound A101 as a pale yellow oil (0.099 g, 92%). ¹H NMR (400 MHz, *d*₄-MeOH) δ 7.98 (s, 1H), 7.52 (d, $J = 8.5$ Hz, 2H), 7.22-7.04 (m, 6H), 4.16 (d, $J = 13.1$ Hz, 2H), 3.76 (s, 3H), 3.71 (s, 2H), 2.96-2.88 (m, 4H), 2.88-2.70 (m, 2H), 2.65-2.55 (m, 1H), 1.76 (d, $J = 12.3$ Hz, 2H), 1.59-1.49 (m, 2H), 1.46 (s, 9H). LCMS-A: rt 6.35 min; m/z 547.3 $[M+H]^+$.

(e) 2-(2-(2-(5-Methoxy-2-((4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (A102)

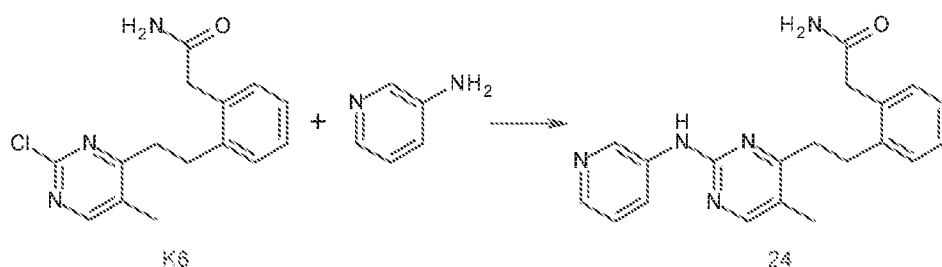
HOBt (0.032 g, 0.24 mmol), EDCI.HCl (0.045 g, 0.24 mmol) and DIPEA (0.16 mL, 0.91 mmol) were added to a solution of 2-(2-(2-(2-((4-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)phenyl)amino)-5-methoxypyrimidin-4-yl)ethyl)phenyl)acetic acid (A101) (0.099 g, 0.18 mmol) in dry THF (6 mL) and dry DMF (1 mL) under nitrogen. After 10 minutes ammonium carbonate (0.087 g, 0.91 mmol) was added in one portion and the resulting mixture was stirred at room temperature for 66 hours. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc (50 mL) and saturated aqueous NaHCO₃ (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried over MgSO₄. The solvent was removed *in vacuo* and the residue purified by silica gel column chromatography (Biotage Isolera, 24 g SiO₂ cartridge, 0-100% EtOAc in petroleum benzene 40-60 °C followed by 0-20% MeOH in EtOAc) to give the title compound A102 as a clear oil (0.094 g, 92%). ¹H NMR (400 MHz, *d*₄-MeOH) δ 8.00 (s, 1H), 7.53 (d, $J = 8.6$ Hz, 2H), 7.22 (dd, $J = 7.0, 3.8$ Hz, 1H), 7.20-7.13 (m, 3H), 7.10 (d, $J = 8.6$ Hz, 2H), 4.18 (d, $J = 13.0$ Hz, 2H), 3.78 (s, 3H), 3.65 (s, 2H), 3.10-3.00 (m, 2H), 3.00-2.92 (m, peak obscured, 2H), 2.90-2.71 (m, peak obscured, 2H), 2.62 (t, $J =$

11.9, 3.2 Hz, 1H), 1.78 (d, $J = 12.2$ Hz, 2H), 1.60-1.49 (m, 2H), 1.47 (s, 9H). LCMS-A: rt 6.20 min; m/z 546.4 $[M+H]^+$.

(f) 2-(2-(2-(5-Methoxy-2-((4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (23)

TFA (0.5 mL) was added to a solution of 2-(2-(2-(5-methoxy-2-((4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (A102) (0.091 g, 0.17 mmol) in DCM (5 mL), and the resulting solution stirred at room temperature for 17 hours. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc (30 mL) and 2 M aqueous NaOH (30 mL). The aqueous layer was extracted with EtOAc (2 $\times$ 30 mL) then the combined organic layers washed with water (30 mL), brine (30 mL) and dried over $MgSO_4$. The volatiles were removed *in vacuo* to give a yellow solid. The solid was suspended in DCM and cyclohexane and the resulting suspension filtered to give the title compound 23 as a white solid (0.031 g, 42%); 1H NMR (400 MHz, d_4 -MeOH) δ 8.04 (s, 1H), 7.54 (d, $J = 8.6$ Hz, 2H), 7.27-7.21 (m, 1H), 7.22-7.10 (m, 5H), 3.82 (s, 3H), 3.67 (s, 2H), 3.25 (m, 2H obscured by solvent), 3.11-3.03 (m, 2H), 3.03-2.95 (m, 2H), 2.87 (td, $J = 12.6, 2.6$ Hz, 2H), 2.70 (tt, $J = 12.0, 3.5$ Hz, 1H), 1.91 (d, $J = 12.6$ Hz, 2H), 1.81-1.67 (m, 2H). LCMS-A: rt 4.58 min; m/z 446.3 $[M+H]^+$.

Example 24: Synthesis of 2-(2-(2-(5-methyl-2-(pyridin-3-ylamino)pyrimidin-4-yl)ethyl)phenyl)acetamide (24)



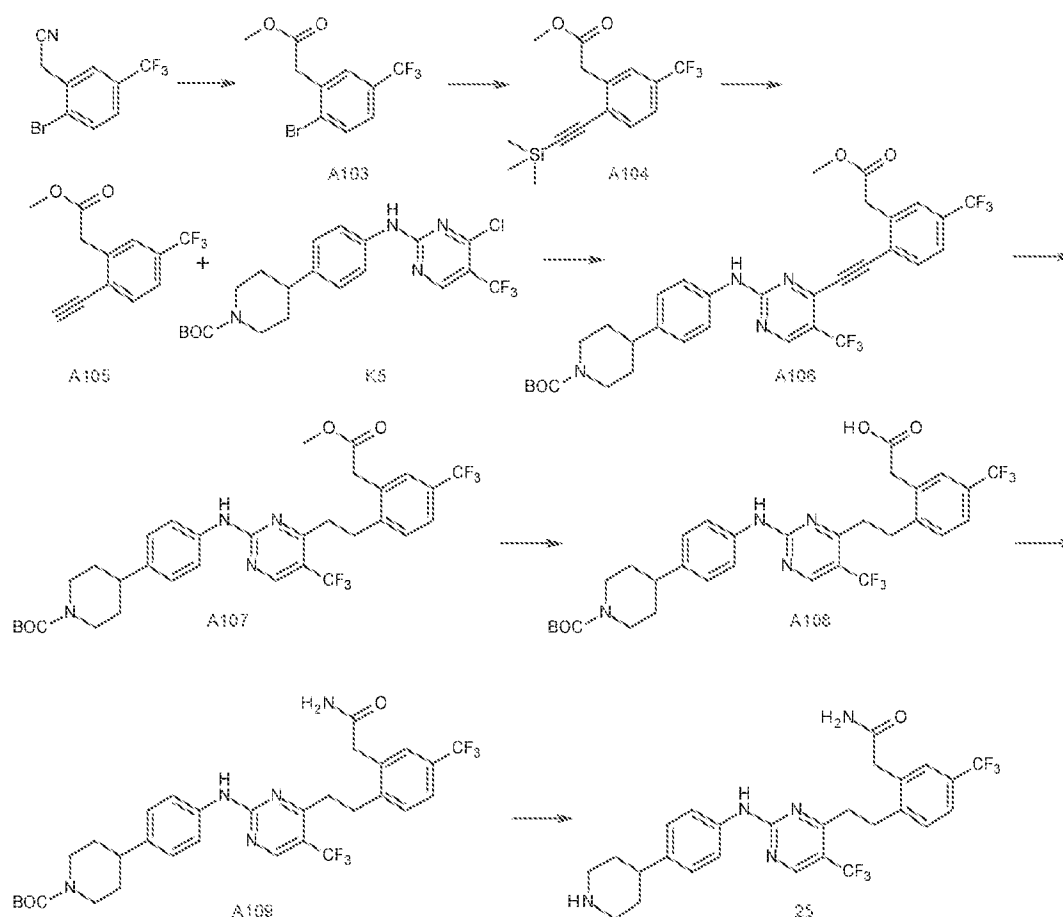
A mixture of 2-(2-(2-(2-chloro-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (K6) (0.050 g, 0.17 mmol), 3-aminopyridine (0.019 g, 0.21 mmol), $Pd(OAc)_2$ (0.8 mg, 0.003 mmol), Cs_2CO_3 (0.169 g, 0.518 mmol) and Xantphos (4 mg, 0.007 mmol) in 1,4-dioxane (1 mL) was heated under microwave irradiation at 150 $^{\circ}C$ for 10 minutes. Water (30 mL) was added and the resulting suspension was sonicated for 1 minute. The precipitate was collected by filtration then adsorbed onto silica gel and purified by silica gel column chromatography (CombiFlash Rf, 12 g SiO_2 cartridge, 0-10% MeOH in DCM) to give the title compound 24 as a light pink solid (6 mg, 10%); 1H NMR (300 MHz, d_4 -MeOH) δ 8.87 (s, 1H), 8.26 (d, $J = 7.4$ Hz, 1H), 8.16 (s, 1H), 8.10 (s, 1H), 7.34 (dd, $J = 8.1, 4.6$ Hz, 1H), 7.23-7.27 (m, 1H), 7.16-7.20 (m,

150

3H), 3.65 (s, 2H), 3.12-3.17 (m, 2H), 2.97-3.02 (m, 2H), 2.12 (s, 3H). LCMS-B: rt 4.649 min; m/z 348 $[M+H]^+$.

Example 25: Synthesis of 2-(2-(2-(2-((4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-5-(trifluoromethyl)phenyl)acetamide (25)

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(a) Methyl 2-(2-bromo-5-(trifluoromethyl)phenyl)acetate (A103)

Concentrated aqueous H_2SO_4 (1 mL) was added to a solution of 2-(2-bromo-5-(trifluoromethyl)phenyl)acetonitrile (2.00 g, 7.57 mmol) in MeOH (30 mL) and the resulting mixture heated at reflux for 14 days. The volatiles were removed *in vacuo* and the residue was taken up in EtOAc (100 mL). The resulting solution was washed with 10% aqueous $NaHCO_3$, dried ($MgSO_4$), and the volatiles removed under reduced pressure to give a clear liquid which was purified by silica gel column chromatography (Biotage Isolera, SiO_2 cartridge, 0-20% EtOAc in petroleum benzine 40-60 °C) to give the title compound A103 as a clear liquid (1.67 g, 74%); 1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.41 (dd, J = 8.3, 2.0 Hz, 1H), 3.85 (s, 2H), 3.74 (s, 3H). LCMS-A: rt 6.223 min.

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(b) Methyl 2-(5-(trifluoromethyl)-2-((trimethylsilyl)ethynyl)phenyl)acetate (A104)

A suspension of methyl 2-(2-bromo-5-(trifluoromethyl)phenyl)acetate (A103) (1.00 g, 3.36 mmol), PdCl₂(PPh₃)₂ (0.118 g, 0.168 mmol), *t*-Bu₃PH.BF₄ (0.049 g, 0.17 mmol), CuI (0.032 g, 0.17 mmol) and trimethylsilylacetylene (0.951 mL, 6.73 mmol) in anhydrous degassed DMF (10 mL) and Et₃N (10 mL) was stirred at 80 °C for 16 hours. The resulting mixture was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-10% EtOAc in petroleum benzine 40-60 °C) to give the title compound A104 as an orange liquid (0.863 g, 82%); ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 0.5 Hz, 1H), 7.50-7.44 (m, 1H), 3.87 (s, 2H), 3.7s (s, 3H), 0.24 (s, 9H). LCMS: rt 6.931 min; *m/z* 315.1 [M+H]⁺.

(c) Methyl 2-(2-ethynyl-5-(trifluoromethyl)phenyl)acetate (A105)

TBAF (1.0 M in THF; 4.29 mL, 4.29 mmol) was added to a solution of methyl 2-(5-(trifluoromethyl)-2-((trimethylsilyl)ethynyl)phenyl)acetate (A104) (0.900 g, 2.86 mmol) in THF (25 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 5 minutes before the addition of EtOAc (50 mL) and 10% aqueous NaHCO₃ (50 mL). The layers were separated and the organic phase dried (MgSO₄) then the solvent was evaporated under reduced pressure. The residue was adsorbed onto silica gel and purified by silica gel column chromatography (Biotage Isolera, SiO₂ cartridge, 0-10% EtOAc in petroleum benzine 40-60 °C) to give the title compound A105 as a light brown coloured liquid (0.498 g, 72%); ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, *J* = 8.1 Hz, 1H), 7.56 (s, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 3.89 (s, 2H), 3.71 (s, 3H), 3.40 (s, 1H). LCMS-A: rt 6.094 min; *m/z* 243.1 [M+H]⁺.

(d) tert-Butyl 4-(4-((2-(2-methoxy-2-oxoethyl)-4-(trifluoromethyl)phenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A106)

A suspension of *tert*-butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (K5) (0.300 g, 0.656 mmol), PdCl₂(PPh₃)₂ (0.046 g, 0.066 mmol), *t*-Bu₃PH.BF₄ (0.019 g, 0.066 mmol), CuI (0.013 g, 0.022 mmol) and methyl 2-(2-ethynyl-5-(trifluoromethyl)phenyl)acetate (A105) (0.191 g, 0.657 mmol) in dry degassed DMF (4 mL) and Et₃N (4 mL) was heated at 120 °C for 20 minutes under nitrogen. The volatiles were evaporated under reduced pressure and the residue adsorbed onto silica gel then purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-50% EtOAc in petroleum benzine 40-60 °C) to give the title compound A106 as a yellow solid (0.196 g, 45%); ¹H NMR (400 MHz, CDCl₃) δ 8.64 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.62 (s, 1H), 7.60-7.53 (m, 4H), 7.21 (d, *J* = 8.5 Hz, 2H), 4.25 (s, 2H), 3.99 (s, 2H), 3.72 (s, 3H), 2.80 (t, *J* =

11.9 Hz, 2H), 2.64 (m, 1H), 1.82 (d, $J = 12.8$ Hz, 2H), 1.68-1.53 (m, 2H), 1.49 (s, 9H). LCMS-A: rt 7.109 min; m/z 663.3 $[M+H]^+$.

(e) *tert*-Butyl 4-((4-((2-(2-methoxy-2-oxoethyl)-4-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A107)

A suspension of 10% Pd/C (0.050 g) and *tert*-butyl 4-((4-((2-(2-methoxy-2-oxoethyl)-4-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A106) (0.196 g, 0.295 mmol) in DMF (20 mL) was stirred under a hydrogen atmosphere at 50 Psi pressure for 24 hours. The resulting mixture was filtered through Celite, washing with MeOH (2×50 mL). The filtrate was adsorbed onto silica gel then purified by column chromatography (Biotage Isolera, SiO₂ cartridge, 0-30% EtOAc in petroleum benzene 40-60 °C) to give the title compound A107 as a light yellow liquid (0.157 g, 80%); ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 7.54 (d, $J = 8.5$ Hz, 2H), 7.52-7.43 (m, 3H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.20 (d, $J = 8.5$ Hz, 2H), 4.25 (brs, 2H), 3.79 (s, 2H), 3.70 (s, 3H), 3.17 (m, 2H), 3.09 (m, 2H), 2.81 (t, $J = 11.4$ Hz, 2H), 2.70-2.56 (m, 1H), 1.83 (d, $J = 12.7$ Hz, 2H), 1.72-1.55 (m, 2H), 1.49 (s, 9H). LCMS-A: rt 7.199 min; m/z 667.3 $[M+H]^+$.

(f) 2-(2-(2-(2-((4-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-5-(trifluoromethyl)phenyl)acetic acid (A108)

tert-Butyl 4-((4-((2-(2-methoxy-2-oxoethyl)-4-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A107) (0.157 g, 0.236 mmol) and LiOH.H₂O (0.080 g, 0.711 mmol) were suspended in MeOH (2 mL), water (2 mL) and THF (2 mL) and the resulting mixture stirred for 16 hours at room temperature. The volatiles were evaporated under reduced pressure to give the title compound A108; LCMS-A: rt 6.828 min; m/z 653.3 $[M+H]^+$.

(g) *tert*-Butyl 4-((4-((2-(2-amino-2-oxoethyl)-4-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A109)

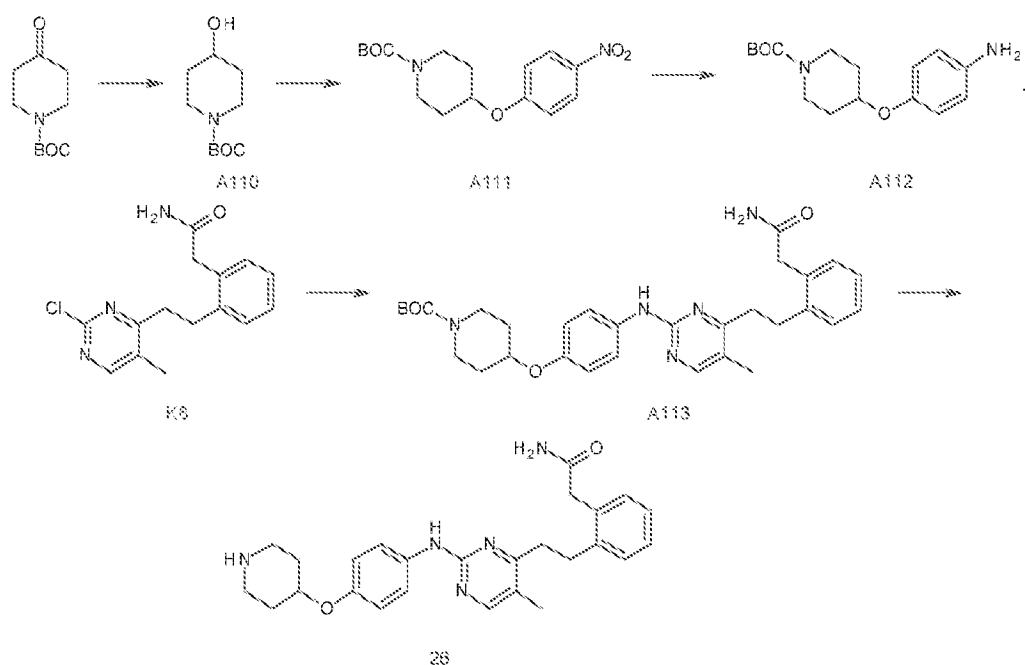
HOBt (0.042 g, 0.31 mmol), EDCI.HCl (0.049 g, 0.31 mmol) and DIPEA (0.204 mL, 1.20 mmol) were added to a solution of 2-(2-(2-(2-((4-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-5-(trifluoromethyl)phenyl)acetic acid (A108) (0.157 g, 0.240 mmol) in dry DMF (5 mL) and dry THF (5 mL). Ammonium carbonate (113 mg, 1.20 mmol) was then added and the resulting mixture was stirred at room temperature for 3 days. The mixture was diluted with EtOAc and washed with 10% aqueous NaHCO₃. The organic layer was dried (MgSO₄) and the volatiles removed under reduced pressure. The residue was adsorbed onto silica gel and purified by silica gel column

chromatography (SiO₂, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound A109 as a colourless solid (0.121 g, 77%); ¹H NMR (400 MHz, d₄-MeOH) δ 8.56 (s, 1H), 7.60 (m, 3H), 7.55-7.48 (m, 1H), 7.42 (m, 1H), 7.22 (d, J = 8.5 Hz, 2H), 4.23 (d, J = 13.3 Hz, 2H), 3.76 (s, 2H), 3.26 (m, 2H), 3.14 (m, 2H), 2.95-2.81 (m, 2H), 2.77-2.64 (m, 1H), 1.83 (m, 2H), 1.70-1.54 (m, 2H), 1.50 (s, 9H). LCMS-A: rt 6.671 min; m/z 652.3 [M+H]⁺.

(h) 2-(2-(2-(2-((4-(Piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-5-(trifluoromethyl)phenyl)acetamide (25)

TFA (1.0 mL) was added to a solution of tert-butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)-4-(trifluoromethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperidine-1-carboxylate (A109) (0.121 g, 0.185 mmol) in DCM (10 mL) and the resulting mixture stirred for 24 hours at room temperature. The volatiles were evaporated under reduced pressure and the residue was dissolved in DCM. Cyclohexane was added and the resultant precipitate was collected by vacuum filtration to give the title compound 25 as a cream solid (0.065 g, 68%); ¹H NMR (400 MHz, d₄-MeOH) δ 8.55 (s, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.57 (s, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 8.6 Hz, 2H), 4.73-4.49 (m, 2H), 3.74 (s, 2H), 3.28-3.21 (m, 2H), 3.17-3.09 (m, 2H), 2.95 (m, 2H), 2.84-2.71 (m, 1H), 1.96 (d, J = 13.6 Hz, 2H), 1.79 (m, 2H). LCMS-A: rt 4.679 min; m/z 552.3 [M+H]⁺.

Example 26: Synthesis of 2-(2-(2-(5-methyl-2-((4-(piperidin-4-yl)oxy)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (26)



(a) *tert*-Butyl 4-hydroxypiperidine-1-carboxylate (A110)

Sodium borohydride (0.95 g, 25 mmol) was added to a solution of 1-Boc-4-piperidone (2.50 g, 12.5 mmol) in MeOH (25 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours, then room temperature for 2 hours. The mixture was diluted with water (100 mL) and brine (100 mL) then extracted with EtOAc (2 × 150 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the title compound A110 as a thick colorless oil (2.47 g, 98%); ¹H NMR (400 MHz, CDCl₃) δ 3.91-3.79 (m, 3H), 3.02 (m, 2H), 1.93-1.78 (m, 2H), 1.56 (d, *J* = 4.2 Hz, 1H), 1.52-1.40 (m, 11H).

(b) *tert*-Butyl 4-(4-nitrophenoxy)piperidine-1-carboxylate (A111)

4-Fluoro-nitrobenzene (0.728 mL, 6.96 mmol) was added to a solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (A110) (1.40 g, 6.96 mmol) and potassium *tert*-butoxide (1.09 g, 9.74 mmol) in anhydrous DMSO (7.5 mL) and the resulting mixture was stirred for 2 hours at room temperature. Water and EtOAc were added to the mixture and the phases were separated. The aqueous phase was extracted with EtOAc, then the combined organic extracts were washed with water, brine and dried over Na₂SO₄. The volatiles were evaporated under reduced pressure and the residue was adsorbed onto silica gel and purified by column chromatography (SiO₂ cartridge, 0-15% EtOAc in cyclohexane) to give the title compound A111 as an oil (2.20 g, 98%); ¹H NMR (300 MHz, CDCl₃) δ 8.09 (d, *J* = 9.4 Hz, 2H), 6.91 (d, *J* = 9.3 Hz, 2H), 4.58 (m, 1H), 3.65 (m, 2H), 3.33 (m, 2H), 1.92 (m, 2H), 1.72 (m, 2H), 1.41 (s, 9H). LCMS-B: rt 8.22 min; *m/z* 323.3 [M+H]⁺.

(c) *tert*-Butyl 4-(4-aminophenoxy)piperidine-1-carboxylate (A112)

Pd/C (10%; 510 mg) was added to a solution of *tert*-butyl 4-(4-nitrophenoxy)piperidine-1-carboxylate (A111) (2.21 g, 6.86 mmol) in methanol (30 mL) and the resulting mixture was stirred under a hydrogen atmosphere overnight. The mixture was filtered through Cellite and the filtrate concentrated under reduced pressure to afford the title compound A112 (1.13 g, 56%); ¹H NMR (300 MHz, CDCl₃) δ 6.68 (d, *J* = 8.8 Hz, 2H), 6.52 (d, *J* = 8.7 Hz, 2H), 4.17 (m, 1H), 3.63 (m, 4H), 3.20 (m, 2H), 1.78 (m, 2H), 1.61 (m, 2H), 1.40 (s, 9H). LCMS-B: rt 5.05 min; *m/z* 293.2 [M+H]⁺.

(d) *tert*-Butyl 4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenoxy)piperidine-1-carboxylate (A113)

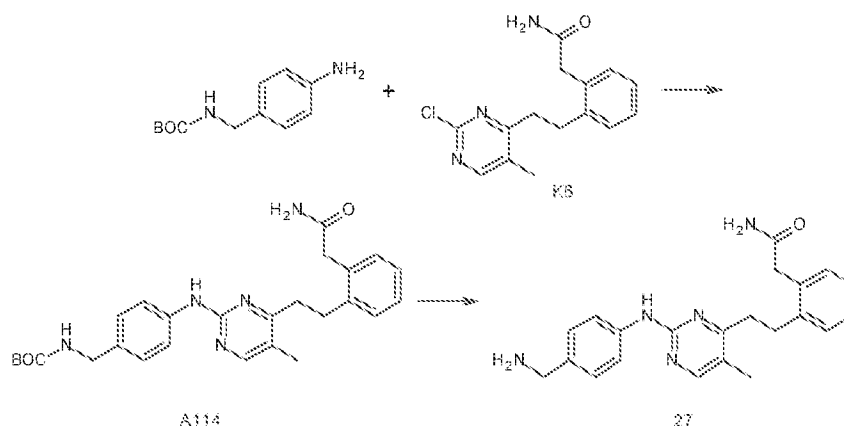
A suspension of 2-(2-(2-(2-chloro-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (K6) (0.150 g, 0.518 mmol), *tert*-butyl 4-(4-aminophenoxy)piperidine-1-carboxylate (A112) (0.182 g, 0.621 mmol), Pd(OAc)₂ (2.3 mg, 0.010 mmol), Cs₂CO₃ (0.506 g, 1.55 mmol) and Xantphos

(12 mg, 0.021 mmol) in 1,4-dioxane (2 mL) was heated under microwave irradiation at 100 °C for 45 minutes. Water (20 mL) and EtOAc (20 mL) were added and the resulting suspension sonicated for 1 minute and then filtered through Celite. The resulting mixture was extracted with EtOAc ($\times 2$) and the combined organic extracts were washed with brine, dried (MgSO₄), filtered and evaporated *in vacuo*. The residue was purified using silica gel column chromatography (CombiFlash Rf, 12 g SiO₂ cartridge, 0-10% MeOH in DCM) to give the title compound A113 as a light pink colored foam (50 mg, 18%); ¹H NMR (300 MHz, *d*₄-MeOH) δ 8.04 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 2H), 7.18-7.27 (m, 5H), 6.92 (d, *J* = 9.0 Hz, 2H), 4.47-4.52 (m, 1H), 4.10-4.13 (m, 2H), 3.67-3.77 (m, 2H), 3.65 (s, 3H), 3.37 (m, 2H), 3.09-3.15 (m, 2H), 2.93-2.98 (m, 2H), 1.91-2.03 (m, 2H), 1.64-1.78 (m, 2H), 1.51 (s, 9H). LCMS-B: rt 7.302 min; *m/z* 546 [M+H]⁺.

(e) 2-(2-(2-(5-methyl-2-((4-(piperidin-4-yloxy)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (26)

TFA (0.5 mL) was added to a cooled (water/ice bath 6 °C) solution of *tert*-butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenoxy)piperidine-1-carboxylate (A113) (0.050 g, 0.092 mmol) in DCM (2 mL) and the resulting mixture was stirred at room temperature for 4 hours. The volatiles were removed *in vacuo* then 2 M aqueous K₂CO₃ solution (10 mL) and water (10 mL) were added to the residue. The resulting suspension was sonicated for 1 minute, filtered and the filter cake dried to give the title compound 26 as a light pink solid (0.034 g, 83%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 9.17 (s, 1H), 8.12 (s, 1H), 7.62 (d, *J* = 8.9 Hz, 2H), 7.43 (s, 1H), 7.12-7.27 (m, 4H), 6.93 (s, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 4.23-4.29 (m, 1H), 3.49 (s, 2H), 3.30-3.34 (m, 2H), 2.83-3.05 (m, 7H), 2.05 (s, 3H), 1.86-1.90 (m, 2H), 1.39-1.42 (m, 2H). LCMS-B: rt 4.717 min; *m/z* 446 [M+H]⁺.

Example 27: Synthesis of 2-(2-(2-(2-((4-(aminomethyl)phenyl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (27)



(a) *tert*-Butyl 4-((4-(2-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)benzylcarbamate (A114)

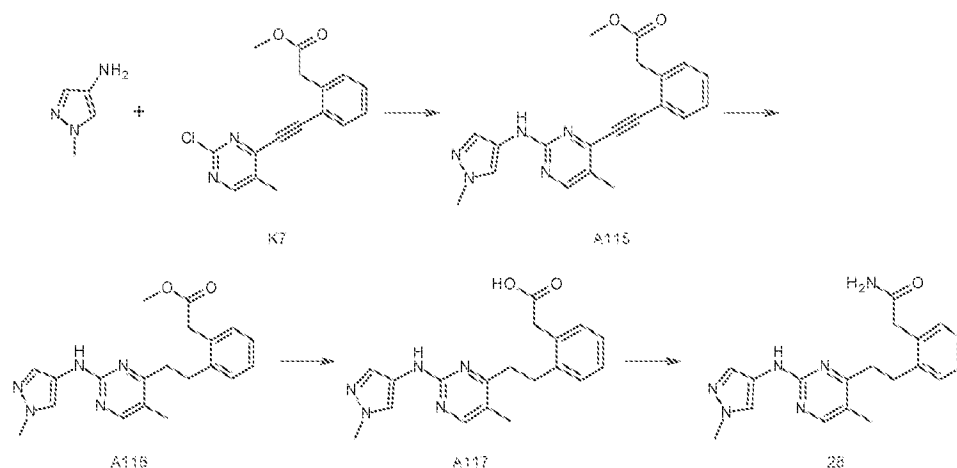
A suspension of 2-(2-(2-(2-chloro-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (K6) (0.150 g, 0.518 mmol), 4-(*N*-Boc-aminomethyl)aniline (0.145 g, 0.621 mmol), Pd(OAc)₂ (2.3 mg, 0.010 mmol), Cs₂CO₃ (0.506 g, 1.55 mmol) and Xantphos (12 mg, 0.021 mmol) in 1,4-dioxane (2 mL) was heated under microwave irradiation at 100 °C for 1.5 hours. The resulting mixture was filtered through a plug of silica gel, washing with 10% MeOH in DCM. The volatiles were removed *in vacuo* and the residue was adsorbed onto silica gel and the product purified using silica gel column chromatography (CombiFlash Rf, 12 g SiO₂ cartridge, 0-5% MeOH in DCM) to give the title compound A114 as a white solid (0.043 g, 17%); ¹H NMR (300 MHz, *d*₄-MeOH) δ 8.07 (brs, 1H), 7.59 (brs, 2H), 7.19 (m, 6H), 4.19 (brs, 2H), 3.64 (brs, 2H), 3.11 (brs, 2H), 2.95-2.98 (m, 2H), 2.08 (brs, 3H), 1.46 (brs, 9H). LCMS-B: rt 6.636 min; *m/z* 476 [M+H]⁺.

(b) 2-(2-(2-(2-((4-(Aminomethyl)phenyl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (27)

TFA (1 mL) was added to a solution of *tert*-butyl 4-((4-(2-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)benzylcarbamate (A114) (0.043 g, 0.090 mmol) in DCM (3 mL) and the resulting solution stirred at room temperature for 4 hours. The volatiles were removed *in vacuo* then 2 M aqueous K₂CO₃ (5 mL) and water (15 mL) were added to the residue. The resulting suspension was sonicated for 1 minute, filtered and the filter cake dried to give the title compound 27 as a light tan solid (0.028 g, 82%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 9.30 (s, 1H), 8.16 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.43 (s, 1H), 7.12-7.27 (m, 6H), 6.93 (s, 1H), 3.64 (s, 2H), 3.49 (s, 2H), 3.34 (brs, 2H), 3.02-3.07 (m, 2H), 2.85-2.90 (m, 2H), 2.06 (s, 3H). LCMS-B: rt 4.666 min; *m/z* 376 [M+H]⁺.

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Example 28: Synthesis of 2-(2-(2-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethynyl)phenyl)acetamide (28)



(a) Methyl 2-(2-(2-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethynyl)phenyl)acetate (A115)

To a solution of methyl 2-(2-(2-chloro-5-methylpyrimidin-4-yl)ethynyl)phenylacetate (K7) (0.200 g, 0.665 mmol) in 1,4-dioxane (8 mL) was added 1-methyl-1H-pyrazol-4-amine (0.065 g, 0.665 mmol), Cs_2CO_3 (0.867 g, 2.66 mmol), $\text{Pd}_2(\text{dba})_3$ (0.061 g, 0.067 mmol) and Xantphos (0.115 g, 0.200 mmol). The resulting mixture was degassed with nitrogen for 5 minutes before heating under microwave irradiation for 30 minutes at 120 °C. The mixture was diluted with EtOAc (100 mL), washed with water (2 × 25 mL), brine (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting brown oil was purified by silica gel column chromatography (Biotage Isolera, 40 g SiO_2 cartridge, 0-100% EtOAc in hexanes) to give the title compound A115 as a yellow solid (0.128 g, 53%). ^1H NMR (400 MHz, d_6 -DMSO) δ 9.47 (s, 1H), 8.39 (s, 1H), 7.89 (s, 1H), 7.67 (d, J = 7.4 Hz, 1H), 7.51-7.44 (m, 3H), 7.43-7.37 (m, 1H), 3.98 (s, 2H), 3.61 (s, 3H), 3.61 (s, 3H), 2.25 (s, 3H). LCMS-A: rt 5.856 min; m/z 362 $[\text{M}+\text{H}]^+$.

(b) Methyl 2-(2-(2-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethynyl)phenyl)acetate (A116)

10% Pd/C (53% water; 0.020 g) was added to a solution of methyl 2-(2-(2-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethynyl)phenyl)acetate (A115) (0.115 g, 0.318 mmol) in DMF (5 mL) and Et_3N (0.5 mL) and the resulting suspension placed under a hydrogen atmosphere and stirred at room temperature for 18 hours. The mixture was filtered through Celite, washing with EtOAc (250 mL). The combined filtrates were washed with water (100 mL) then brine (100 mL) and the washing repeated 3 times. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure and the resulting oil

purified by silica gel column chromatography (Biotage Isolera, 24 g SiO₂ cartridge, 0-100% EtOAc in hexanes) to give the title compound A116 as a yellow solid (0.097 g, 83%); ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H), 7.83 (s, 1H), 7.46 (s, 1H), 7.25-7.17 (m, 4H), 6.75 (s, 1H), 3.89 (s, 3H), 3.72 (s, 2H), 3.67 (s, 3H), 3.09 (dd, *J* = 9.5, 6.3 Hz, 2H), 2.91 (dd, *J* = 9.5, 6.4 Hz, 2H), 2.07 (s, 3H). LCMS-A: rt 5.160 min; *m/z* 366 [M+H]⁺.

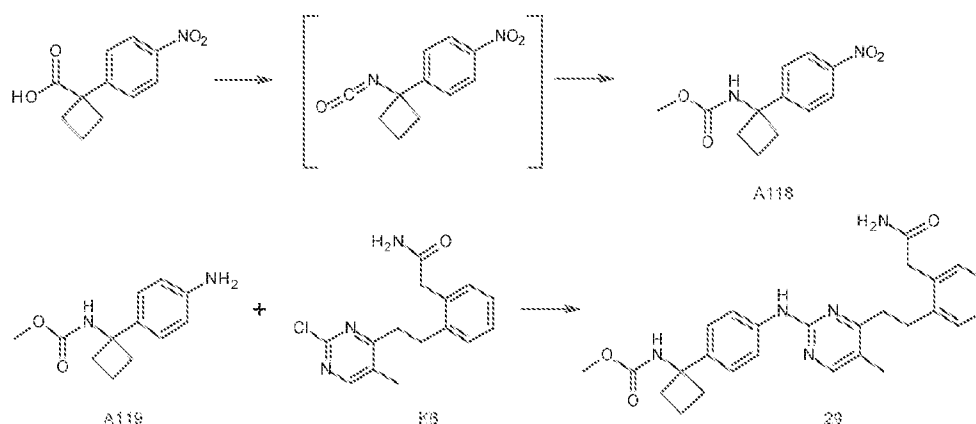
(c) 2-(2-(2-(5-Methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A117)

LiOH·H₂O (0.534 g, 12.7 mmol) was added to a solution of methyl 2-(2-(2-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetate (A116) (0.093 g, 0.25 mmol) in H₂O (1 mL) and THF (10 mL) and the resulting mixture heated at 40 °C for 18 hours. The volatiles were removed *in vacuo* and the residue was diluted with EtOAc (100 mL), washed with aqueous 2 M HCl (50 mL), water (100 mL), brine (50 mL) and dried over MgSO₄. The combined aqueous layers were additionally extracted with chloroform/isopropanol (4 : 1, 2 × 50 mL). The organic extracts were then combined, dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the title compound A117 as a yellow solid (0.067 g, 75%); LCMS-A: rt 4.718 min; *m/z* 352 [M+H]⁺.

(d) 2-(2-(2-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (28)

HOBt (0.074 g, 0.55 mmol), EDCI·HCl (0.117 g, 0.610 mmol) and DIPEA (0.16 mL, 0.94 mmol) were added to a solution of 2-(2-(2-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A117) (0.066 g, 0.19 mmol) in dry DMF (5 mL) under an atmosphere of nitrogen. After 10 minutes ammonium carbonate (0.180 g, 1.88 mmol) was added in one portion and the resulting mixture stirred for 18 hours at room temperature. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc (50 mL) and aqueous saturated NaHCO₃ (50 mL). The aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (25 mL) and dried over Na₂SO₄. The solvent was removed *in vacuo* and the residue purified by silica gel column chromatography (Biotage Isolera, 24 g SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C followed by 0-30% MeOH in EtOAc) to give the title compound 28 as a yellow solid (0.040 g, 61%); ¹H NMR (400 MHz, *d*₇-DMSO) δ 9.18 (s, 1H), 8.10 (s, 1H), 7.86 (s, 1H), 7.43 (s, 2H), 7.28-7.10 (m, 4H), 6.93 (s, 1H), 3.78 (s, 3H), 3.49 (s, 2H), 3.07-2.98 (m, 2H), 2.90-2.81 (m, 2H), 2.04 (s, 3H). LCMS-A: rt 4.464 min; *m/z* 351 [M+H]⁺.

Example 29: Synthesis of methyl 1-(4-(4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-ylamino)phenyl)cyclobutylcarbamate (29)



(a) Methyl 1-(4-nitrophenyl)cyclobutylcarbamate (A118)

A drop of DMF and oxalyl chloride (0.283 mL, 3.30 mmol) was added to a stirred solution of 1-(4-nitrophenyl)cyclobutanecarboxylic acid (503 mg, 2.27 mmol) in DCM (7 mL) under a nitrogen atmosphere and the resulting mixture was stirred for 25 minutes at room temperature. The volatiles were removed *in vacuo* and the residue was dissolved in acetone (4.50 mL). A solution of sodium azide (400 mg, 5.23 mmol) in water (4.50 mL) was added with the temperature maintained below 0 °C. After stirring for 30 minutes, the mixture was diluted with chloroform and washed with cold water and saturated aqueous NaCl. The organics were dried with Na₂SO₄ and concentrated carefully. Toluene (10.0 mL) was added and the resulting solution was heated at 80 °C for 1 hour. MeOH (10 mL) was added and the resulting mixture heated at 60 °C for 1.5 hours under a nitrogen atmosphere. The volatiles were evaporated under reduced pressure then the residue adsorbed on silica gel and purified using silica gel column chromatography (CombiFlash Rf, SiO₂ cartridge, 0-20% EtOAc in cyclohexane) to give the title compound A118 (404 mg, 71%); ¹H NMR (300 MHz, CDCl₃); δ 8.17 (d, *J* = 9.0 Hz, 2H), 7.59 (d, *J* = 8.9 Hz, 2H), 5.74 (br s, 1H), 3.57 (s, 3H), 2.52 (m, 4H), 2.15 (m, 1H), 1.92 (m, 1H); LCMS-B: rt 6.55 min; *m/z* 251.3 [M+H]⁺.

(b) Methyl 1-(4-aminophenyl)cyclobutylcarbamate (A119)

A suspension of Pd/C (10%) (120 mg) and methyl 1-(4-nitrophenyl)cyclobutylcarbamate (A118) (404 mg, 1.61 mmol) in MeOH (17.0 mL) was vigorously stirred overnight under a hydrogen atmosphere. The resulting mixture was filtered through Celite then the filtrate concentrated *in vacuo*. The residue was purified using silica gel column chromatography (CombiFlash Rf, SiO₂ cartridge, 0-75% EtOAc in cyclohexane) to give the title compound A119 (237 mg, 67%); ¹H NMR (300 MHz, CDCl₃); δ 7.21 (d, *J* = 8.3 Hz, 2H), 6.63 (d, *J* = 8.5

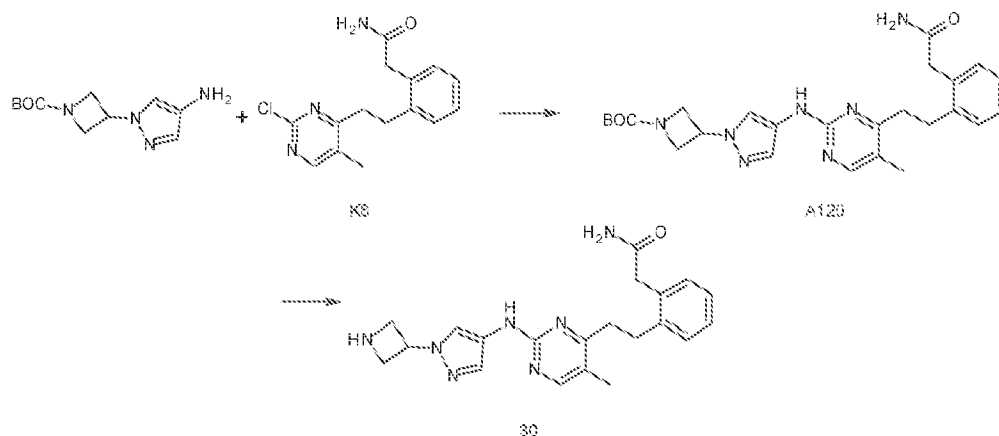
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Hz, 2H), 5.57 (brs, 1H), 3.66 (s, 2H), 3.58 (s, 3H), 2.48 (m, 4H), 2.02 (m, 1H), 1.80 (m, 1H).
LCMS-B: rt 2.35 min; m/z 221.2 $[M+H]^+$.

(c) Methyl 1-(4-(4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-ylamino)phenyl)cyclobutylcarbamate (29)

A suspension of 2-(2-(2-(2-chloro-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (K6) (150 mg, 0.518 mmol), $Pd(OAc)_2$ (11.6 mg, 0.052 mmol), Xantphos (45.0 mg, 0.078 mmol), Cs_2CO_3 (486 mg, 1.49 mmol) and methyl 1-(4-aminophenyl)cyclobutylcarbamate (A119) (125 mg, 0.569 mmol) in 1,4-dioxane (4.0 mL) was heated under microwave irradiation for 10 minutes at 150 °C. The resulting mixture was filtered through Celite, and washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by semi preparative HPLC to give the title compound 29 (86 mg, 35%); 1H NMR (300 MHz, $CDCl_3$): δ 8.17 (br s, 1H), 7.56 (m, 2H), 7.42 (m, 2H), 7.28 (4H, obscured by solvent peak), 5.65 (br s, 1H), 5.42 (br s, 1H), 5.30 (br s, 1H), 3.70 (s, 2H), 3.61 (s, 3H), 3.13 (m, 2H), 2.99 (m, 2H), 2.57 (s, 3H), 2.12-1.62 (m, 6H). LCMS-B: rt 6.28 min; m/z 474.2 $[M+H]^+$.

Example 30: Synthesis of 2-(2-(2-(2-((1-(azetidin-3-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (30)



(a) *tert*-Butyl 3-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)-1H-pyrazol-1-yl)azetidine-1-carboxylate (A120)

A suspension of 2-(2-(2-(2-chloro-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (K6) (0.150 g, 0.518 mmol), 4-amino-1-(1-Boc-azetidin-3-yl)-1H-pyrazole (0.195 g, 0.777 mmol), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol), Cs_2CO_3 (0.506 g, 1.55 mmol) and Xantphos (11.9 mg, 0.021 mmol) in 1,4-dioxane (2 mL) was heated under microwave irradiation at 100 °C for 1.5 hours. 4-Amino-1-(1-Boc-azetidin-3-yl)-1H-pyrazole (65.0 mg, 0.259 mmol) was added and the mixture was heated for a further 1 hour at 100 °C. The resulting mixture was adsorbed onto silica gel and purified using column chromatography (CombiFlash Rf, 12 g SiO_2

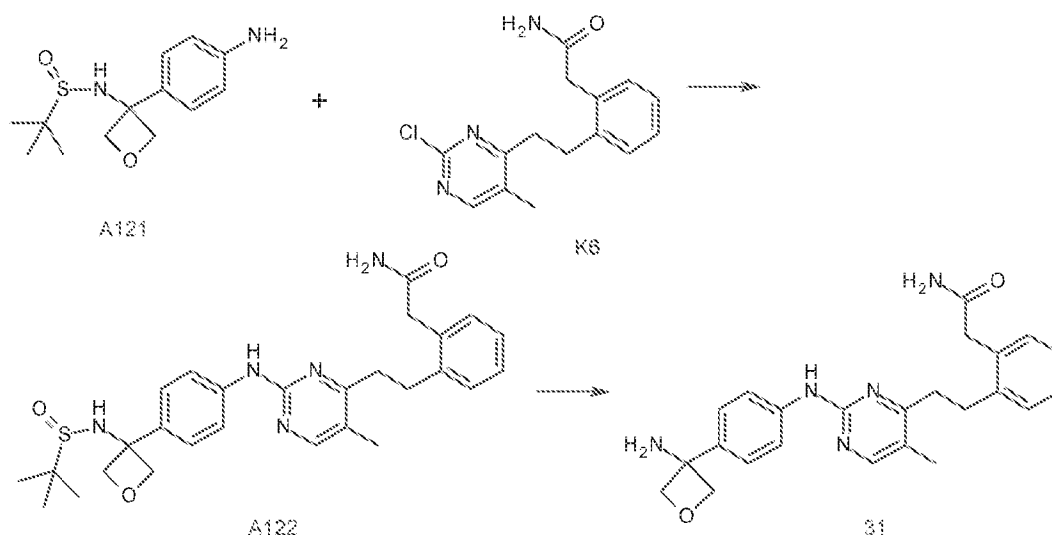
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cartridge, 0-5% MeOH in DCM) to give the title compound A120 as a light pink colored foam (0.050 g, 19%); ^1H NMR (300 MHz, d_4 -MeOH) δ 8.06 (d, J = 8.8 Hz, 2H), 7.66 (s, 1H), 7.16-7.27 (m, 4H), 5.12-5.21 (m, 1H), 4.39 (t, J = 8.7 Hz, 2H), 4.25-4.30 (m, 2H), 3.65 (s, 2H), 3.32 (s, 1H), 3.10-3.16 (m, 2H), 2.95-3.00 (m, 2H), 2.10 (s, 3H), 1.48 (s, 9H). LCMS-B: rt 6.184 min; m/z 492 $[\text{M}+\text{H}]^+$.

(b) 2-(2-(2-(2-((1-(Azetidin-3-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (30)

TFA (1 mL) was added to a solution of *tert*-butyl 3-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)-1H-pyrazol-1-yl)azetidine-1-carboxylate (A120) (0.050 g, 0.102 mmol) in DCM (3 mL) and the resulting mixture stirred at room temperature for 3 hours. The volatiles were removed under reduced pressure then 2 M aqueous K_2CO_3 (5 mL) and water (15 mL) were added to the residue. The resulting aqueous solution was extracted with EtOAc (3×15 mL) then the combined organic extracts were dried (MgSO_4), filtered, evaporated *in vacuo* and adsorbed onto silica gel. The product was purified using column chromatography (CombiFlash Rf, 4 g SiO_2 Cartridge, 5-50% MeOH in DCM) to give the title compound 30 as a yellow oil (0.6 mg, 1.5%); ^1H NMR (300 MHz, d_4 -MeOH) δ 8.08 (d, J = 2.0 Hz, 2H), 7.66 (s, 1H), 7.18-7.26 (m, 4H), 5.19-5.26 (m, 1H), 4.67 (t, J = 9.0 Hz, 1H), 4.54 (dd, J = 9.4, 5.3 Hz, 1H), 4.56 (t, J = 9.8 Hz, 1H), 4.30 (dd, J = 10.4, 5.5 Hz, 1H), 3.65 (s, 2H), 3.14 (t, J = 2.9 Hz, 2H), 2.98-3.01 (m, 2H), 1.93 (s, 3H). LCMS-B: rt 4.426 min; m/z 392 $[\text{M}+\text{H}]^+$.

Example 31: Synthesis of 2-(2-(2-(2-(4-(3-aminooxetan-3-yl)phenylamino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (31)



(a) *N*-(3-(4-Aminophenyl)oxetan-3-yl)-2-methylpropane-2-sulfonamide (A121)

Compound prepared using the procedure described in US2011/0172203 A1 (paragraphs 2413 to 2417, which are hereby incorporated by reference)

5 (b) 2-(2-(2-(2-(4-(3-(1,1-Dimethylethylsulfonamido)oxetan-3-yl)phenylamino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (A122)

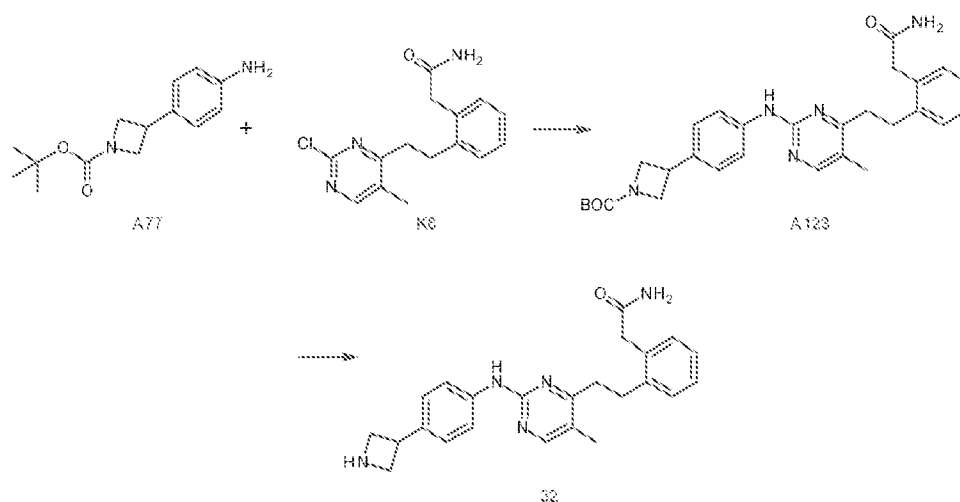
A suspension of 2-(2-(2-(2-chloro-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (K6) (200 mg, 0.690 mmol), Pd(OAc)₂ (16 mg, 0.069 mmol), Xantphos (59.9 mg, 0.104 mmol), Cs₂CO₃ (648 mg, 1.99 mmol) and *N*-(3-(4-aminophenyl)oxetan-3-yl)-2-methylpropane-2-sulfonamide (A121) (204 mg, 0.759 mmol) in 1,4-dioxane (1.73 mL) was heated under microwave irradiation for 10 minutes at 150 °C under nitrogen. The resulting mixture was filtered through Celite, washing with EtOAc. The volatiles were removed *in vacuo* and the residue was purified by silica gel column chromatography (CombiFlash Rf, SiO₂ cartridge, 0-30% MeOH in DCM) to give the title compound A122 (102 mg, 28%); ¹H NMR (300 MHz, *d*₂-MeOH) δ 8.07 (s, 1H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.19 (m, 4H), 5.17 (d, *J* = 6.6 Hz, 1H), 5.07 (d, *J* = 6.5 Hz, 1H), 5.03 (d, *J* = 6.7 Hz, 1H), 4.93 (d, *J* = 6.4 Hz, 1H), 3.64 (s, 2H), 3.12 (m, 2H), 2.95 (m, 2H), 2.07 (s, 3H), 1.27 (s, 9H). LCMS-B: rt 5.80 min; 522.2 *m/z* [M+H]⁺.

20 (c) 2-(2-(2-(2-(4-(3-Aminooxetan-3-yl)phenylamino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (31)

TFA (0.5 mL) was added to a solution of 2-(2-(2-(2-(4-(3-(1,1-dimethylethylsulfonamido)oxetan-3-yl)phenylamino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (A122) (30 mg, 0.058 mmol) in DCM (3.0 mL) under a nitrogen atmosphere and the resulting mixture stirred at room temperature for 30 minutes, then at 35 °C overnight. The volatiles were evaporated under reduced pressure, keeping the temperature below 30 °C. The resulting oil was purified by semi preparative HPLC, to give the title compound 31 (5.0 mg, 21%); ¹H NMR (300 MHz, *d*₂-MeOH) δ 8.24 (br s, 1H), 8.15 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.22 (m, 4H), 5.13 (d, *J* = 7.7 Hz, 2H), 4.97 (d, *J* = 7.7 Hz, 2H), 3.67 (s, 2H), 3.16 (m, 2H), 3.00 (m, 2H), 2.13 (s, 3H). LCMS: rt 4.72 min; *m/z* 418.2 [M+H]⁺.

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Example 32: Synthesis of 2-(2-(2-(2-((4-(azetidin-3-yl)phenyl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (32)



(a) *tert*-Butyl 3-(4-((2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenylazetidine-1-carboxylate (A123)

A suspension of 2-(2-(2-(2-chloro-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (K6) (0.150 g, 0.518 mmol), *tert*-butyl 3-(4-aminophenyl)azetidine-1-carboxylate (A77) (0.141 g, 0.569 mmol), Pd(OAc)₂ (2.3 mg, 0.010 mmol), Cs₂CO₃ (0.506 g, 1.55 mmol) and Xantphos (11.9 mg, 0.021 mmol) in 1,4-dioxane (2 mL) was heated under microwave irradiation at 100 °C for 1.5 hours. The resulting mixture was dry loaded onto silica gel and purified using silica gel column chromatography (CombiFlash Rf, 12 g SiO₂ Cartridge, 0-5% MeOH in DCM) to give the title compound A123 as a light orange foam (0.087 g, 33%); ¹H NMR (300 MHz, CDCl₃) δ 8.12 (s, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.53 (s, 1H), 7.26-7.28 (m, 6H), 5.59 (brs, 2H), 4.32 (t, *J* = 8.7 Hz, 2H), 3.97 (dd, *J* = 6.0, 8.4 Hz, 2H), 3.70-3.76 (m, 3H), 3.08-3.13 (m, 2H), 2.90-2.98 (m, 2H), 2.13 (s, 3H), 1.48 (s, 9H). LCMS-B: *rt* 7.208 min; *m/z* 502 [M+H]⁺.

(b) 2-(2-(2-(2-((4-(Azetidin-3-yl)phenyl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (32)

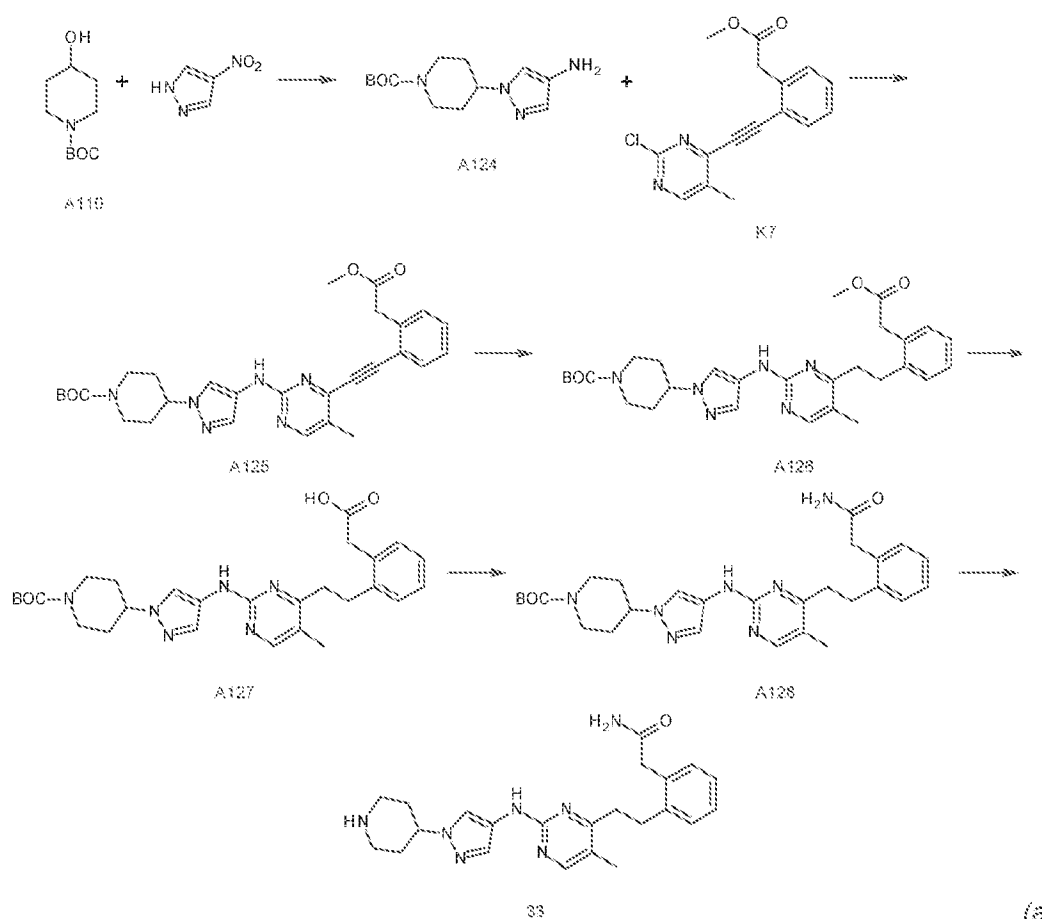
TFA (1 mL) was added to a solution of *tert*-butyl 3-(4-((2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenylazetidine-1-carboxylate (A123) (0.087 g, 0.17 mmol) in DCM (3 mL) and the resulting mixture stirred at room temperature for 3 hours. The volatiles were removed *in vacuo* then 2 M aqueous K₂CO₃ solution (5 mL) and water (15 mL) were added to the residue. The resulting suspension was sonicated for 1 minute, filtered and the filter cake dried. The resulting residue was purified by semi preparative HPLC to give the title compound 32 as a light tan solid (7.6 mg, 10%); ¹H NMR (300 MHz, *d*₇-MeOH) δ 8.12 (s, 1H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.18-7.28 (m, 4H), 4.31-4.39 (m, 2H).

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4.19-4.27 (m, 3H), 3.66 (s, 2H), 3.13-3.18 (m, 2H), 2.96-3.01 (m, 2H), 2.12 (s, 3H). LCMS-B: rt 4.725 min; m/z 402 $[M+H]^+$.

Example 33: Synthesis of 2-{2-[2-{5-Methyl-2-[(1-{piperidin-4-yl}-1H-pyrazol-4-yl)amino]pyrimidin-4-yl)ethyl]phenyl}acetamide (33)

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tert-Butyl 4-(4-amino-1H-pyrazol-1-yl)piperidine-1-carboxylate (A124)

Diisopropyl azodicarboxylate (3.60 mL, 18.3 mmol) was added dropwise to a solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (A110) (2.45 g, 12.2 mmol), 4-nitro-1H-pyrazole (1.38 g, 12.2 mmol) and PPh_3 (4.79 g, 18.3 mmol) in THF (25 mL) at 0 °C. The resulting mixture was maintained at this temperature for 10 minutes and then warmed to room temperature at which it was stirred for 6 days. The mixture was diluted with hexanes (80 mL) and EtOAc (20 mL) and stirred for 5 hours at room temperature before filtering, washing the filler cake with hexanes (50 mL) and concentrating the filtrate *in vacuo*. The resulting oil was purified by silica gel column chromatography (Biotage Isolera, 2 × 40 g SiO_2 cartridges, 0-50% EtOAc in cyclohexane) to give a residue that was dissolved in EtOH (200 mL). 10% Pd/C (53% water; 0.500 g) was added and the resulting suspension stirred under an atmosphere of hydrogen at room temperature for 18 hours. The mixture was filtered through

Celite, washing with EtOAc (ca. 100 mL) and then the filtrate was concentrated under reduced pressure. The resulting oil was dissolved in EtOAc (200 mL) and washed with water (2 × 100 mL) and then aqueous 2 M HCl (100 mL). The acidic layer was basified with aqueous 2 M NaOH to pH 13 and extracted with EtOAc (2 × 100 mL). The combined organic layers from the basified extraction were washed with brine (50 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the title compound A124 as a purple oil (1.39 g, 34%); ¹H NMR (400 MHz, CDCl₃) δ 7.15 (d, J = 0.9 Hz, 1H), 7.02 (d, J = 0.9 Hz, 1H), 4.20 (s, 2H), 4.11 (m, 1H), 2.95-2.76 (m, 4H), 2.11-2.02 (m, 2H), 1.83 (qd, J = 12.3, 4.5 Hz, 2H), 1.46 (s, 9H).

(b) *tert*-Butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)-5-methylpyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A125)

A suspension of methyl 2-(2-((2-chloro-5-methylpyrimidin-4-yl)ethynyl)phenyl)acetate (K7) (0.100 g, 0.333 mmol), *tert*-butyl 4-(4-amino-1H-pyrazol-1-yl)piperidine-1-carboxylate (A124) (0.089 g, 0.333 mmol), Cs₂CO₃ (0.433 g, 1.33 mmol), Pd₂(dba)₃ (0.030 g, 0.033 mmol) and Xantphos (0.058 g, 0.100 mmol) in 1,4-dioxane (6 mL) was degassed with nitrogen for 5 minutes before heating under microwave irradiation for 30 minutes at 120 °C. The resulting mixture was diluted with EtOAc (100 mL) and washed with water (2 × 25 mL), brine (25 mL), dried (Na₂SO₄) then concentrated under reduced pressure. The resulting brown oil was purified by silica gel column chromatography (Biotage Isolera, 24 g SiO₂ cartridge, 0-100% EtOAc in hexanes) to give the title compound A125 as a yellow foam (0.096 g, 54%); ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 7.89 (s, 1H), 7.57 (dd, J = 7.6, 1.3 Hz, 1H), 7.44 (s, 1H), 7.36-7.22 (m, 2H), 7.19 (s, 1H), 6.87 (s, 1H), 4.22-4.12 (m, 3H), 3.88 (s, 2H), 3.62 (s, 3H), 2.82 (t, J = 11.9 Hz, 2H), 2.26 (s, 3H), 2.11-2.02 (m, 2H), 1.89 (qd, J = 12.4, 4.4 Hz, 2H), 1.40 (s, 9H). LCMS-A: rt 6.358 min; m/z 531 [M+H]⁺.

(c) *tert*-Butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A126)

A suspension of 10% Pd/C (53% water; 0.020 g) and *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)-5-methylpyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A125) (0.092 g, 0.17 mmol) in DMF (5 mL) and Et₃N (0.5 mL) was stirred at room temperature for 18 hours under a hydrogen atmosphere. The resulting mixture was filtered through Celite, and the filter cake washed with EtOAc (250 mL). The combined filtrates were washed with water (3 × 100 mL) and brine (3 × 100 mL). The organic layer was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel column chromatography (Biotage Isolera, 40 g SiO₂ cartridge, 0-100%

EtOAc in hexanes) to give the title compound A126 as a pale brown oil (80 mg, 86%); ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 7.89 (s, 1H), 7.51 (d, J = 0.4 Hz, 1H), 7.25-7.15 (m, 4H), 6.92 (s, 1H), 4.31-4.15 (m, 3H), 3.70 (s, 2H), 3.66 (s, 3H), 3.08 (dd, J = 9.4, 6.3 Hz, 2H), 2.90 (dd, J = 9.5, 6.3 Hz, 4H), 2.15-2.07 (m, 2H), 2.05 (s, 3H), 2.00-1.85 (m, 2H), 1.46 (s, 9H). LCMS-A: rt 6.195 min; m/z 535.3 [M+H]⁺.

(d) 2-(2-(2-(2-((1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetic acid (A127)

LiOH.H₂O (0.302 g, 7.20 mmol) was added to a solution of *tert*-butyl 4-(4-((4-(2-(2-methoxy-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A126) (0.077 g, 0.14 mmol) in H₂O (1 mL) and THF (10 mL) and the resulting mixture was heated to 40 °C for 18 hours. The volatiles were removed *in vacuo* and the residue was diluted with EtOAc (100 mL), washed with aqueous 2 M HCl (50 mL), water (100 mL), brine (50 mL) and dried over MgSO₄. The volatiles were removed *in vacuo* to give the title compound A127 as a pale yellow solid (0.068 g, 91%); LCMS-A: rt 5.366 min; m/z 521 [M+H]⁺.

(e) *tert*-Butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A128)

HOBt (0.051 g, 0.379 mmol), EDCI.HCl (0.081 g, 0.42 mmol) and DIPEA (0.11 mL, 0.65 mmol) were added to a solution of 2-(2-(2-(2-((1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetic acid (A127) (0.068 g, 0.131 mmol) in dry DMF (5 mL) under an atmosphere of nitrogen. After 10 minutes ammonium carbonate (0.126 g, 1.31 mmol) was added in one portion and the resulting mixture stirred for 18 hours at room temperature. Additional HOBt (0.051 g, 0.38 mmol), EDCI.HCl (0.081 g, 0.42 mmol), DIPEA (0.11 mL, 0.65 mmol) and ammonium carbonate (0.126 g, 1.31 mmol) were added to the reaction mixture and the mixture stirred for 12 days at room temperature. The volatiles were removed *in vacuo* then the residue diluted with EtOAc (50 mL) and washed with saturated aqueous NaHCO₃ (50 mL). The aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (25 mL) and dried over Na₂SO₄. The solvent was removed *in vacuo* to afford a yellow oil that was purified by silica gel column chromatography (Biotage Isolera, 25 g SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C followed by 0-30% MeOH in EtOAc) to give the title compound A127 as an off white solid (0.044 g, 65%); ¹H NMR (400 MHz, CDCl₃) δ 8.05 (s, 1H), 7.85 (s, 1H), 7.50 (d, J = 0.5 Hz, 1H), 7.26-7.17 (m, 5H), 5.79 (s, 1H), 5.62 (s, 1H), 4.26-4.19 (m,

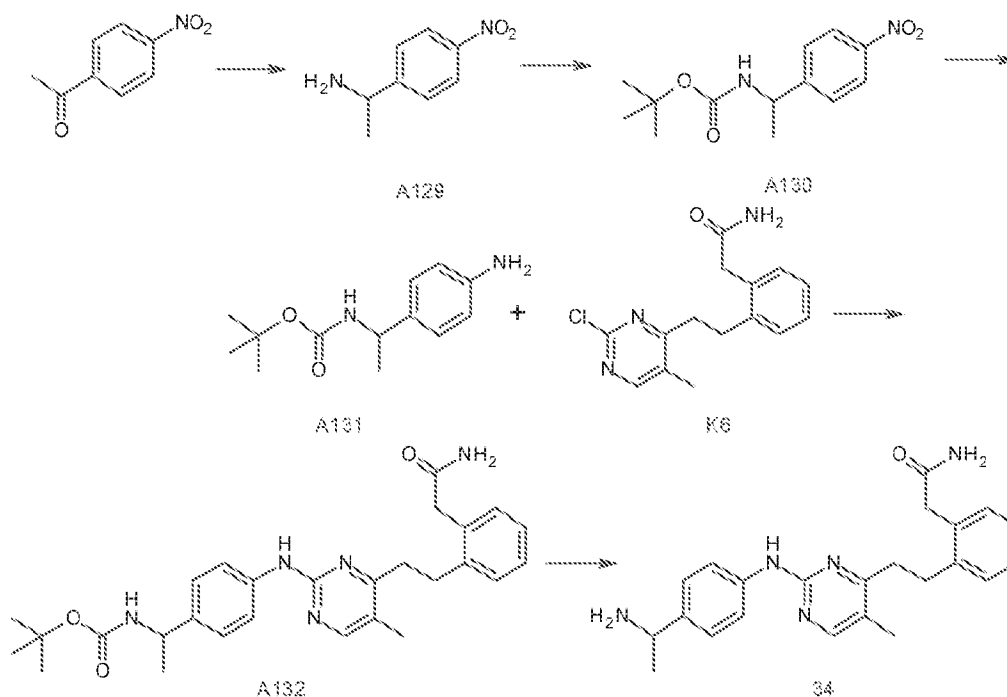
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3H), 3.65 (s, 2H), 3.07 (dd, $J = 9.5, 6.2$ Hz, 2H), 2.93-2.82 (m, 4H), 2.15-2.08 (m, 2H), 2.04 (s, 3H), 1.91 (qd, $J = 12.3, 4.3$ Hz, 2H), 1.46 (s, 9H). LCMS-A: rt 5.178 min; m/z 520 $[M+H]^+$.

(f) 2-(2-(2-(5-methyl-2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (33)

TFA (0.5 mL) was added to a solution of *tert*-butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A128) (0.040 g, 0.077 mmol) in DCM (5 mL) and the resulting mixture stirred for 18 hours at room temperature. The volatiles were evaporated under reduced pressure and the residue partitioned between 2 M NaOH (10 mL) and EtOAc (25 mL). The organic layer was separated and washed with water (25 mL), brine (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound 33 as an off white solid (0.015 g, 49%); 1H NMR (400 MHz, d_4 -MeOH) δ 8.05 (s, 1H), 7.99 (d, $J = 0.5$ Hz, 1H), 7.56 (d, $J = 0.6$ Hz, 1H), 7.27-7.22 (m, 1H), 7.22-7.15 (m, 3H), 4.23 (tt, $J = 11.7, 4.1$ Hz, 1H), 3.64 (s, 2H), 3.23-3.09 (m, 4H), 3.02-2.91 (m, 2H), 2.76 (td, $J = 12.8, 2.5$ Hz, 2H), 2.14-2.05 (m, 5H), 1.98-1.85 (m, 2H). LCMS-A: rt 3.968 min; m/z 420 $[M+H]^+$.

Example 34: Synthesis of 2-(2-(2-(2-((4-(1-aminoethyl)phenyl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (34)



(a) 1-(4-Nitrophenyl)ethanamine (A129)

A suspension of 4'-nitroacetophenone (5.00 g, 30.3 mmol) and ammonium acetate (28.4 g, 378 mmol) in MeOH (75 mL) was stirred at room temperature for 20 minutes. Sodium cyanoborohydride (1.38 g, 21.2 mmol) was added and the resulting mixture stirred for 48 hours. Aqueous HCl (6 M, 40 mL) was added and the mixture was filtered. The filtrate was washed with Et₂O (3 × 40 mL) then the aqueous phase was basified to pH 10 using KOH. The basified aqueous layer was extracted with DCM (3 × 30 mL) and the combined organic phases were dried (MgSO₄), filtered and evaporated *in vacuo* to give the title compound A129 as an amorphous orange solid (3.00 g, 60%); ¹H NMR (300 MHz, CDCl₃) δ 8.22 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 4.27-4.33 (m, 1H), 2.20 (brs, 2H), 1.45 (d, *J* = 6.6 Hz, 3H).

(b) *tert*-Butyl (1-(4-nitrophenyl)ethyl)carbamate (A130)

A solution of di-*tert*-butyl dicarbonate (3.94 g, 18.1 mmol) in DCM (50 mL) was slowly added over 1 hour by syringe pump to a solution of 1-(4-nitrophenyl)ethanamine (A129) (3.00 g, 18.05 mmol) and Et₃N (3.77 mL, 27.1 mmol) in DCM (120 mL). The resulting mixture was then stirred at room temperature for 20 hours. Water (50 mL) was added and the mixture extracted with DCM (x 2). The combined organic extracts were washed with water, brine, dried (Na₂SO₄), filtered and the volatiles removed *in vacuo*. The residue was purified using silica gel column chromatography (CombiFlash Rf, 120 g SiO₂ cartridge, 10-20% EtOAc in cyclohexane) to give the title compound A130 as a white solid (3.78 g, 78%); ¹H NMR (300 MHz, CDCl₃) δ 8.21 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 4.87 (s, 2H), 1.38-1.58 (m, 12H).

(c) *tert*-Butyl (1-(4-aminophenyl)ethyl)carbamate (A131)

A suspension of 10% Pd/C (1.25 g) and *tert*-butyl (1-(4-nitrophenyl)ethyl)carbamate (A130) (3.78 g, 14.2 mmol) in EtOAc (50 mL) was stirred under a hydrogen atmosphere for 3 hours. The resulting solution was filtered through a pad of Celite, washing with EtOAc, then the filtrate was concentrated *in vacuo* to give the title compound A131 as a viscous oil (3.01 g, 89%); ¹H NMR (300 MHz, CDCl₃) δ 7.11 (d, *J* = 8.1 Hz, 2H), 6.70 (d, *J* = 8.0 Hz, 2H), 4.70 (brs, 2H), 1.44 (m, 14H). LCMS-B: 4.444 min; *m/z* 237 [M+H]⁺.

(d) *tert*-Butyl (1-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenyl)ethyl)carbamate (A132)

A suspension of 2-(2-(2-(2-chloro-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (K6) (0.200 g, 0.690 mmol), *tert*-butyl (1-(4-aminophenyl)ethyl)carbamate (A131) (0.326 g, 1.38 mmol),

Pd(OAc)₂ (3 mg, 0.01 mmol), Cs₂CO₃ (0.675 g, 2.07 mmol) and Xantphos (16 mg, 0.028 mmol) in 1,4-dioxane (3 mL) was heated under microwave irradiation at 105 °C for 6 hours. The resulting mixture was filtered through a plug of silica gel, washing with 20% MeOH in K1 DCM and then the volatiles evaporated *in vacuo*. The residue was purified using silica gel column chromatography (CombiFlash Rf, 12 g SiO₂ Cartridge, 5-80% EtOAc in cyclohexane) to give the title compound A132 as a white solid (0.099 g, 29%); LCMS-B: rt 6.832 min; *m/z* 490 [M+H]⁺.

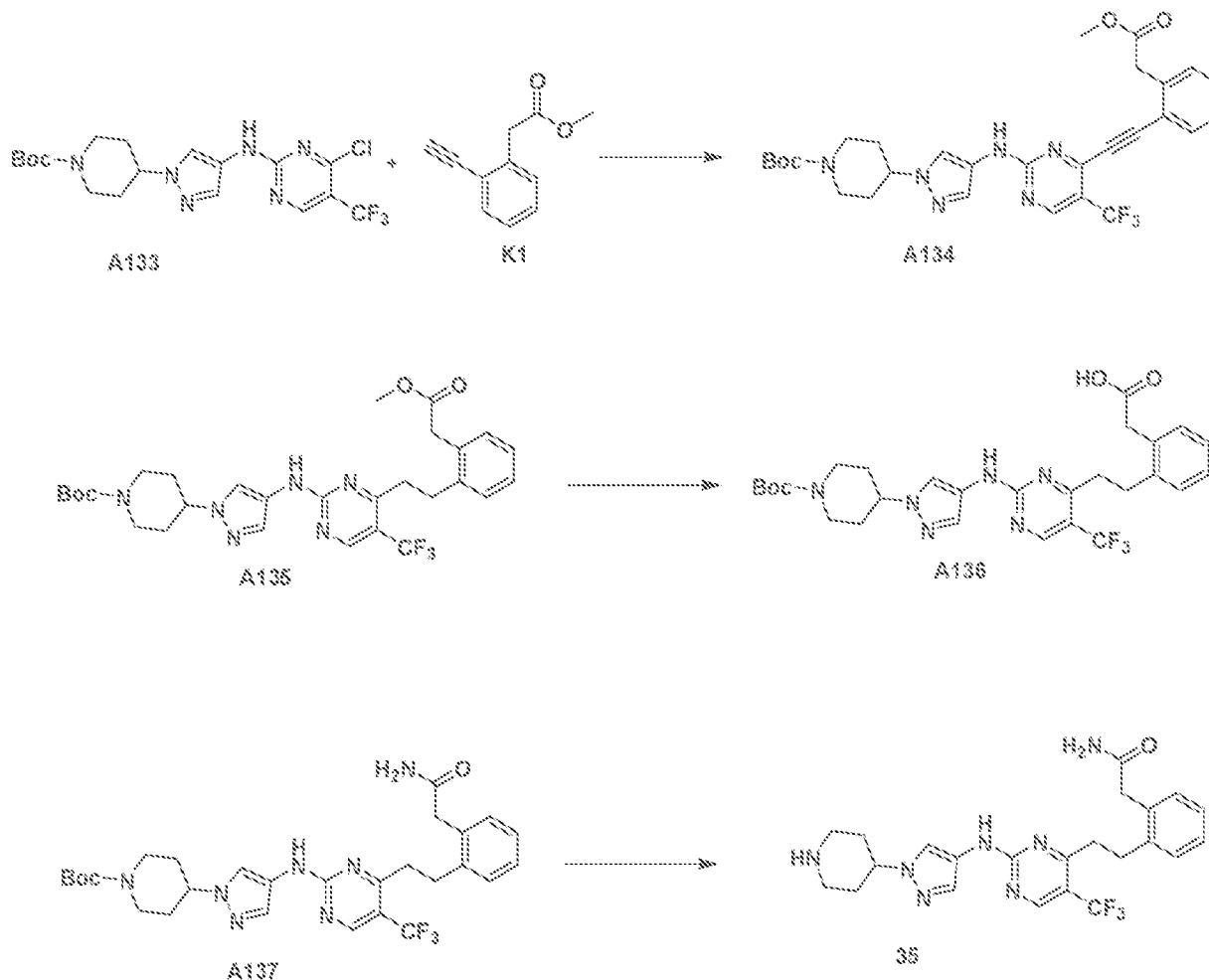
A137

(e) 2-(2-(2-(2-((4-(1-Aminoethyl)phenyl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (34)

TFA (1 mL) was added to a solution of *tert*-butyl (1-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-yl)amino)phenyl)ethyl)carbamate (A132) (0.099 g, 0.20 mmol) in DCM (5 mL) and the resulting mixture stirred at room temperature for 3 hours. The volatiles were evaporated under reduced pressure then 2 M aqueous K₂CO₃ solution (10 mL) and water (15 mL) were added to the residue. The resulting suspension was sonicated for 1 minute, filtered and the filter cake dried to give the title compound 34 as a light tan solid (77 mg, 97%); ¹H NMR (300 MHz, *d*₆-DMSO) δ 9.26 (s, 1H), 8.15 (s, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.42 (s, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.14-7.23 (m, 4H), 6.92 (s, 1H), 3.92 (d, *J* = 6.4 Hz, 1H), 3.50 (s, 2H), 3.32 (brs, 2H), 3.02-3.07 (m, 2H), 2.88-2.90 (m, 2H), 2.06 (s, 3H), 1.23 (d, *J* = 6.5 Hz, 3H). LCMS-B: rt 4.691 min; *m/z* 390 [M+H]⁺.

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Example 35: 2-(2-(2-(2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide
(35)



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(a) *tert*-Butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A133)

A 1.0 M solution of ZnCl_2 in diethyl ether (20.7 mL, 20.7 mmol) was added to a solution of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (4.48 g, 20.7 mmol) in *t*-BuOH (100 mL) and DCE (100 mL). The mixture was stirred for 10 minutes then diluted with *t*-BuOH (100 mL) and DCE (100 mL) before *tert*-butyl 4-(4-amino-1H-pyrazol-1-yl)piperidine-1-carboxylate (5.00 g, 18.8 mmol) and Et_3N (10.4 mL) were added. The mixture was stirred at room temperature overnight, the volatiles were removed *in vacuo* and the resultant residue was suspended in water (500 mL) and sonicated for 15 minutes. The solid was isolated by vacuum filtration and the filter cake washed with water (100 mL) and acetone (25 mL) to give the title compound (A133) as a tan solid (5.92 g, 71%); LCMS-A: rt 6.895 min; m/z 445.1 $[\text{M}-\text{H}]^-$.

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(b) *tert*-butyl 4-(4-((4-((2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A134)

A suspension of *tert*-butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A133) (700 mg, 1.57 mmol), K₁ (300 mg, 1.72 mmol), PPh₃ (21 mg, 0.078 mmol) and CuI (15 mg, 0.078 mmol) in Et₃N (1 mL) and DMF (4 mL) was sonicated for 10 minutes before PdCl₂(PPh₃)₂ (55 mg, 0.078 mmol) was added. The reaction mixture was irradiated in the microwave at 120 °C for 40 minutes. The resultant mixture was adsorbed onto silica gel and purified by column chromatography (Biotage Isolera, 40 g SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C), a second silica gel column was run (Biotage Isolera, 40 g SiO₂ cartridge, 0-50% EtOAc in petroleum benzine 40-60 °C) to give the title compound (A134) as a yellow solid (392 mg, 43%). LCMS-A: rt 7.064 min; m/z 585 [M+H]⁺.

(c) *tert*-Butyl 4-(4-((4-((2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (RCE_013_72_A) (A135)

A solution of *tert*-butyl 4-(4-((4-((2-(2-methoxy-2-oxoethyl)phenyl)ethynyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A134) (392 mg, 0.671 mmol) in EtOAc (40 mL) and DMF (2 mL) was stirred with 10% Pd/C (wetted with ca. 53% water, 100 mg) under a hydrogen atmosphere at room temperature overnight. The mixture was filtered through Celite and the filter cake was washed with EtOAc (50 mL). The volatiles were removed *in vacuo* and the resulting yellow oil was adsorbed onto silica gel and purified by silica gel column chromatography (Biotage Isolera, 40 g SiO₂ cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C then 0-20% MeOH in EtOAc) to give the title compound (A135) as a yellow solid (300 mg, 76%). ¹H NMR (400 MHz, Chloroform-d) δ 8.44 (s, 1H), 7.85 (s, 1H), 7.64 – 7.46 (m, 1H), 7.22 – 7.06 (m, 4H), 4.32 – 4.04 (m, 3H), 3.67 (s, 2H), 3.60 (s, 3H), 3.14 – 2.94 (m, 4H), 2.87 – 2.75 (m, 2H), 2.14 – 1.99 (m, 2H), 1.97 – 1.79 (m, 2H), 1.40 (s, 9H).

(d) 2-(2-(2-(2-((1-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A136)

A mixture of *tert*-butyl 4-(4-((4-((2-(2-methoxy-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A135) (300 mg, 0.510 mmol) and LiOH·H₂O (855 mg, 20.4 mmol) in THF (20 mL) and H₂O (1 mL) was stirred at 40 °C overnight. The mixture was diluted with DCM (50 mL) and water (50 mL) and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined washings were

dried (Na_2SO_4) and the volatiles were removed *in vacuo* to yield the title compound (A136) as a yellow oil (270 mg, 92%). LCMS-A: rt 6.679 min; m/z 575.2 $[\text{M}+\text{H}]^+$.

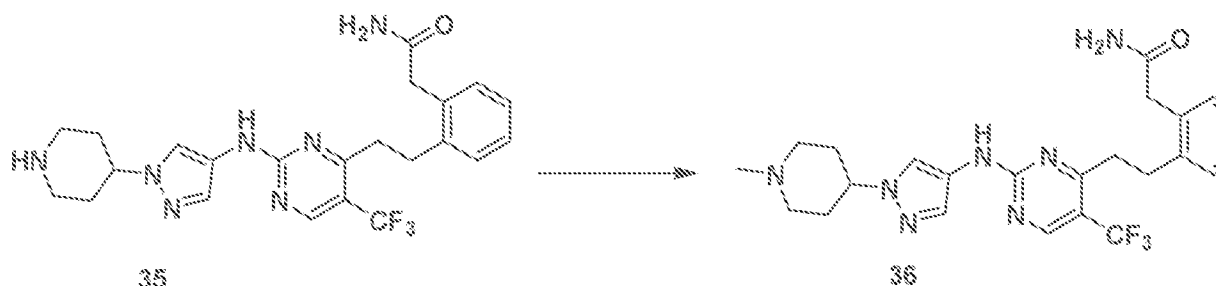
(e) *tert*-Butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A137)

Ammonium carbonate (903 mg 9.40 mmol) was added to a suspension of 2-(2-(2-(2-((1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetic acid (A136) (270 mg, 0.470 mmol), HOBT (317 mg, 2.35 mmol) and EDCI-HCl (450 mg, 2.35 mmol) in Et_3N (1.0 mL) and DMF (25 mL) and the resulting solution was stirred at 40 °C overnight. The volatiles were removed *in vacuo* and the resulting residue was dissolved in EtOAc (250 mL) and washed with water (250 mL). The organics were adsorbed onto silica gel and the product was purified by silica gel column chromatography (Biotage Isolera, 40 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzene 40-60 °C, then 0-20% MeOH in EtOAc) to yield the title compound (A137) as a white solid (171 mg, 63%). LCMS-A: rt 6.481 min; m/z 574.3 $[\text{M}+\text{H}]^+$.

(f) 2-(2-(2-(2-((1-(Piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (35)

TFA (2 mL) was added to a solution of *tert*-butyl 4-(4-((4-(2-(2-amino-2-oxoethyl)phenethyl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)piperidine-1-carboxylate (A137) (171 mg, 0.298 mmol) in DCM (25 mL) and the mixture was stirred at room temperature overnight. The volatiles were removed *in vacuo* and the resultant solid was dissolved in CHCl_3 (1 mL). Cyclohexane (25 mL) was added and the resultant precipitate was removed by filtration, washed with cyclohexane (25 mL) and air dried to yield the title compound as a white solid (101 mg, 72%). LCMS-A: rt 4.717 min; m/z 474.2 $[\text{M}+\text{H}]^+$.

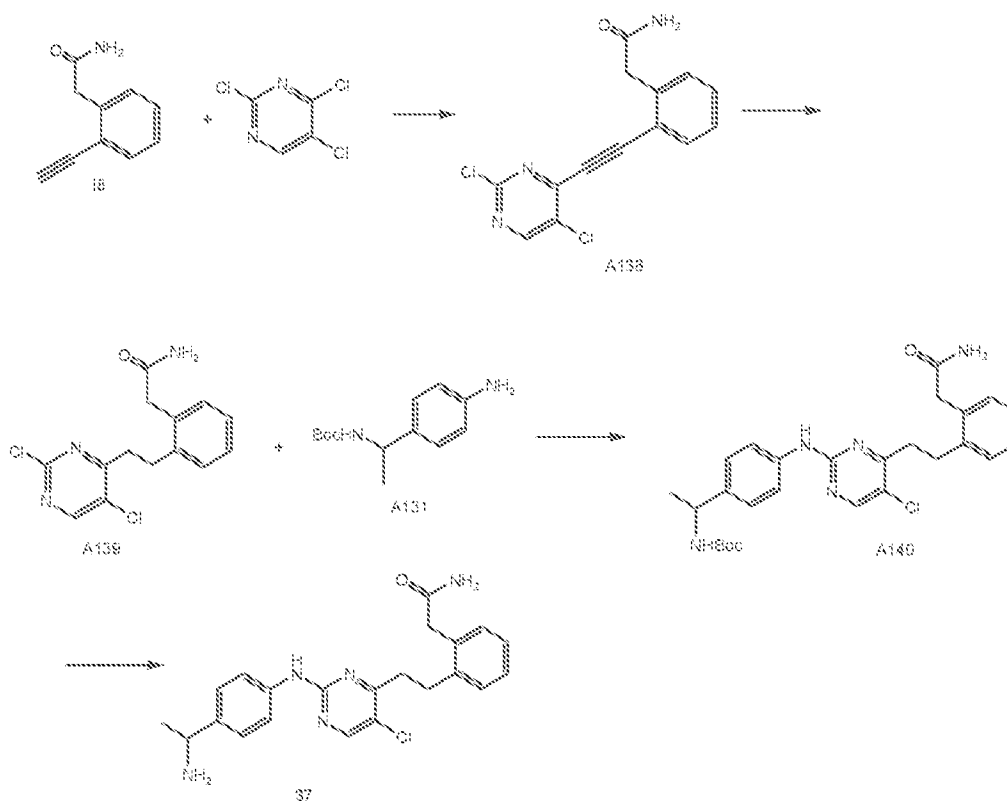
Example 36: Synthesis of 2-(2-(2-(2-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (36)



2-(2-(2-((1-(1-Methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (36)

NaBH(OAc)₃ (147 mg, 0.693 mmol) was added cautiously to a stirred solution of 2-(2-(2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (35) (82 mg, 0.17 mmol) in 37% aqueous formaldehyde solution (39 μ L, 0.52 mmol) and MeOH (5.0 mL). The reaction mixture was stirred for 1 hr and then quenched with water (50 mL). The resultant precipitate was removed by filtration, washed with cyclohexane and dried under high vacuum to yield the title compound as a white solid (82 mg, 97%). LCMS-A: rt 4.751 min; m/z 488.3 [M+H]⁺.

Example 37: Synthesis of 2-(2-(2-(4-(1-aminoethyl)phenylamino)-5-chloropyrimidin-4-yl)ethyl) phenyl)acetamide (37)



(a) 2-(2-((2,5-Dichloropyrimidin-4-yl)ethynyl)phenyl)acetamide (A138)

To a solution of 18 (0.75 g, 4.7 mmol) and 2,4,5-trichloropyrimidine (0.70 mL, 6.1 mmol) in 1,4-dioxane (10 mL) and Et₃N (2.6 mL, 19 mmol) containing CuI (0.018 g, 0.094 mmol) was added PdCl₂(PPh₃)₂ (0.033 g, 0.047 mmol). The reaction mixture was heated at 70 °C for 2 hours under a nitrogen atmosphere. The solvent was removed *in vacuo* and the residue was diluted with 20% diethyl ether in cyclohexane. The precipitate was filtered, washed with

water and dried *in vacuo* to give the title compound (A138) as a light brown solid (1.22 g, 85%). LCMS-C: rt 4.88 min; *m/z* 306 [M+H]⁺.

(b) 2-(2-(2-(2,5-Dichloropyrimidin-4-yl)ethyl)phenyl)acetamide (A139)

A solution of 2-(2-(2-(2,5-dichloropyrimidin-4-yl)ethynyl)phenyl)acetamide (A138) (1.2 g, 4.0 mmol) in DMF (40 mL) and MeOH (8 mL) was stirred with platinum(II)oxide (0.27 g, 1.2 mmol) under an atmosphere of hydrogen for 144 hours at ambient temperature. The reaction mixture was diluted with EtOAc and filtered through a plug of Celite. The solvents were removed *in vacuo* and the crude residue was purified by silica gel column chromatography (Combiflash Rf, 0-10% MeOH in DCM) to give the title compound (A139) as a light yellow solid (0.63 g, 51%). LCMS-C: rt 4.82 min; *m/z* 310 [M+H]⁺.

(c) *tert*-Butyl 1-(4-(4-(2-(2-amino-2-oxoethyl)phenethyl)-5-chloropyrimidin-2-ylamino)phenyl)ethylcarbamate (A140)

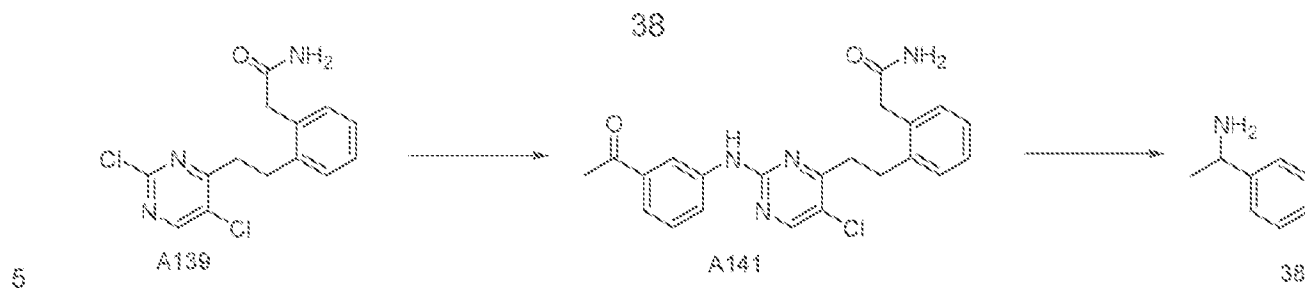
A mixture of 2-(2-(2-(2,5-dichloropyrimidin-4-yl)ethyl)phenyl)acetamide (A139) (0.050 g, 0.16 mmol), (A131) (0.046 g, 0.19 mmol), Xantphos (0.014 g, 0.024 mmol) and Cs₂CO₃ (0.16 g, 0.48 mmol) in 1,4-dioxane (1 mL) was bubbled with nitrogen for 10 minutes. Palladium (II) acetate (0.0036 g, 0.016 mmol) was added and the mixture was heated at 90 °C under microwave irradiation for 90 minutes. The mixture was portioned between water and EtOAc. The layers were separated and the water layer was extracted with EtOAc (twice). The combined organic extracts were washed with brine, dried (Na₂SO₄) and the solvent evaporated *in vacuo* to give the crude product. Purification by silica gel column chromatography (3 times) (Combiflash Rf, 0-10% MeOH in DCM twice then 0-100% EtOAc in cyclohexane) to give the title compound (A140) as a colourless oil (0.007 g, 9%). LCMS-C: rt 5.54 min; *m/z* 510 [M+H]⁺.

(d) 2-(2-(2-(2-(4-(1-Aminoethyl)phenylamino)-5-chloropyrimidin-4-yl)ethyl)phenyl) acetamide (37)

To a solution of *tert*-butyl 1-(4-(4-(2-(2-amino-2-oxoethyl)phenethyl)-5-chloropyrimidin-2-ylamino)phenyl)ethylcarbamate (A140) (0.0070 g, 0.014 mmol) in DCM (1 mL) was added TFA (0.50 mL). The mixture was stirred at ambient temperature for 2 hours before the volatiles were removed *in vacuo*. The crude residue was purified using an SCX cartridge, (MeOH then 2 N ammonia in EtOH eluent) to give the title compound (37) as a grey solid (0.005 g, 89%). LCMS-C: rt 4.29 min; *m/z* 410 [M+H]⁺.

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Example 38: Synthesis of 2-{2-[2-(2-[(3-(1-aminoethyl)phenyl)amino]-5-chloropyrimidin-4-yl)ethyl]phenyl}acetamide (38)



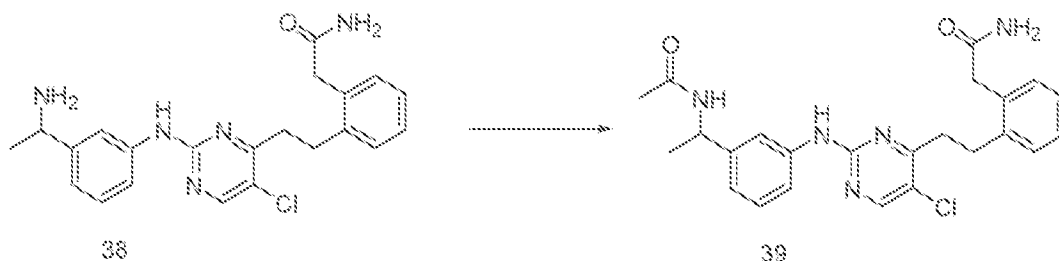
(a) 2-(2-(2-(2-((3-Acetylphenyl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (A141)

A solution of 2-(2-(2-(2,5-dichloropyrimidin-4-yl)ethyl)phenyl)acetamide (A139) (0.158 g, 0.509 mmol) in 2-propanol (2 mL) containing 1-(3-aminophenyl)ethanone (0.138 g, 1.01 mmol) was heated under microwave irradiation at 150 °C for 2 hours. The reaction mixture was adsorbed onto silica gel and the product was purified using silica gel column chromatography (CombiFlash Rf, 12 g SiO₂ Cartridge, 10-65% EtOAc in cyclohexane) to give the title compound (A141) as a white solid (0.125 g, 60%). LCMS-B: rt 6.804 min; *m/z* 409 [M+H]⁺.

(b) 2-(2-(2-(2-((3-(1-Aminoethyl)phenyl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (38)

Ammonium acetate (0.339 g, 4.40 mmol) was added to a solution of 2-(2-(2-(2-((3-acetylphenyl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (A141) (0.120 g, 0.293 mmol) in MeOH (5 mL) and the mixture was stirred for 20 minutes under a nitrogen atmosphere. Sodium cyanoborohydride (0.013 g, 0.21 mmol) was added and the mixture was stirred for 6 hours. Additional sodium cyanoborohydride (0.013 g, 0.21 mmol) was added and the mixture was stirred for 16 hours at room temperature. The mixture was diluted with water (10 mL), acidified with 20% aqueous HCl (10 mL) and washed with Et₂O (2 × 30 mL). The aqueous phase was basified with solid potassium hydroxide to pH 10 and extracted with DCM (3 × 30 mL). The combined organic phases were washed with water, brine, dried (Na₂SO₄) and the solvent evaporated *in vacuo*. The crude product was adsorbed onto silica gel and purified by column chromatography (CombiFlash Rf, 12 g SiO₂ Cartridge, 0-30% MeOH in DCM) to give the title compound (38) as a white foam (0.057 g, 47%). LCMS-B: rt 5.45 min; *m/z* 410 [M+H]⁺.

Example 39: Synthesis of 2-(2-(2-(2-((3-(1-acetamidoethyl)phenyl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (39)

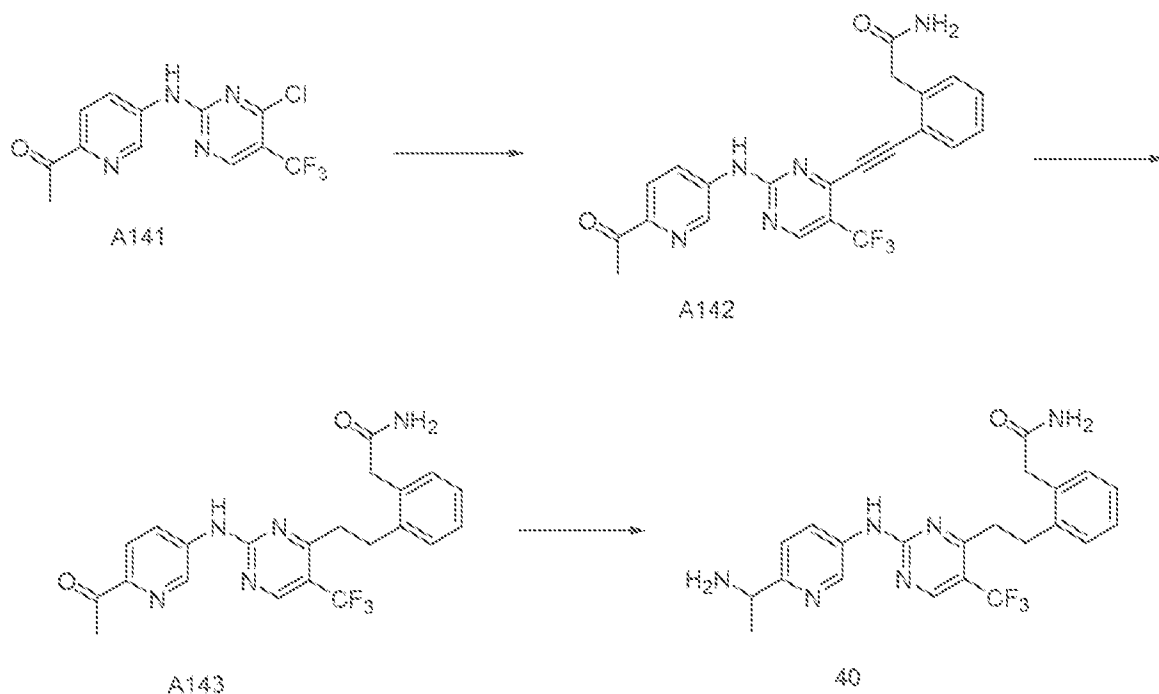


A solution of 2-(2-(2-(2-((3-(1-aminoethyl)phenyl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (38) (0.045 g, 0.11 mmol) in pyridine (3 mL) containing acetic anhydride (62 μL, 0.66 mmol) and 4-dimethylaminopyridine (2.6 mg, 0.022 mmol) was stirred at room temperature for 22 hours under a nitrogen atmosphere. The mixture was

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acidified with 1 M hydrochloric acid (30 mL) and extracted with DCM (3 × 20 mL). The combined organic phases were washed with water, brine, dried (Na₂SO₄) and the solvent evaporated *in vacuo*. The crude product was adsorbed onto silica gel and the product was purified by column chromatography (CombiFlash Rf, 4 g SiO₂ Cartridge, 0-10% MeOH in DCM) to yield the title compound (39) as a white solid (0.035 g, 70%). LCMS-B: rt 6.20 min; *m/z* 452 [M+H]⁺.

Example 40: Synthesis of 2-(2-(2-(2-((6-(1-aminoethyl)pyridin-3-yl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (40)



(a) 1-(5-((4-Chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyridin-2-yl)ethanone (A141)

A suspension of 1-(5-aminopyridin-2-yl)ethanone (2.08 g, 15.3 mmol) in DMF (30 mL) and DIPEA (6.65 mL, 38.2 mmol) was stirred at room temperature for 15 minutes.

2,4-Dichloro-5-(trifluoromethyl)pyrimidine (2.47 mL, 18.33 mmol) was added in 4 portions over 5 minutes. The reaction mixture was stirred at 60 °C for 2 hours under a nitrogen atmosphere before it was diluted with water and EtOAc. The aqueous was extracted several times with EtOAc and the combined organic phases were washed with water, brine, dried (Na₂SO₄), filtered and the solvent evaporated *in vacuo*. The crude product was adsorbed onto silica gel and purified by column chromatography (CombiFlash Rf, 40 g SiO₂ Cartridge, 0-30% EtOAc in cyclohexane) to give 2.17 g of a white solid. The 1:1 regioisomeric mixture was dissolved in a minimum volume of cold (5 °C) acetonitrile (4-8 mL), sonicated for 10

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seconds then filtered and dried to give the title compound (A141) as a white solid (1.14 g, 23%). LCMS-B: rt 7.34 min; m/z 317 $[M+H]^+$.

(b) 2-(2-((2-((6-Acetylpyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethynyl)phenyl)acetamide (A142)

1-(5-((4-Chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyridin-2-yl)ethanone (A141) (0.313 g, 0.988 mmol) and **18** (0.189 g, 1.18 mmol) were added to a solution of $\text{PdCl}_2(\text{PPh}_3)_2$ (0.017 g, 0.025 mmol), CuI (0.010 g, 0.049 mmol) and PPh_3 (0.013 g, 0.049 mmol) in DMF (3 mL) and Et_3N (0.552 mL, 3.95 mmol). The reaction mixture was heated under microwave irradiation at 120 °C for 15 minutes. The reaction mixture was diluted with water and then filtered. The solid was washed with water and dried before being suspended in EtOAc, ultrasonicated for 20 seconds, filtered and dried to give the title compound (A142) as a light brown solid (0.347 g, 79%). LCMS-B: $t_r = 6.78$ min; $m/z = 440$ $[\text{M}+\text{H}]^+$.

(c) 2-(2-(2-(2-((6-Acetylpyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (A143)

A solution of 2-(2-(2-(2-((6-acetylpyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (A142) (0.347 g, 0.790 mmol) in DMF (20 mL), EtOH (3 mL) and Et_3N (1 mL) containing 10% palladium on carbon (0.110 g) was stirred under a hydrogen atmosphere for 20 hours. The reaction mixture was filtered through a pad of Celite and the solvent was concentrated *in vacuo*. The crude material was adsorbed onto silica gel and purified by silica gel column chromatography (CombiFlash Rf, 24 g SiO_2 Cartridge, 0-10% MeOH in DCM) to give the title compound (A143) as a white solid (0.200 g, 57%). LCMS-B: 6.80 min; m/z 444 $[\text{M}+\text{H}]^+$.

(d) 2-(2-(2-(2-((6-(1-Aminoethyl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (**40**)

Ammonium acetate (0.250 g, 3.23 mmol) was added to a solution of 2-(2-(2-(2-((6-acetylpyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (A143) (0.072 g, 0.162 mmol) in MeOH (4 mL) and THF (2 mL) and the mixture was stirred for 20 minutes under a nitrogen atmosphere. Sodium cyanoborohydride (7 mg, 0.1 mmol) was added and the mixture was stirred for 5 hours. Additional sodium cyanoborohydride (7 mg, 0.1 mmol) was added and the mixture was stirred for a total of 22 hours at 35 °C. The aqueous phase was basified with solid potassium hydroxide (pH 10) and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and adsorbed on to silica. The product was purified by silica column chromatography (CombiFlash Rf, 12 g SiO_2 Cartridge, 0-20% MeOH in DCM) to give the title compound (**40**) as a white solid (0.042 g, 58%). LCMS-B: 4.30 min; m/z 445 $[\text{M}+\text{H}]^+$.

Biological Assays

The activity of compounds of the invention can be profiled using biochemical and cellular assays.

5

Primary potency at VEGFR3 can be assessed using an Alpha Screen™ technology biochemical assay.

10

The ability of compounds of the invention to inhibit VEGFR3 within cells can be assessed with an ELISA type assay.

VEGFR3 Biochemical assay

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

15

A biotin labelled peptide is used as substrate (amino acid sequence: Biotin-Glu-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu-Glu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH₂). VEGFR3 cytoplasmic domain (amino acids 798-1298) was purchased as N-terminal GST-fusion protein ("the enzyme").

20

The 15 µL assay reactions are run in Greiner brand white 384-well low volume plates. All reactions contained 10 mM HEPES pH 7.4, 10 mM MgCl₂, 0.01% (v/v) Tween-20, 50 µM Na₂VO₄, 0.01% (w/v) albumin from chicken egg white, 1 mM Dithiothreitol, 111 nM peptide substrate, 500 µM ATP, and 3.8 ng/reaction enzyme, with the enzyme being omitted from negative control reactions. Compounds were added in a volume of 100 nL from dilution series prepared in DMSO, positive and negative control reactions receiving the same volume DMSO without compound. The plates were sealed with adhesive seals and incubated for 90 minutes at 30 degree Celsius. The reactions were stopped with the

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detection reagents added at the same time as follows: Product formation was quantified as amplified luminescence between PerkinElmer AlphaScreen™ beads, using Streptavidin-coated donor and anti-phosphotyrosine (P-Tyr-100) acceptor beads. To each reaction, 5 µL containing 10 mM HEPES pH 7.4, 25 mM NaCl, 100 mM EDTA, 0.01% (v/v) Tween-20, and 6.25 µg/mL of each bead type were added. Plates were incubated for 6 hours before being

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read on a PerkinElmer EnVision™ plate reader in HTS Alphascreen™ mode. IC₅₀ values were obtained by calculating percent inhibition (%I) for each reaction relative to controls on the same plate ($\%I = (I - CN) / (CP - CN)$ where CN/ CP are the averages of the negative/ positive reactions, respectively), then fitting the %I data vs. compound concentration [I] to $\%I = (A + ((B - A) / (1 + ((C / [I])^D))))$ where A is the lower asymptote, B is the upper asymptote, C is the IC₅₀ value, and D is the slope factor.

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The above assay was also run in a modified form in some cases (indicated below with *). In these cases, VEGFR3 cytoplasmic domain (amino acids 818-1177, lacking 949-1002 of UniProt accession number P35916) was expressed and purified as N-terminal Hexa-His-fusion protein ("the enzyme"), rather than using the N-terminal GST-fusion protein. The assay conditions were the same as above but with 1 μ M ATP and 8 ng/reaction of the enzyme. The comparable performance of both assay versions was monitored using benchmark compounds as described in the literature.

VEGFR3 Biochemical assay results

Compound	IC ₅₀ (nM)
1	161
2	39
3	97
4	35
5	28
6	23
7	40
8	34
9	68
10	76
11	26
12	20
13	67
14	81
15	31
16	22
17	67
18	46
19	70
20	37
21	44
22	101
23	72
24	34

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25	278
26	24
27	118
28	24
29	17
30	9
31	23
32	52
33	28
34	71
35	23
36	50
37	12
38	76
39	10
40	187
41	26

VEGFR3 Phospho ELISA assay

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

- 5 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% CO₂ 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
10 further period (overnight at 37 °C and 5% CO₂).

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
15 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 mM KCl, 8.1 mM Na₂HPO₄, 1.5 mL KH₂PO₄, 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.

5 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 μ L of sample or vehicle control was added to the cell monolayers. Cells are treated for 1 hour at 37 °C and 5% CO₂. 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% CO₂.

10 The media and compounds were removed and the cell monolayer washed once in Dulbecco's Phosphate Buffered Saline (Cat # 21600-044, Invitrogen). 130 μ L 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 μ L Protease Inhibitor Cocktail (Cat # P8340, Sigma-Aldrich), 10 μ L PMSF (Phenylmethanesulfonyl fluoride, Cat # P7626, Sigma-Aldrich, prepared as 500 mM DMSO stock) per 1 mL of Phosphosafe™ Extraction Reagent
15 (Cat # 71296, Merck).

The harvested samples were then diluted 1:2 in IC Diluent #18 (5% Tween 20/PBS) and 100 μ L transferred to the Total and Phospho VEGFR3 coated, blocked and washed 96 well
20 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 μ L 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
25 temperature. The plate was then washed three times in wash buffer and tapped dry. 100 μ L of streptavidin-HRP 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 μ L Substrate solution (3,3',5,5'-Tetramethylbenzidine (TMB) Liquid Substrate System for ELISA, Cat # T0440, Sigma-Aldrich) was added and the
30 plate incubated for 20 minutes in the dark at room temperature followed by the addition of 50 μ L stop solution (2 M H₂SO₄).

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 μ L 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 μ L 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 μ L 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 IC_{50} determined from curve.

VEGFR3 Phospho ELISA assay results

Compound	IC50 (nM)
2	121
3	156
4	2216
5	210
6	62
9	379
11	39
12	116
13	1034
16	214
18	18
24	169
26	83
28	190
31	107
33	1254
37	26

VEGFR2 Phospho ELISA assay

5 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% CO₂ 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% CO₂).

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 mM KCl, 8.1 mM Na_2HPO_4 , 1.5 mM 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.

5 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.

15 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) per 1mL of Phosphosafe™ Extraction Reagent (Cat # 71296, Merck).

20 The harvested samples were then diluted 1:2 in IC Diluent #12 (1% NP-40, 20 mM 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.

25 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 CaCl₂, 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.

30 100 μL of streptavidin-HRP 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).

35

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 μ L of Detection antibody (Anti-Phospho-Tyrosine-
 5 HRP Detection Antibody, Part # 841403 in Phospho VEGFR2 kit) was diluted in IC Diluent
 14 (20 mM Tris, 137 mM Ca_2Cl , 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 μ L Substrate solution (3,3',5,5'-
 10 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 μ L 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.

IC₅₀ 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
 20 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.

25 %I is plotted against compound concentration and data fitted using a Sigmoidal dose
 response with IC₅₀ determined from plotted curve.

VEGFR2 Phospho ELISA assay results

Compound	IC ₅₀ (nM)
2	4397
4	>10000
18	2548
24	>10000

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26	4071
28	6840
31	5100
33	>10000
37	200

P397Y-FAK inhibition MSD platform cellular biomarker assay

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

5 96-well plates (cat#MA6000, Meso Scale Discovery) are coated with 30 μ L/well of mouse monoclonal FAK antibody [63D5] (cat#ab72140, Abcam) pre-diluted in PBS to a concentration of 1 mg/mL. The plates are sealed with adhesive film and incubated for 16 hours at 4 °C. The antibody is then flicked out of the plates and 150 μ L of 3% [w/v] Blocker A (cat#R93AA-1, Meso Scale Discovery) is added. The plates are resealed with adhesive film
10 and incubated at room temperature on a shaker set at medium speed for 2 hours. The plates are then washed three times with a solution containing 50 mM Tris-HCl pH 7.5, 0.15 M NaCl and 0.02% Tween-20, before cell lysate addition described below.

Cells are split 1:2 into T150 cell culture flasks 2 days prior to compound treatment. On the
15 day prior to compound treatment, 200 μ L media containing 20,000 cells is seeded into all wells of white, clear-bottom, TC treated, μ clear, 96-well microtitre plates (cat#655098, Greiner Bio-One), and the plates are incubated at 37°C and 5% CO₂ for 36 hours. 1 μ L/well of compound is then added from dilution series prepared in DMSO. Negative control wells receive the same volume of DMSO without compounds, and positive control wells receive 2
20 μ M of a control compound in the same volume of DMSO. Cells are treated for 1 hour at 37 °C and 5% CO₂. The media/compounds are then flicked off and 55 μ L/well of ice-cold complete lysis buffer is added. Complete lysis buffer is prepared by adding 1 tablet PhosSTOP complete phosphatase inhibitor (cat#04906837001, Roche) and 1 tablet Complete, Mini, EDTA-free, protease inhibitor (cat#04693159001, Roche) per 10 mL of
25 incomplete lysis buffer (150 mM NaCl, 20 mM Tris-HCl pH 7.5, 1 mM EDTA, 1 mM EGTA, 1% Triton-X 100). Plates are incubated on ice for 30 minutes, with 30 seconds high speed plate shaking every 5 minutes. 40 μ L/well of cell lysate is transferred to the coated, blocked and washed 96-well microtitre plates described above. The 96-well plates are sealed with adhesive film and incubated for 16 hours at 4 °C. The plates are then washed three times
30 with a solution containing 50 mM Tris-HCl pH 7.5, 0.15 M NaCl and 0.02% Tween-20 and tapped dry. 25 μ L/well of detection solution (1% [w/v] Blocker A (cat#R93AA-1, Meso Scale

Discovery) in 50 mM Tris-HCl pH 7.5, 0.15 M NaCl and 0.02% Tween-20, with 1:600 rabbit polyclonal FAK phospho Y397 antibody (cat#ab39967, Abcam), 1:1000 anti-rabbit sulfo-tag antibody (cat#R32AB-1 Meso Scale Discovery) and 1:40 reconstituted Blocker D-M (cat#D609-0100, Rockland Immunochemicals for Research) is added, and the plates
 5 resealed with adhesive film and incubated for 1 hour at room temperature on a plate shaker set to medium speed. Plates are then washed three times with a solution containing 50 mM Tris-HCl pH 7.5, 0.15 M NaCl and 0.02% Tween-20 and tapped dry. 150 μ L/well of Read Buffer T + Surfactant (cat#R92TC-1, Meso Scale Discovery) is then added, and pFAK-397 levels quantified using a Meso Scale Discovery SECTOR Imager 6000 instrument.

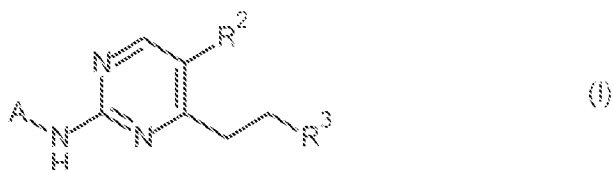
10 IC_{50} values are determined by first calculating percent inhibition (%) for each lysate relative to controls on the same plate ($\%I = (S - CP) / (CN - CP)$) where S is the sample result, CN is the average result of DMSO only treated negative controls, and CP is the average result of 2 μ M treated positive controls. %I is plotted against compound concentration [I] and the data fitted using the following equation, $\%I = (A + ((B - A) / (1 + ((C / [I])^D))))$, where A is the lower asymptote, B is the upper asymptote, C is the IC_{50} value, and D is the slope factor.

P397Y-FAK Inhibition MSD platform cellular biomarker assay results for MDA-231-LNA cells

Compound	IC_{50} (nM)
3	62
5	>2000
6	940
11	16
12	30
16	>2000
18	25
19	7
20	<50%
21	119
22	944
24	>2000
26	>2000
28	>2000
31	>2000
33	>2000

CLAIMS

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

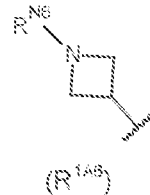
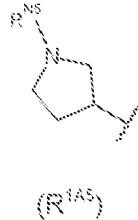
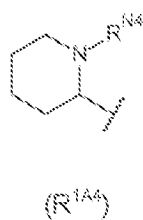
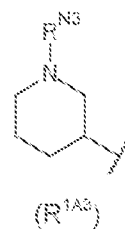
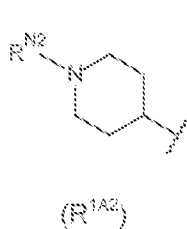
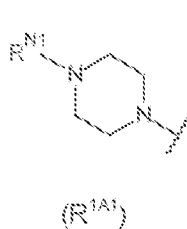


5 wherein:

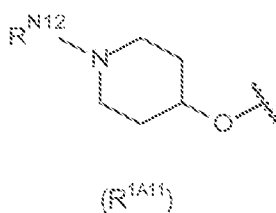
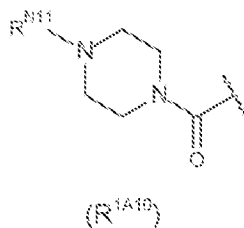
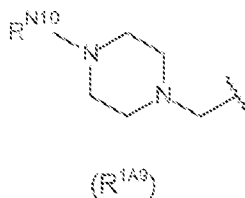
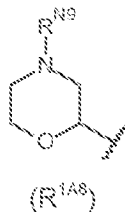
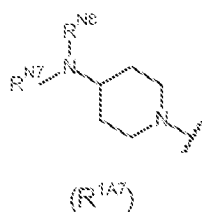
A is an optionally substituted 5-10 membered heteroaryl group linked to the NH group through an aromatic ring carbon atom, in which the heteroaryl ring system contains 1 to 4 heteroatoms selected from N, O and S, and;

A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear one, two or three 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_{1-2} alkyl and Z^1 is selected from H, C_{1-2} alkyl optionally substituted by OH, $C(=O)OC_{1-3}$ alkyl and $C(=O)Me$;
- (ii) $XNHZ^2$, where X is selected from CMe_2 , cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidene and Z^2 is selected from H, C_{1-3} alkyl optionally substituted by OH, $C(=O)OC_{1-3}$ alkyl and $C(=O)Me$;
- (iii) a group selected from R^{1A1} to R^{1A11} ;



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wherein:

R^{N1} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N2} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N3} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

5 R^{N4} is selected from H and CH₃;

R^{N5} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N6} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N7} and R^{N8} are independently selected from H and CH₃;

R^{N9} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

10 R^{N10} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N11} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me; and

R^{N12} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

and where each R¹⁰ is independently selected from:

(i) C₁₋₃ alkyl;

15 (ii) CF₃;

(iii) F;

(iv) Cl;

(v) O-(C₁₋₃ alkyl);

(vi) CN; and

20 (vii) =O;

R² is selected from H, halo, C₁₋₄ alkyl, CF₂, CF₂H, CN and methoxy;

R³ is selected from substituted phenyl and a substituted 6 membered heteroaryl group,

where the heteroaryl ring system contains 1 or 2 N heteroatoms, where

R³ bears a substituent R⁴ either alpha or beta to the -C₂H₄- group, and may additionally bear

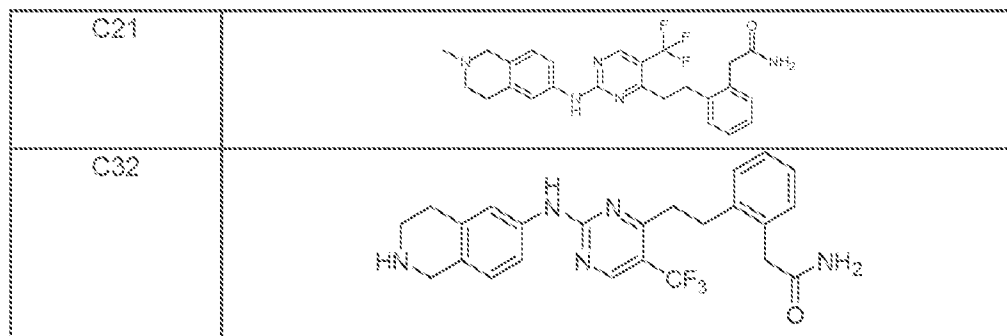
25 further substituents selected from F, methyl and CF₃; and

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R^4 is $-\text{CH}_2-\text{C}(\text{O})\text{N}(\text{R}^{\text{N13}})\text{Z}^3$, where R^{N13} is selected from H and CH_3 ; and Z^3 is selected from H, CH_3 and OCH_3 .

2. A compound according to claim 1, with the proviso that it is not the following compound:

5

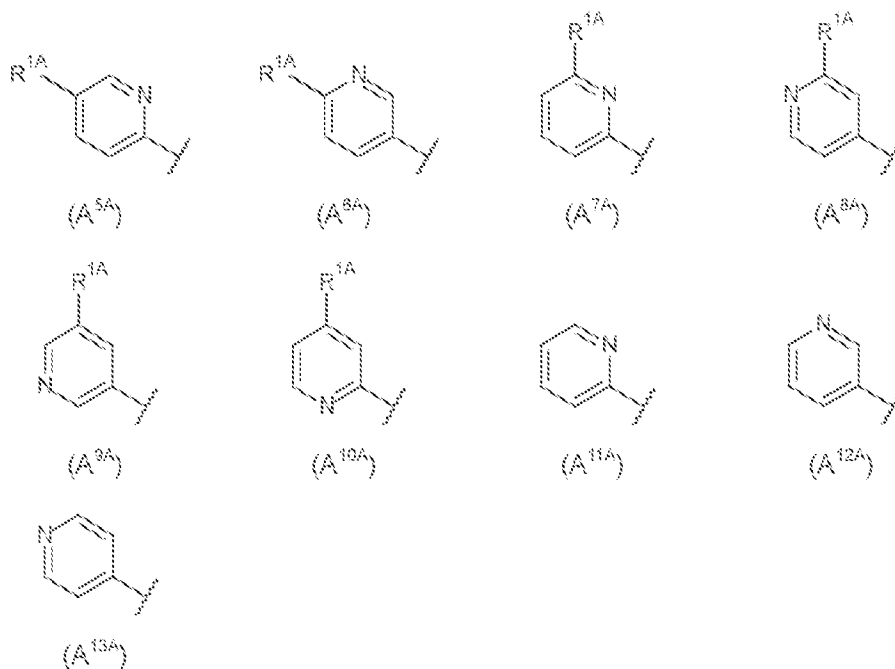


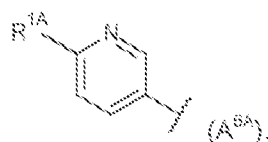
3. A compound according to claim 1, wherein A is an optionally substituted 6 membered heteroaryl group.

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4. A compound according to claim 3, wherein A is optionally substituted pyridyl.

5. A compound according to claim 4, wherein A is selected from:





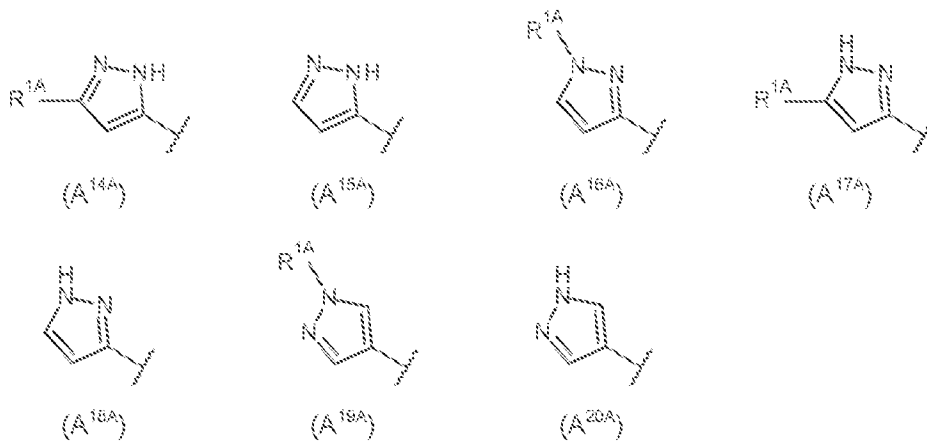
6. A compound according to claim 5, wherein A is

7. A compound according to claim 1, wherein A is an optionally substituted 5 membered heteroaryl group.

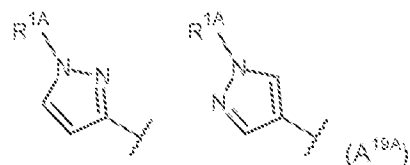
5

8. A compound according to claim 7, wherein A is optionally substituted pyrazolyl.

9. A compound according to claim 8, wherein A is selected from:



10. A compound according to claim 9, wherein A is



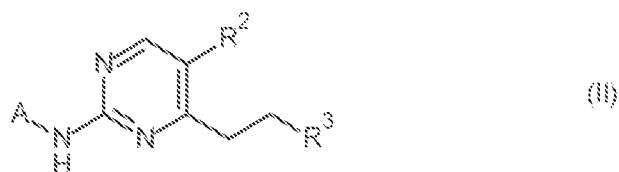
11. A compound according to any one of claims 1 to 10, where no R^{1C} substituents are present on A.

15 12. A compound according to any one of claims 1 to 10, where R^{1C} is methyl.

13. A compound according to any one of claims 1 to 10, where a single R^{1C} substituent is present.

20 14. A compound of formula (II) or isomers, salts, solvates or prodrugs thereof.

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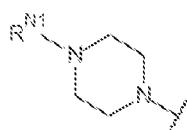
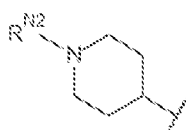
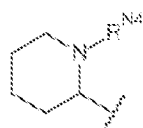
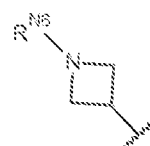
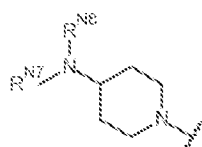
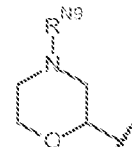
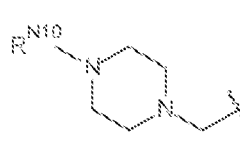
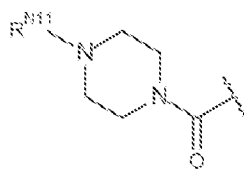
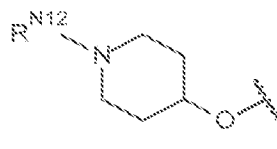


wherein:

A is optionally substituted phenyl;

when A is optionally substituted phenyl, A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear one or two substituents R^{1B} 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_{1-2} alkyl and Z^1 is selected from H, C_{1-3} alkyl optionally substituted by OH, $C(=O)OC_{1-3}$ alkyl and $C(=O)Me$;
- (ii) $XNHZ^2$, where X is selected from CMe_2 , cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidene and Z^2 is selected from H, C_{1-3} alkyl optionally substituted by OH, $C(=O)OC_{1-3}$ alkyl and $C(=O)Me$;
- (iii) a group selected from R^{1A1} to R^{1A11} ;

(R^{1A1})(R^{1A2})(R^{1A3})(R^{1A4})(R^{1A5})(R^{1A6})(R^{1A7})(R^{1A8})(R^{1A9})(R^{1A10})(R^{1A11})

wherein:

R^{N1} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

R^{N2} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

R^{N3} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

5 R^{N4} is selected from H and CH_3 ;

R^{N5} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

R^{N6} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

R^{N7} and R^{N8} are independently selected from H and CH_3 ;

R^{N9} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

10 R^{N10} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

R^{N11} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$; and

R^{N12} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

and where each R^{16} is independently selected from:

(i) C_{1-3} alkyl;

15 (ii) CF_3 ;

(iii) F;

(iv) Cl;

(v) $O-(C_{1-3} \text{ alkyl})$;

(vi) CN;

20 R^2 is selected from H, halo, C_{1-4} alkyl, CF_3 , CF_2H , CN and methoxy;

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, 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 ; and

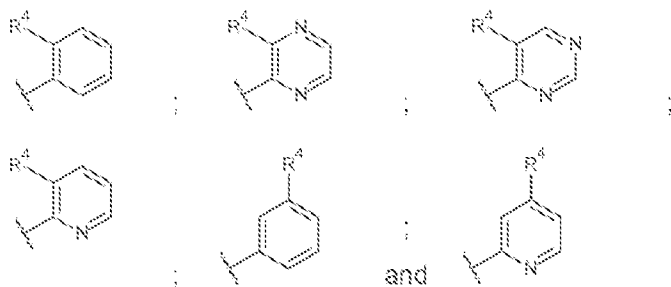
25 R^4 is $-CH_2-C(O)N(R^{N13})Z^3$, where R^{N13} is selected from H and CH_3 ; and Z^3 is selected from H, CH_2 and OCH_2 .

15. A compound according to claim 14, with the proviso it is not any of the following compounds:

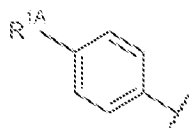
C1		C16	
C2		C17	

C3		C18	
C4		C19	
C5		C20	
C6		C22	
C7		C23	
C8		C24	
C9		C25	
C10		C26	
C11		C27	
C12		C28	
C13		C29	
C14		C30	
C15		C31	

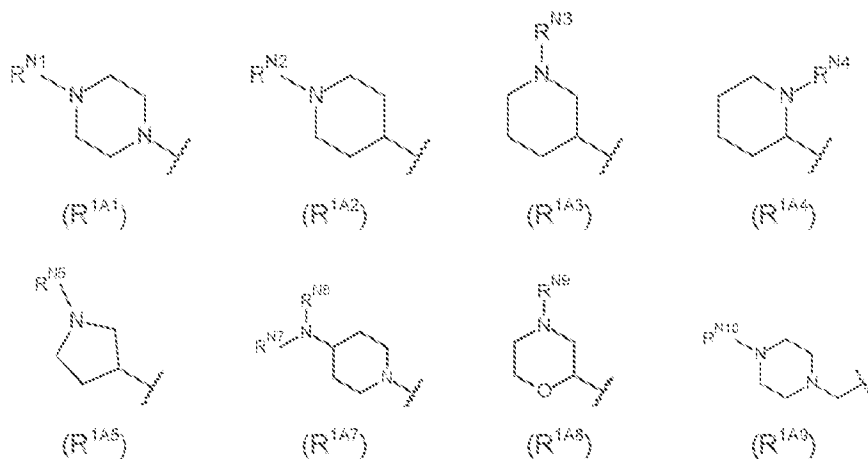
16. A compound according to claim 14, with the proviso that:
when R^3 is selected from:



A is either:



where R^{1A} is selected from



5 and R^{N1} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

R^{N2} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

R^{N3} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

R^{N4} is selected from H and CH_3 ;

R^{N5} is selected from H, C_{1-2} alkyl, and $C(=O)Me$;

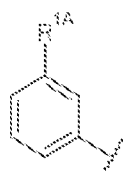
10 R^{N7} and R^{N6} are independently selected from H and CH_3 ;

R^{N6} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

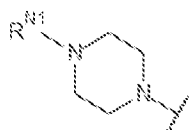
R^{N10} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

or

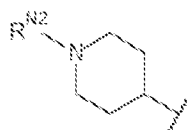
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where R^{1A} is



(R^{1A1})



(R^{1A2})

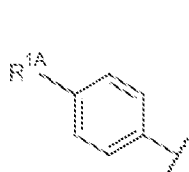
and R^{N1} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

R^{N2} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

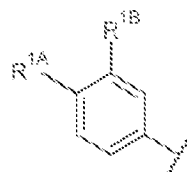
then R^2 is not selected from CF_3 , halo, CF_2H and CN.

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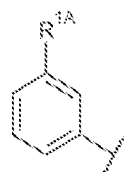
17. A compound according to any one of claims 14 to 16, wherein A is selected from:



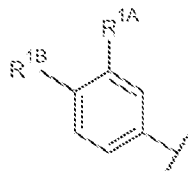
(A^{2A})



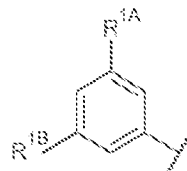
(A^{2B})



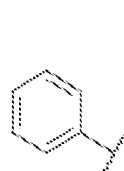
(A^{3A})



(A^{3B})



(A^{3C})



(A^{4A})

18. A compound according to any one of claims 14 to 17, where no R^{1B} substituents are present on A.

10

19. A compound according to any one of claims 14 to 17, where R^{1B} is methyl.

20. A compound according to any one of claims 14 to 17, where a single R^{1B} substituent is present.

15

21. A compound according to any one of claims 1 to 20, wherein R^{1A} is $CH(R^{O1})NHZ^1$, and Z^1 selected from H, CH_2CH_2OH and $C(=O)Me$.

22. A compound according to any one of claims 1 to 20, wherein R^{1A} is $CH(R^{C1})NHZ^1$, and R^{C1} is selected from H and methyl.

5 23. A compound according to any one of claims 1 to 20, wherein R^{1A} is $CH(R^{C1})NHZ^1$, Z^1 selected from H, CH_2CH_2OH and $C(=O)Me$, and R^{C1} is selected from H and methyl.

24. A compound according to any one of claims 1 to 20, wherein R^{1A} is $XNHZ^2$, and Z^2 is selected from H and $C(=O)OMe$.

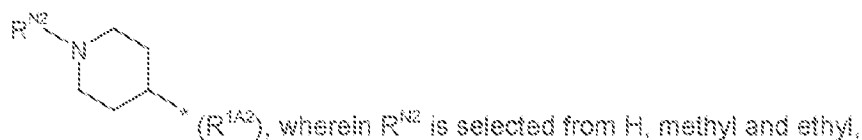
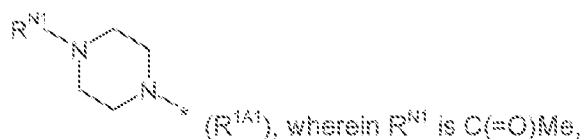
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25. A compound according to any one of claims 1 to 20, wherein R^{1A} is $XNHZ^2$, and X is selected from CMe_2 , cyclobutylidene and oxetanylidene.

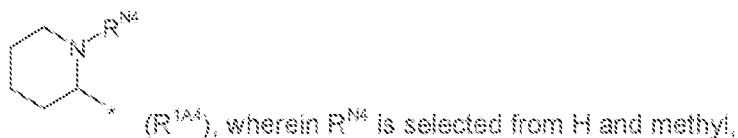
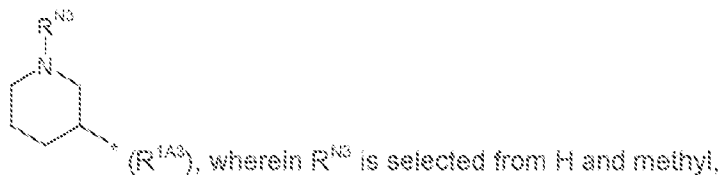
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26. A compound according to any one of claims 1 to 20, wherein R^{1A} is $XNHZ^2$, Z^2 is selected from H and $C(=O)OMe$ and X is selected from CMe_2 , and cyclobutylidene.

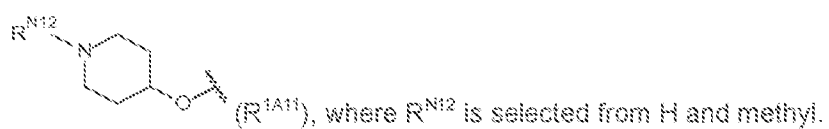
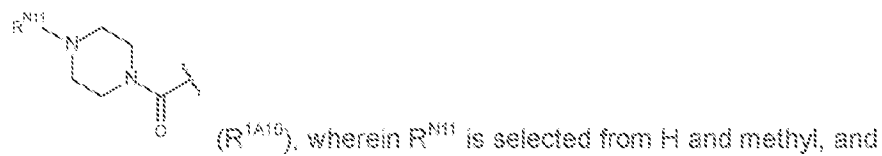
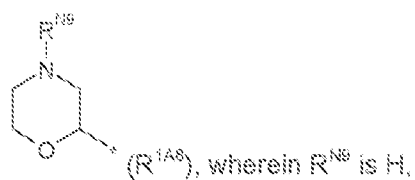
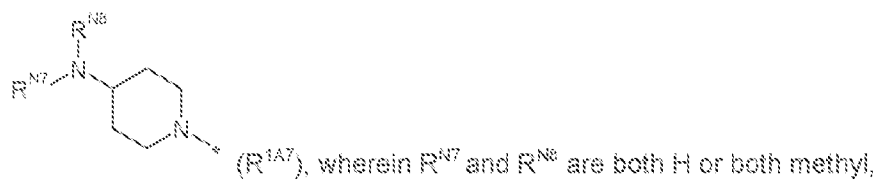
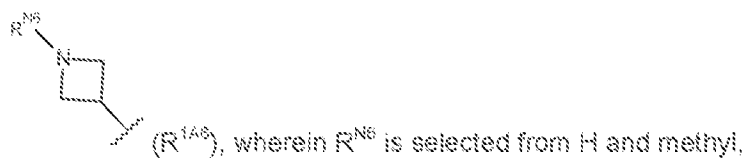
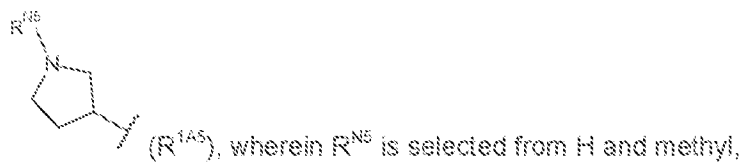
27. A compound according to any one of claims 1 to 20, wherein R^{1A} is selected from:



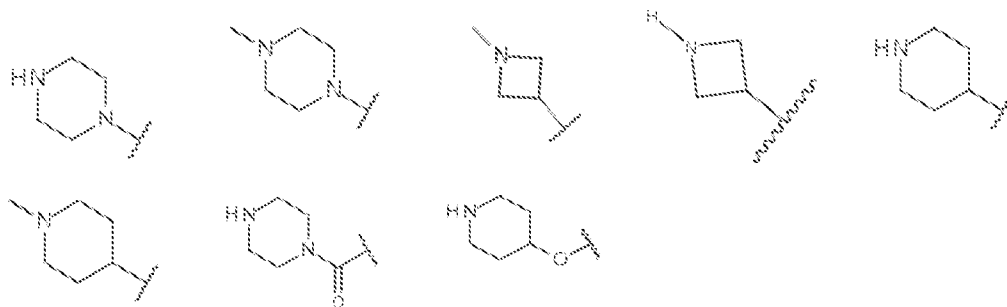
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10 28. A compound according any one of claims 1 to 20, wherein R^{1A} is selected from:



29. A compound according to any one of claims 1 to 28, wherein R² is H.

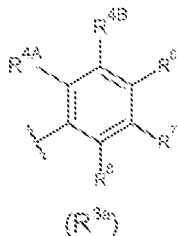
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30. A compound according to claim 29, wherein R^2 is methyl.

31. A compound according to claim 29, wherein R^2 is CF_3 .

5

32. A compound according to any one of claims 1 to 31, wherein R^3 has the structure:



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

10

33. A compound according to claim 32, wherein the group of R^{4A} and R^{4B} that is not R^4 , and R^6 , R^7 and R^8 are all H.

34. A compound according to claim 32, wherein one of the group of R^{4A} and R^{4B} that is not R^4 , R^6 , R^7 and R^8 is not H.

15

35. A compound according to claim 34, wherein the group that is not H is either R^6 or R^7 .

36. A compound according to claim 31, wherein the group R^{4A} is R^4 , and R^{4B} , R^6 , R^7 and R^8 are all H.

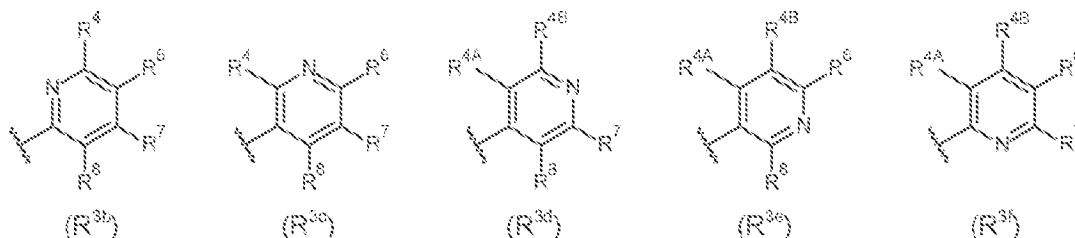
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37. A compound according to any one of claims 1 to 31, wherein R^5 is a substituted 6 membered heteroaryl group, where the heteroaryl ring system contains 1 or 2 N heteroatoms.

25

38. A compound according to claim 37, wherein R^5 is selected from one of the following structures:

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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 .

39. A compound according to claim 38, wherein the group of R^{4A} and R^{4B} (if present) that
 5 is not R^4 , and R^6 , R^7 and R^8 (if present) are all H.

40. A compound according to claim 38, wherein one of the group of R^{4A} and R^{4B} (if
 present) that is not R^4 , and R^6 , R^7 and R^8 (if present) is not H.

10 41. A compound according to any one of claims 38 to 40, wherein R^3 is of structure R^{3d}
 and R^{3e} .

42. A compound according to any one of claims 1 to 41, wherein R^4 is alpha to the $-\text{C}_2\text{H}_4-$
 group.

15

43. A compound according to any one of claims 1 to 41, wherein R^4 is beta to the $-\text{C}_2\text{H}_4-$
 group.

44. A compound according to any one of claims 1 to 43, wherein R^{N13} is H or Me.

20

45. A compound according to any one of claims 1 to 44, wherein Z^3 is H, Me or OMe.

46. A compound of formula (Ia) or isomers, salts, solvates or prodrugs thereof which is a
 compound of formula (I) according to claim 1 wherein:

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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 or 2 N
 atoms, and;

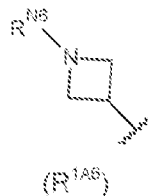
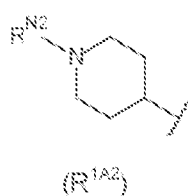
A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further
 bear a substituent R^{1C} which are not alpha to the NH group, where R^{1A} is selected from:

30

- (i) $\text{CH}(R^{C1})\text{NHZ}^1$, where R^{C1} is selected from C_{1-2} alkyl and Z^1 is selected from H and C_{1-3}
 alkyl optionally substituted by OH,;

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- (ii) XNHZ^2 , where X is cyclobutylidene, and Z^2 is $\text{C}(=\text{O})\text{OC}_{1-3}$ alkyl;
 (iii) a group selected from:



wherein:

$\text{R}^{\text{N}2}$ is selected from H and C_{1-4} alkyl;

5 $\text{R}^{\text{N}6}$ is H;

and where R^{10} is C_{1-3} alkyl;

R^2 is selected from C_{1-4} alkyl and CF_3 ;

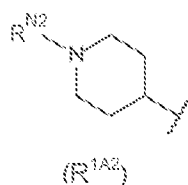
R^3 is substituted phenyl, where R^3 bears a substituent R^4 alpha to the $-\text{C}_2\text{H}_4-$ group, and may additionally bear a further substituent F; and

10 R^4 is $-\text{CH}_2-\text{C}(\text{O})\text{N}(\text{R}^{\text{N}13})\text{Z}^3$, where $\text{R}^{\text{N}13}$ is H; and Z^3 is H.

47. A compound of formula (Ib) or isomers, salts, solvates or prodrugs thereof which is a compound of formula (I) according to claim 1 wherein:

15 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 or 2 N atoms, and;

A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear a substituent R^{10} which are not alpha to the NH group, where R^{1A} is R^{1A2} ;



wherein:

20 $\text{R}^{\text{N}2}$ is selected from H and C_{1-4} alkyl;

and where R^{10} is C_{1-3} alkyl;

R^2 is selected from C_{1-4} alkyl;

R^3 is substituted phenyl, where R^3 bears a substituent R^4 alpha to the $-\text{C}_2\text{H}_4-$ group; and

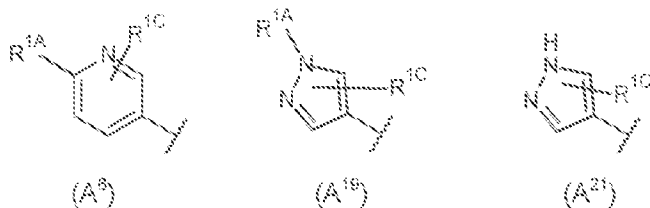
R^4 is $-\text{CH}_2-\text{C}(\text{O})\text{N}(\text{R}^{\text{N}13})\text{Z}^3$, where $\text{R}^{\text{N}13}$ is H; and Z^3 is H.

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48. A compound of formula (Ic) or isomers, salts, solvates or prodrugs thereof which is a compound of formula (I) according to claim 1 wherein:

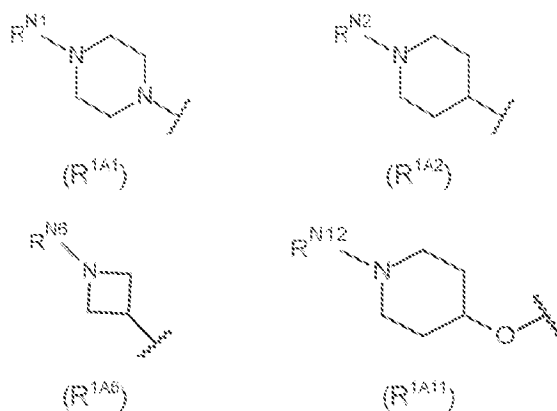
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A selected from:



wherein R^{1A} is selected from:

- 5 (i) CH(R^{C1})NHZ¹, where R^{C1} is selected from H and methyl and Z¹ is selected from H and CH₂CH₂OH;
- (ii) XNHZ², where X is selected from cyclobutylidene and oxetanylidene and Z² is selected from H and C(=O)OMe;
- (iii) a group selected from R^{1A1}, R^{1A2}, R^{1A8} and R^{1A11};

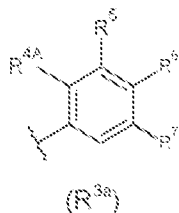


wherein:

- 10 R^{N1} is selected from H and Me;
- R^{N2} is selected from H and Me;
- R^{N8} is selected from H and Me; and
- R^{N12} is selected from H and Me;

and where there may be a single R^{1C} group which is methyl;

- 15 R² is selected from H, methyl and CF₃;
- R³ is:



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where R^5 , R^6 and R^7 are independently selected from H, F, methyl and CF_3 , and only one of them is not H; and

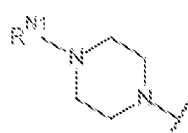
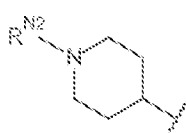
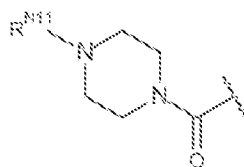
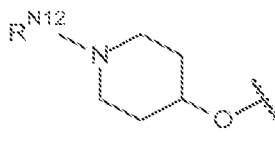
R^4 is $-CH_2-C(O)NH_2$.

- 5 49. A compound of formula (IIa) or isomers, salts, solvates or prodrugs thereof which is a compound of formula (II) according to claim 14 wherein:

A is substituted phenyl;

A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear a substituent R^{1B} which is not alpha to the NH group, where R^{1A} is selected from:

- 10 (i) $CH(R^{C1})NHZ^1$, where R^{C1} is selected from H and C_{1-2} alkyl and Z^1 is selected from H, C_{1-3} alkyl optionally substituted by OH and $C(=O)Me$;
- (ii) $XNHZ^2$, where X is selected from cyclobutylidene and oxetanylidene and Z^2 is selected from H and $C(=O)OC_{1-3}$ alkyl;
- (iii) a group selected from:

(R^{1A1})(R^{1A2})(R^{1A6})(R^{1A10})(R^{1A11})

- 15 wherein:

R^{N1} is H;

R^{N2} is selected from H and C_{1-4} alkyl;

R^{N6} is H;

R^{N11} is H; and

- 20 R^{N12} is H;

and where each R^{1B} is independently selected from:

(i) C_{1-3} alkyl;

(iii) F;

R^2 is selected from H, halo, C_{1-4} alkyl, CF_3 and methoxy;

- 25 R^3 is substituted phenyl, where R^3 bears a substituent R^4 alpha to the $-C_2H_4-$ group, and may additionally bear a further substituent selected from F, methyl and CF_3 ; and

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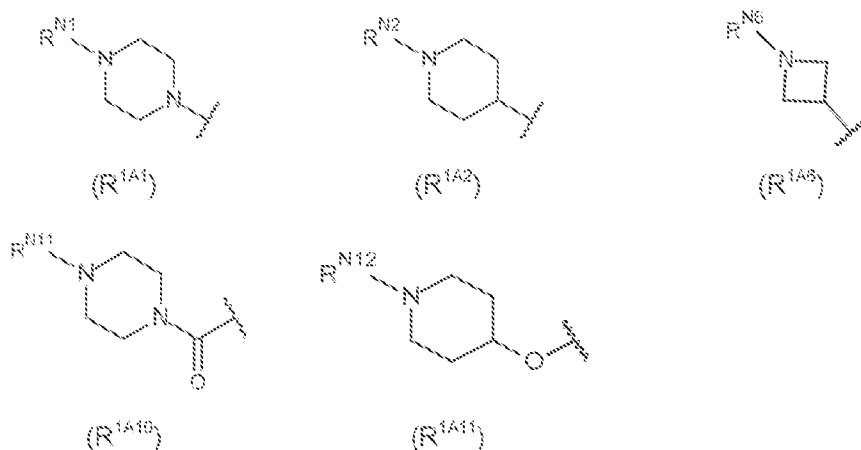
R^4 is $-\text{CH}_2-\text{C}(\text{O})\text{N}(\text{R}^{\text{N}13})\text{Z}^3$, where $\text{R}^{\text{N}13}$ is H; and Z^3 is H.

50. A compound of formula (IIb) or isomers, salts, solvates or prodrugs thereof which is a compound of formula (II) according to claim 14 wherein:

5 A is substituted phenyl;

A may bear a substituent $\text{R}^{1\text{A}}$ which is not alpha to the NH group and may optionally further bear a substituent $\text{R}^{1\text{B}}$ which is not alpha to the NH group, where $\text{R}^{1\text{A}}$ is selected from:

- (i) $\text{CH}(\text{R}^{\text{C}1})\text{NHZ}^1$, where $\text{R}^{\text{C}1}$ is selected from H and C_{1-2} alkyl and Z^1 is selected from H and C_{1-3} alkyl optionally substituted by OH;
- 10 (ii) XNHZ^2 , where X is oxetanylidine and Z^2 is H;
- (iii) a group selected from:



wherein:

$\text{R}^{\text{N}1}$ is H;

$\text{R}^{\text{N}2}$ is selected from H and C_{1-4} alkyl;

15 $\text{R}^{\text{N}6}$ is H;

$\text{R}^{\text{N}11}$ is H; and

$\text{R}^{\text{N}12}$ is H;

and where each $\text{R}^{1\text{B}}$ is C_{1-3} alkyl;

R^2 is selected from halo, C_{1-4} alkyl, CF_3 and methoxy;

20 R^3 is substituted phenyl, where R^3 bears a substituent R^4 alpha to the $-\text{C}_2\text{H}_4-$ group, and may additionally bear a further substituent selected from methyl and CF_3 ; and

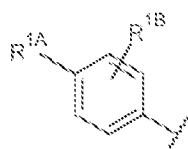
R^4 is $-\text{CH}_2-\text{C}(\text{O})\text{N}(\text{R}^{\text{N}13})\text{Z}^3$, where $\text{R}^{\text{N}13}$ is H; and Z^3 is H.

51. A compound of formula (IIc) or isomers, salts, solvates or prodrugs thereof which is a compound of formula (II) according to claim 14 wherein:

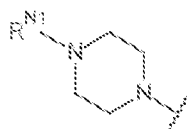
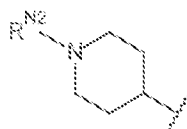
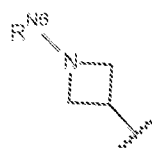
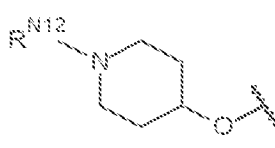
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A is:

(A²)wherein R^{1A} is selected from:

- (i) CH(R^{C1})NHZ¹, where R^{C1} is selected from H and methyl and Z¹ is selected from H and CH₂CH₂OH;
- 5 (ii) XNHZ², where X is selected from cyclobutylidene and oxetanylidine and Z² is selected from H and C(=O)OMe;
- (iii) a group selected from R^{1A1}, R^{1A2}, R^{1A6} and R^{1A11};

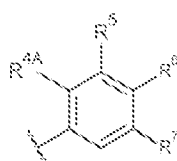
(R^{1A1})(R^{1A2})(R^{1A6})(R^{1A11})

wherein:

- R^{N1} is selected from H and Me;
- 10 R^{N2} is selected from H and Me;
- R^{N6} is selected from H and Me; and
- R^{N12} is selected from H and Me;

and where there may be a single R^{1B} group which is selected from F and methyl;R² is selected from H, methyl and CF₃;

- 15 R³ is:

(R^{3a})

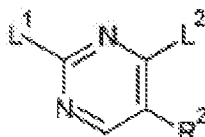
where R⁵, R⁶ and R⁷ are independently selected from H, F, methyl and CF₃, and only one of them is not H; and

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R^4 is $-\text{CH}_2-\text{C}(\text{O})\text{NH}_2$.

52. A compound selected from compounds 1 to 42 as described herein.

5 53. A process for the preparation of a compound according to any one of claims 1 to 52 or isomers, salts, solvates or prodrug thereof, comprising reacting a compound of formula F1



F1

with a compound of formula $\text{A}-\text{NH}_2$ to displace the group L^1 and with a compound of formula HCER^3 to displace the group L^2 , or

10 with a compound of formula HCER^3 to displace the group L^2 and with a compound of formula $\text{A}-\text{NH}_2$ to displace the group L^1 ,

wherein A, R^2 and R^3 are as defined in claim 1 or 13 and L^1 and L^2 are leaving groups.

15 54. A pharmaceutical agent comprising a compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52.

55. A composition comprising a compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, and a pharmaceutically acceptable carrier or diluents.

20

56. A compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55 for use in a method of therapy.

25 57. The use of a compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55 in the preparation of a medicament for treating a disease ameliorated by the inhibition of VEGFR3.

30 58. The use of a compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55 in the preparation of a medicament for treating cancer.

59. A compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55 for use in a method of treatment of a disease ameliorated by the inhibition of VEGFR3.

5

60. A compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 51, agent according to claim 53 or composition according to claim 54 for use in the method for treating cancer.

10

61. A compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55 for use in a method of treatment of the human or animal body.

15

62. A method of inhibiting VEGFR3 *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55.

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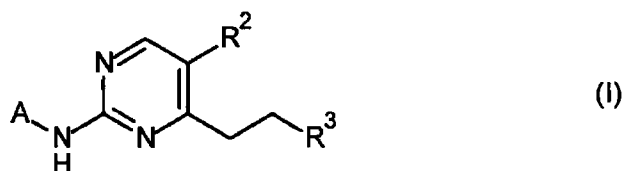
63. The use of claim 58 or the compound or isomer, salt, solvate or prodrug thereof of claim 60, wherein the cancer is selected from melanoma, breast cancer and cancer of the head or neck.

64. An anti-cancer agent comprising a compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55 and an anti-tumour agent.

AMENDED CLAIMS

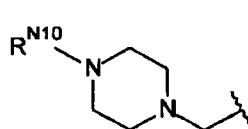
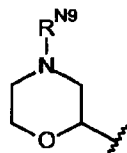
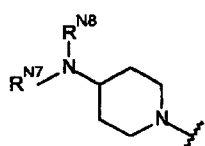
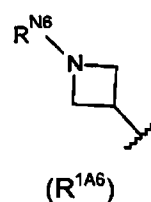
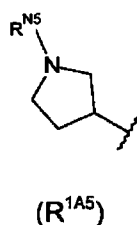
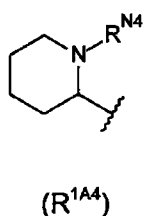
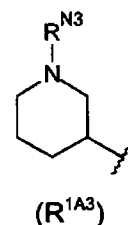
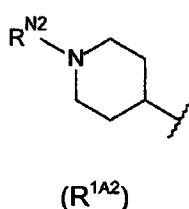
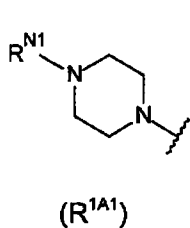
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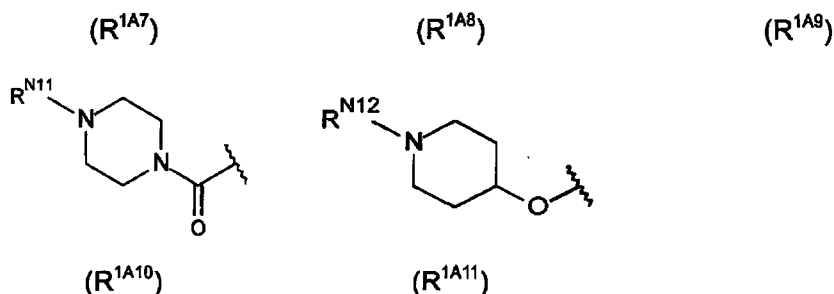
1. A compound of the formula (I) or isomers, salts, solvates or prodrugs thereof:



wherein:

- 5 A is an optionally substituted 5-10 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, and;
- A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear one, two or three substituents R^{1C} which are not alpha to the NH group, where R^{1A} is
- 10 selected from:
- (i) $CH(R^{C1})NHZ^1$, where R^{C1} is selected from H, C_{1-2} alkyl and Z^1 is selected from H, C_{1-3} alkyl optionally substituted by OH, $C(=O)OC_{1-3}$ alkyl and $C(=O)Me$;
 - (ii) $XNHZ^2$, where X is selected from CMe_2 , cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidene and Z^2 is selected from H, C_{1-3} alkyl optionally substituted by OH, $C(=O)OC_{1-3}$ alkyl and $C(=O)Me$;
 - 15 (iii) a group selected from R^{1A1} to R^{1A11} :





wherein:

R^{N1} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N2} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N3} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

5 R^{N4} is selected from H and CH₃;

R^{N5} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N6} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N7} and R^{N8} are independently selected from H and CH₃;

R^{N9} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

10 R^{N10} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

R^{N11} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me; and

R^{N12} is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and C(=O)Me;

and where each R^{1C} is independently selected from:

(i) C₁₋₃ alkyl;

15 (ii) CF₃;

(iii) F;

(iv) Cl;

(v) O-(C₁₋₃ alkyl);

(vi) CN; and

20 (vii) =O;

R² is selected from H, halo, C₁₋₄ alkyl, CF₃, CF₂H, CN and methoxy;

R³ is selected from substituted phenyl and a substituted 6 membered heteroaryl group,

where the heteroaryl ring system contains 1 or 2 N heteroatoms, where

R³ bears a substituent R⁴ either alpha or beta to the -C₂H₄- group, and may additionally bear
25 further substituents selected from F, methyl and CF₃; and

R⁴ is -CH₂-C(O)N(R^{N13})Z³, where R^{N13} is selected from H and CH₃; and Z³ is selected from
H, CH₃ and OCH₃.

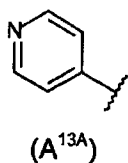
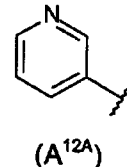
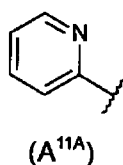
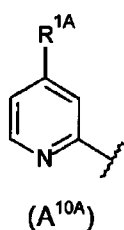
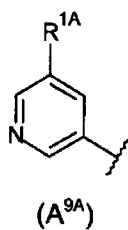
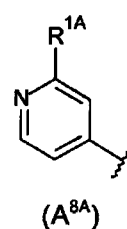
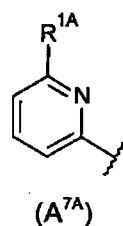
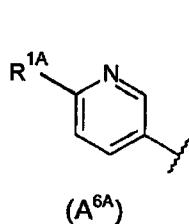
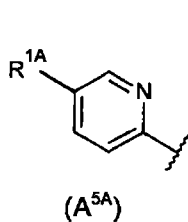
2. A compound according to claim 1, with the proviso that it is not the following
30 compound:

C21	
C32	

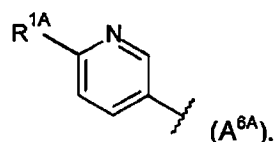
3. A compound according to claim 1, wherein A is an optionally substituted 6 membered heteroaryl group.

5 4. A compound according to claim 3, wherein A is optionally substituted pyridyl.

5. A compound according to claim 4, wherein A is selected from:



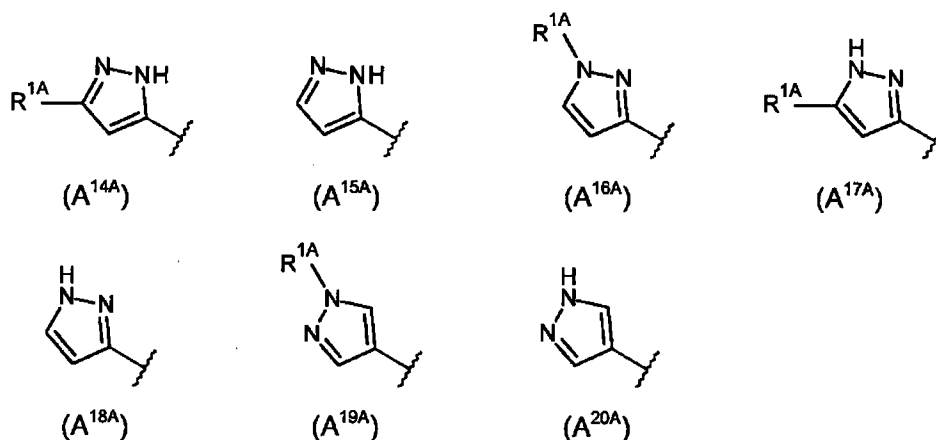
6. A compound according to claim 5, wherein A is



7. A compound according to claim 1, wherein A is an optionally substituted 5 membered heteroaryl group.

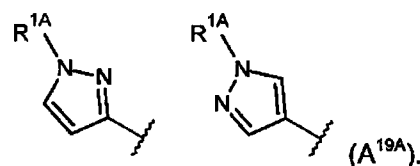
8. A compound according to claim 7, wherein A is optionally substituted pyrazolyl.

9. A compound according to claim 8, wherein A is selected from:



5

10. A compound according to claim 9, wherein A is



11. A compound according to any one of claims 1 to 10, where no R^{1C} substituents are present on A.

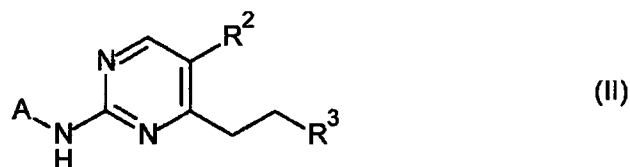
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12. A compound according to any one of claims 1 to 10, where R^{1C} is methyl.

13. A compound according to any one of claims 1 to 10, where a single R^{1C} substituent is present.

15

14. A compound of formula (II) or isomers, salts, solvates or prodrugs thereof:

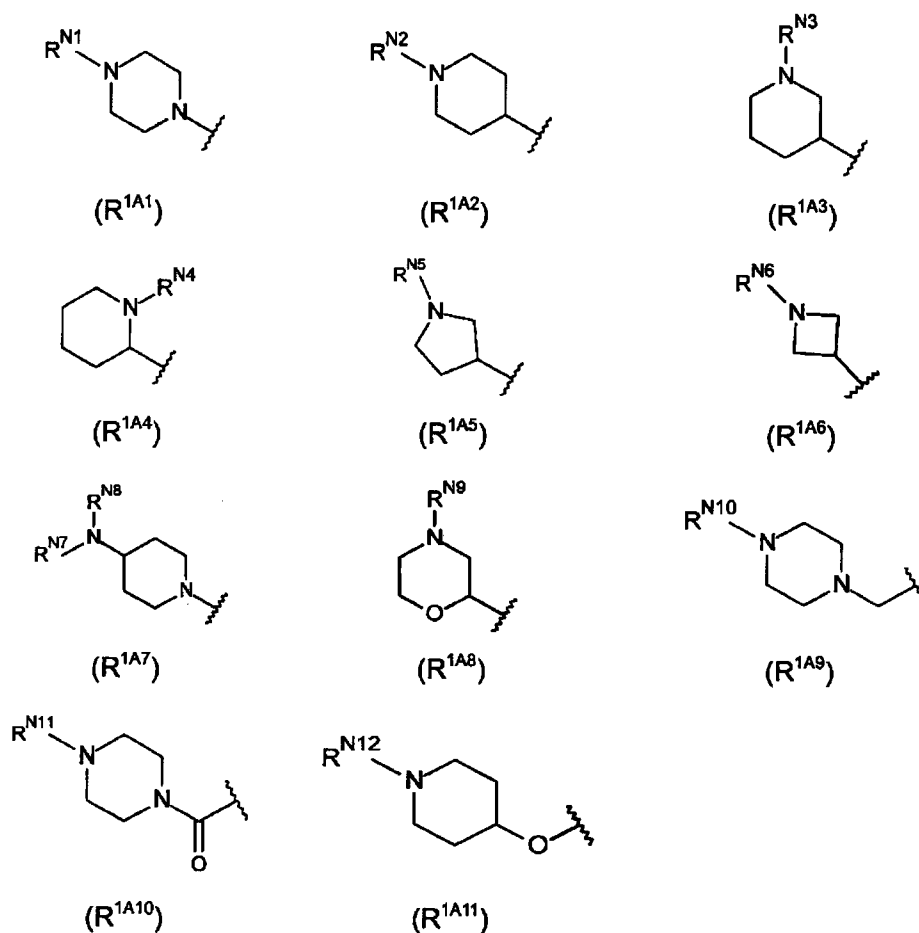


wherein:

A is optionally substituted phenyl;

when A is optionally substituted phenyl, A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear one or two substituents R^{1B} which are not alpha to the NH group, where R^{1A} is selected from:

- 5 (i) $CH(R^{C1})NHZ^1$, where R^{C1} is selected from H, C_{1-2} alkyl and Z^1 is selected from H, C_{1-3} alkyl optionally substituted by OH, $C(=O)OC_{1-3}$ alkyl and $C(=O)Me$;
- (ii) $XNHZ^2$, where X is selected from CMe_2 , cyclopropylidene, cyclobutylidene, cyclopentylidene and oxetanylidene and Z^2 is selected from H, C_{1-3} alkyl optionally substituted by OH, $C(=O)OC_{1-3}$ alkyl and $C(=O)Me$;
- (iii) a group selected from R^{1A1} to R^{1A11} :



10 wherein:

R^{N1} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

R^{N2} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

R^{N3} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

R^{N4} is selected from H and CH_3 ;

15 R^{N5} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

R^{N6} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

R^{N7} and R^{N8} are independently selected from H and CH_3 ;

R^{N9} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

R^{N10} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

R^{N11} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$; and

5 R^{N12} is selected from H, C_{1-4} alkyl, C_{3-4} cycloalkyl and $C(=O)Me$;

and where each R^{1B} is independently selected from:

(i) C_{1-3} alkyl;

(ii) CF_3 ;

(iii) F;

10 (iv) Cl;

(v) $O-(C_{1-3} \text{ alkyl})$;

(vi) CN;

R^2 is selected from H, halo, C_{1-4} alkyl, CF_3 , CF_2H , CN and methoxy;

R^3 is selected from substituted phenyl and a substituted 6 membered heteroaryl group,

15 where the heteroaryl ring system 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 ; and

R^4 is $-CH_2-C(O)N(R^{N13})Z^3$, where R^{N13} is selected from H and CH_3 ; and Z^3 is selected from H, CH_3 and OCH_3 .

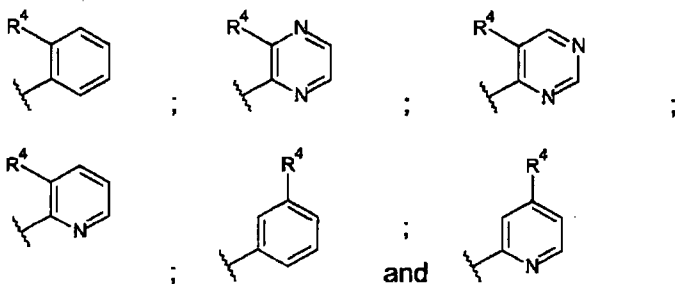
20

15. A compound according to claim 14, with the proviso it is not any of the following compounds:

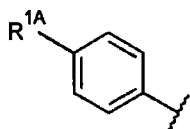
C1		C16	
C2		C17	
C3		C18	
C4		C19	
C5		C20	

C6		C22	
C7		C23	
C8		C24	
C9		C25	
C10		C26	
C11		C27	
C12		C28	
C13		C29	
C14		C30	
C15		C31	

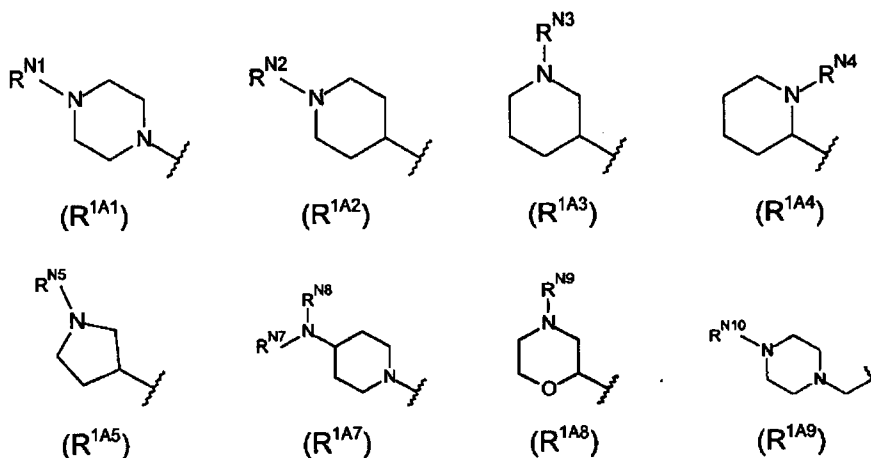
16. A compound according to claim 14, with the proviso that:
when R³ is selected from:



A is either:



where R^{1A} is selected from



and R^{N1} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

R^{N2} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

5 R^{N3} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

R^{N4} is selected from H and CH_3 ;

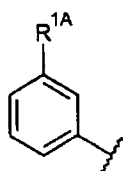
R^{N5} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

R^{N7} and R^{N8} are independently selected from H and CH_3 ;

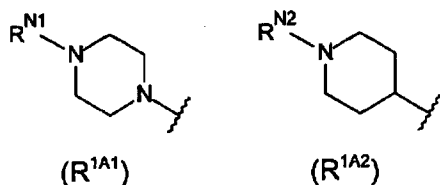
R^{N9} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

10 R^{N10} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

or



where R^{1A} is

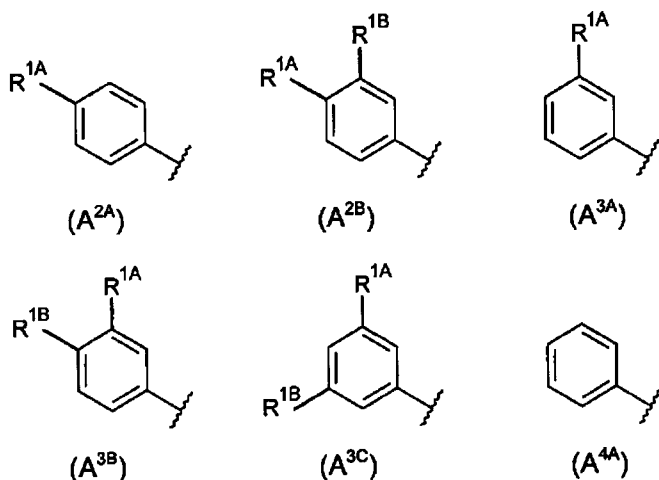


and R^{N1} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

R^{N2} is selected from H, C_{1-3} alkyl, and $C(=O)Me$;

then R^2 is not selected from CF_3 , halo, CF_2H and CN.

17. A compound according to any one of claims 14 to 16, wherein A is selected from:



5 18. A compound according to any one of claims 14 to 17, where no R^{1B} substituents are present on A.

19. A compound according to any one of claims 14 to 17, where R^{1B} is methyl.

10 20. A compound according to any one of claims 14 to 17, where a single R^{1B} substituent is present.

21. A compound according to any one of claims 1 to 20, wherein R^{1A} is $CH(R^{C1})NHZ^1$, and Z^1 selected from H, CH_2CH_2OH and $C(=O)Me$.

15

22. A compound according to any one of claims 1 to 20, wherein R^{1A} is $CH(R^{C1})NHZ^1$, and R^{C1} is selected from H and methyl.

20

23. A compound according to any one of claims 1 to 20, wherein R^{1A} is $CH(R^{C1})NHZ^1$, Z^1 selected from H, CH_2CH_2OH and $C(=O)Me$. and R^{C1} is selected from H and methyl.

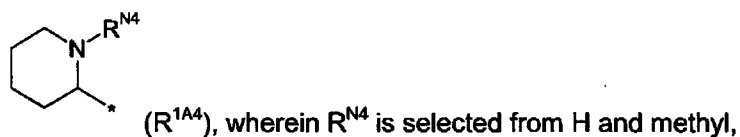
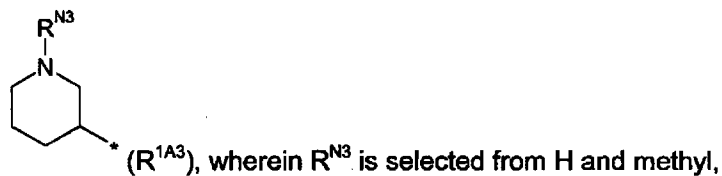
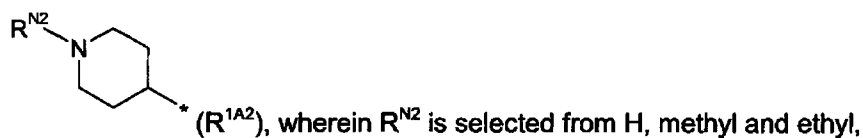
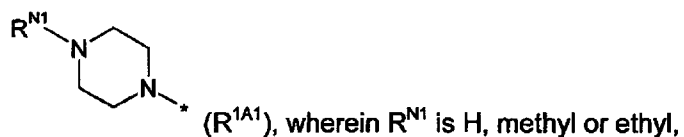
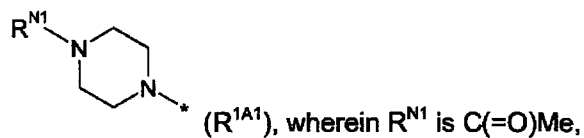
24. A compound according to any one of claims 1 to 20, wherein R^{1A} is $XNHZ^2$, and Z^2 is selected from H and $C(=O)OMe$.

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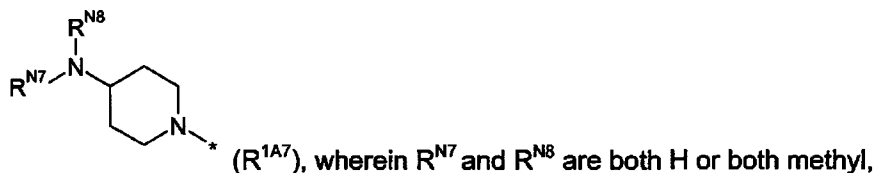
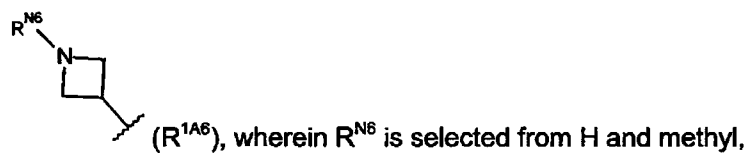
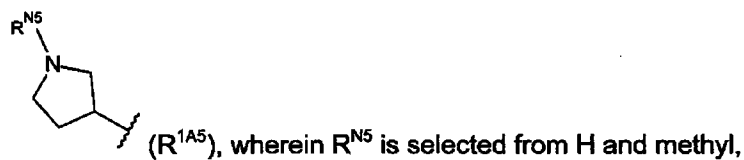
25. A compound according to any one of claims 1 to 20, wherein R^{1A} is $XNHZ^2$, and X is selected from CMe_2 , cyclobutylidene and oxetanylidene.

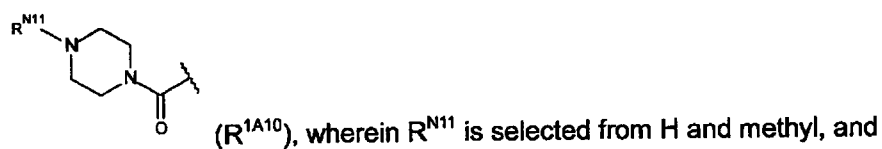
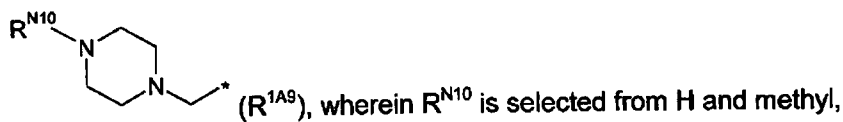
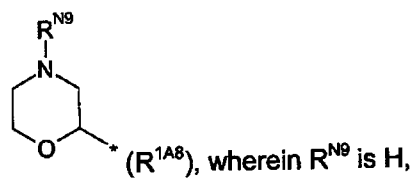
26. A compound according to any one of claims 1 to 20, wherein R^{1A} is $XNHZ^2$, Z^2 is selected from H and $C(=O)OMe$ and X is selected from CMe_2 , and cyclobutylidene.

5 27. A compound according to any one of claims 1 to 20, wherein R^{1A} is selected from:



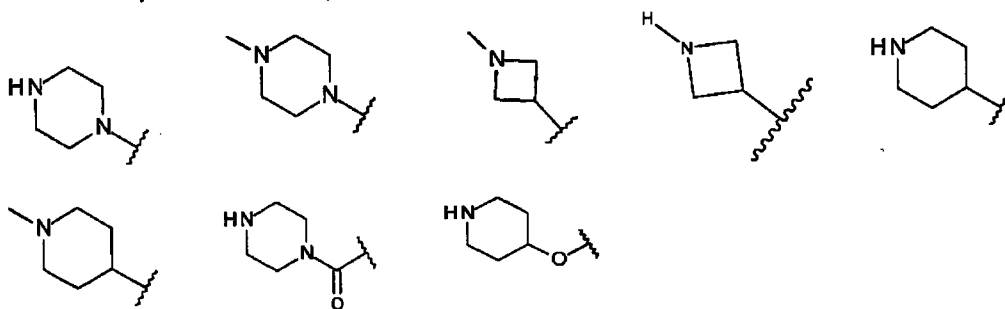
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28. A compound according any one of claims 1 to 20, wherein R^{1A} is selected from:



29. A compound according to any one of claims 1 to 28, wherein R^2 is H.

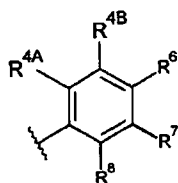
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30. A compound according to claim 29, wherein R^2 is methyl.

31. A compound according to claim 29, wherein R^2 is CF_3 .

15

32. A compound according to any one of claims 1 to 31, wherein R^3 has the structure:



(R^{3a})

where R⁶, R⁷ and R⁸ are independently selected from H, F, methyl and CF₃; and one of R^{4A} and R^{4B} is R⁴, and the other of R^{4A} and R^{4B} is selected from H, F, methyl and CF₃.

33. A compound according to claim 32, wherein the group of R^{4A} and R^{4B} that is not R⁴, and R⁶, R⁷ and R⁸ are all H.

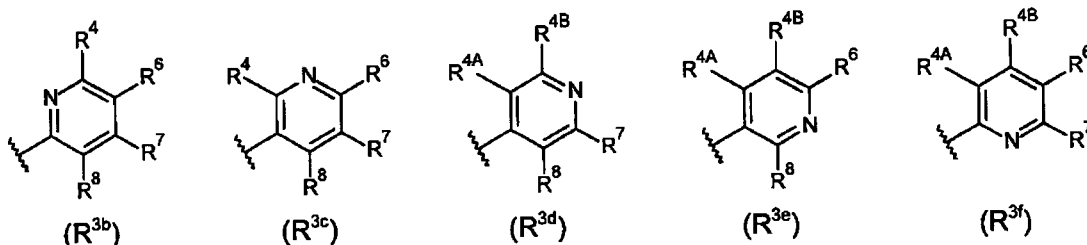
34. A compound according to claim 32, wherein one of the group of R^{4A} and R^{4B} that is not R⁴, R⁶, R⁷ and R⁸ is not H.

35. A compound according to claim 34, wherein the group that is not H is either R⁶ or R⁷.

36. A compound according to claim 31, wherein the group R^{4A} is R⁴, and R^{4B}, R⁶, R⁷ and R⁸ are all H.

37. A compound according to any one of claims 1 to 31, wherein R³ is a substituted 6 membered heteroaryl group, where the heteroaryl ring system contains 1 or 2 N heteroatoms.

38. A compound according to claim 37, wherein R³ is selected from one of the following structures:



where R⁶, R⁷ and R⁸ (if present) are independently selected from H, F, methyl and CF₃; one of R^{4A} and R^{4B} (if present) is R⁴, and the other is selected from H, F, methyl and CF₃.

39. A compound according to claim 38, wherein the group of R^{4A} and R^{4B} (if present) that is not R⁴, and R⁶, R⁷ and R⁸ (if present) are all H.

40. A compound according to claim 38, wherein one of the group of R^{4A} and R^{4B} (if present) that is not R⁴, and R⁶, R⁷ and R⁸ (if present) is not H.

41. A compound according to any one of claims 38 to 40, wherein R^3 is of structure R^{3d} and R^{3e} .

42. A compound according to any one of claims 1 to 41, wherein R^4 is alpha to the $-C_2H_4-$ group.

43. A compound according to any one of claims 1 to 41, wherein R^4 is beta to the $-C_2H_4-$ group.

44. A compound according to any one of claims 1 to 43, wherein R^{N13} is H or Me.

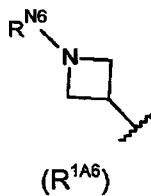
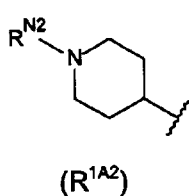
45. A compound according to any one of claims 1 to 44, wherein Z^3 is H, Me or OMe.

46. A compound of formula (Ia) or isomers, salts, solvates or prodrugs thereof which is a compound of formula (I) according to claim 1 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 or 2 N atoms, and;

A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear a substituent 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 C_{1-2} alkyl and Z^1 is selected from H and C_{1-3} alkyl optionally substituted by OH,;
- (ii) $XNHZ^2$, where X is cyclobutylidene, and Z^2 is $C(=O)OC_{1-3}$ alkyl;
- (iii) a group selected from:



wherein:

R^{N2} is selected from H and C_{1-4} alkyl;

R^{N6} is H;

and where R^{1C} is C_{1-3} alkyl;

R^2 is selected from C_{1-4} alkyl and CF_3 ;

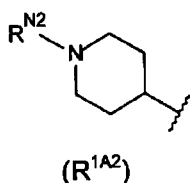
R^3 is substituted phenyl, where R^3 bears a substituent R^4 alpha to the $-C_2H_4-$ group, and may additionally bear a further substituent F; and

R^4 is $-CH_2-C(O)N(R^{N13})Z^3$, where R^{N13} is H; and Z^3 is H.

47. A compound of formula (Ib) or isomers, salts, solvates or prodrugs thereof which is a compound of formula (I) according to claim 1 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 or 2 N atoms, and;

A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear a substituent R^{1C} which are not alpha to the NH group, where R^{1A} is R^{1A2} .



wherein:

R^{N2} is selected from H and C₁₋₄ alkyl;

and where R^{1C} is C₁₋₃ alkyl;

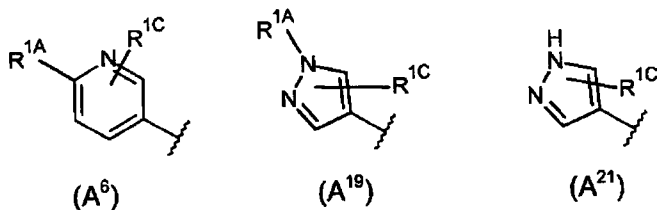
R^2 is selected from C₁₋₄ alkyl;

R^3 is substituted phenyl, where R^3 bears a substituent R^4 alpha to the -C₂H₄- group; and

R^4 is -CH₂-C(O)N(R^{N13})Z³, where R^{N13} is H; and Z³ is H.

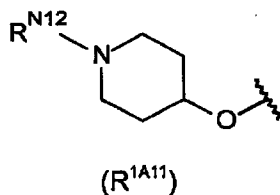
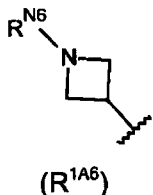
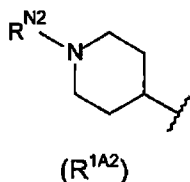
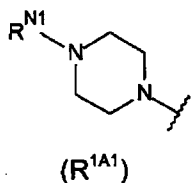
48. A compound of formula (Ic) or isomers, salts, solvates or prodrugs thereof which is a compound of formula (I) according to claim 1 wherein:

A selected from:



wherein R^{1A} is selected from:

- (i) CH(R^{C1})NHZ¹, where R^{C1} is selected from H and methyl and Z¹ is selected from H and CH₂CH₂OH;
- (ii) XNHZ², where X is selected from cyclobutylidene and oxetanylidene and Z² is selected from H and C(=O)OMe;
- (iii) a group selected from R^{1A1} , R^{1A2} , R^{1A6} and R^{1A11} .



wherein:

R^{N1} is selected from H and Me;

R^{N2} is selected from H and Me;

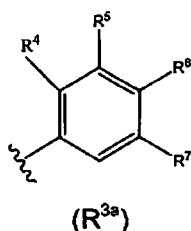
R^{N6} is selected from H and Me; and

5 R^{N12} is selected from H and Me;

and where there may be a single R^{1C} group which is methyl;

R^2 is selected from H, methyl and CF_3 ;

R^3 is:



where R^5 , R^6 and R^7 are independently selected from H, F, methyl and CF_3 , and only one of them is not H; and

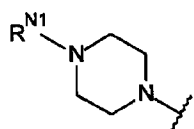
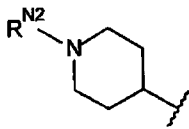
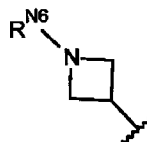
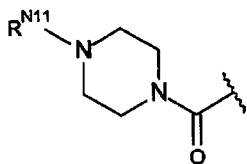
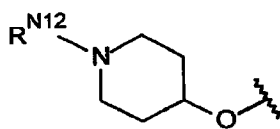
10 R^4 is $-CH_2-C(O)NH_2$.

49. A compound of formula (IIa) or isomers, salts, solvates or prodrugs thereof which is a compound of formula (II) according to claim 14 wherein:

15 A is substituted phenyl;

A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear a substituent R^{1B} which is 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 and C_{1-2} alkyl and Z^1 is selected from H, C_{1-3} alkyl optionally substituted by OH and $C(=O)Me$;
- 20 (ii) $XNHZ^2$, where X is selected from cyclobutylidene and oxetanylidene and Z^2 is selected from H and $C(=O)OC_{1-3}$ alkyl;
- (iii) a group selected from:

(R^{1A1})(R^{1A2})(R^{1A6})(R^{1A10})(R^{1A11})

wherein:

R^{N1} is H;

R^{N2} is selected from H and C₁₋₄ alkyl;

R^{N6} is H;

R^{N11} is H; and

R^{N12} is H;

and where each R^{1B} is independently selected from:

(i) C₁₋₃ alkyl;

(iii) F;

R^2 is selected from H, halo, C₁₋₄ alkyl, CF₃ and methoxy;

R^3 is substituted phenyl, where R^3 bears a substituent R^4 alpha to the -C₂H₄- group, and may additionally bear a further substituent selected from F, methyl and CF₃; and

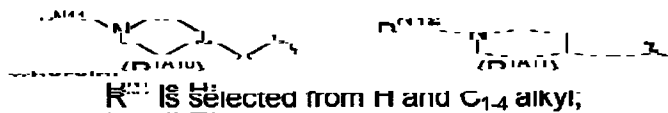
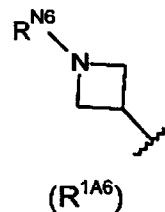
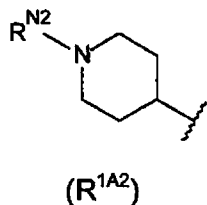
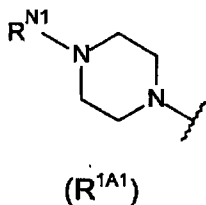
R^4 is -CH₂-C(O)N(R^{N13})Z³, where R^{N13} is H; and Z³ is H.

50. A compound of formula (IIb) or isomers, salts, solvates or prodrugs thereof which is a compound of formula (II) according to claim 14 wherein:

A is substituted phenyl;

A may bear a substituent R^{1A} which is not alpha to the NH group and may optionally further bear a substituent R^{1B} which is not alpha to the NH group, where R^{1A} is selected from:

- (i) CH(R^{C1})NHZ¹, where R^{C1} is selected from H and C₁₋₂ alkyl and Z¹ is selected from H and C₁₋₃ alkyl optionally substituted by OH;
- (ii) XNHZ², where X is oxetanylidine and Z² is H;
- (iii) a group selected from:



R¹⁰ is selected from H and C₁₋₄ alkyl;

and where each R¹⁰ is C₁₋₃ alkyl;

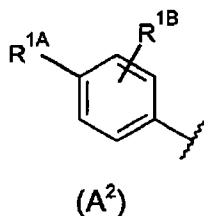
R^c is selected from halo, C₁₋₄ alkyl, CF₃ and methoxy;

R^j is substituted phenyl, where R^j bears a substituent R⁴ alpha to the -C₂H₄- group, and may additionally bear a further substituent selected from methyl and CF₃; and

R⁴ is -CH₂-C(O)N(Rⁿ¹⁰)Z⁵, where Rⁿ¹⁰ is H; and Z⁵ is H.

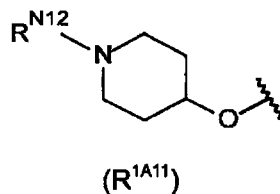
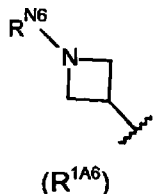
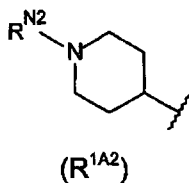
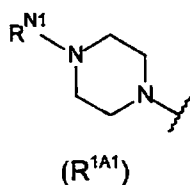
51. A compound of formula (IIc) or isomers, salts, solvates or prodrugs thereof which is a compound of formula (II) according to claim 14 wherein:

A is:



wherein R^{1A} is selected from:

- (i) CH(R^{C1})NHZ¹, where R^{C1} is selected from H and methyl and Z¹ is selected from H and CH₂CH₂OH;
- (ii) XNHZ², where X is selected from cyclobutylidene and oxetanylidine and Z² is selected from H and C(=O)OMe;
- (iii) a group selected from R^{1A1}, R^{1A2}, R^{1A6} and R^{1A11}.



wherein:

R^{N1} is selected from H and Me;

R^{N2} is selected from H and Me;

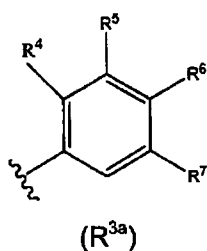
R^{N6} is selected from H and Me; and

5 R^{N12} is selected from H and Me;

and where there may be a single R^{1B} group which is selected from F and methyl;

R² is selected from H, methyl and CF₃;

R³ is:



where R⁵, R⁶ and R⁷ are independently selected from H, F, methyl and CF₃, and only one of them is not H; and

R⁴ is -CH₂-C(O)NH₂.

52. A compound selected from

2-(2-(2-(2-((4-(piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (1)

15 2-(2-(2-(5-methyl-2-((4-(piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (2)

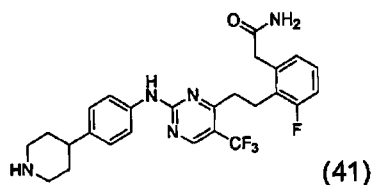
2-(2-(2-(2-((4-(aminomethyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (3)

2-(2-(2-(5-methyl-2-((6-(piperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (4)

20 2-(2-(2-(5-methyl-2-((6-(1-methylpiperidin-4-yl)pyridin-3-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (5)

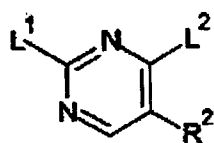
- 2-(2-(2-(2-((4-(piperazine-1-carbonyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (6)
- 2-(2-(2-(2-((3-fluoro-4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (7)
- 5 2-(2-(2-(2-((3-fluoro-4-(1-methylpiperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (8)
- 2-(5-fluoro-2-(2-(2-((4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (9)
- 2-(5-fluoro-2-(2-(2-((4-(1-methylpiperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (10)
- 10 2-(2-(2-(2-((3-methyl-4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (11)
- 2-(2-(2-(2-((3-methyl-4-(1-methylpiperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (12)
- 15 2-(2-(2-(2-((6-(piperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (13)
- 2-(2-(2-(2-((6-(1-methylpiperidin-4-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (14)
- 2-(4-fluoro-2-(2-(2-((4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (15)
- 20 2-(2-(2-(5-methyl-2-((4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (16)
- 2-(2-(2-(2-((4-(1-methylpiperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-4-(trifluoromethyl)phenyl)acetamide (17)
- 25 2-(2-(2-(2-(4-(1-aminoethyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (18)
- 2-(2-(2-(2-((4-(((2-hydroxyethyl)amino)methyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (19)
- 2-(2-(2-(2-((4-(azetidin-3-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (20)
- 30 2-(4-methyl-2-(2-(2-((4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)phenyl)acetamide (21)
- 2-(2-(2-(2-((4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-6-(trifluoromethyl)phenyl)acetamide (22)
- 35 2-(2-(2-(5-methoxy-2-((4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (23)

- 2-(2-(2-(5-methyl-2-(pyridin-3-ylamino)pyrimidin-4-yl)ethyl)phenyl)acetamide (24)
- 2-(2-(2-(2-(4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)ethyl)-5-(trifluoromethyl)phenyl)acetamide (25)
- 2-(2-(2-(5-methyl-2-(4-(piperidin-4-yloxy)phenyl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (26)
- 5 2-(2-(2-(2-(4-(aminomethyl)phenyl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (27)
- 2-(2-(2-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (28)
- 10 methyl 1-(4-(4-(2-(2-amino-2-oxoethyl)phenethyl)-5-methylpyrimidin-2-ylamino)phenyl)cyclobutylcarbamate (29)
- 2-(2-(2-(2-(1-(azetidin-3-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (30)
- 2-(2-(2-(2-(4-(3-aminooxetan-3-yl)phenylamino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (31)
- 15 2-(2-(2-(2-(4-(azetidin-3-yl)phenyl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (32)
- 2-(2-(2-(5-Methyl-2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)ethyl)phenyl)acetamide (33)
- 20 2-(2-(2-(2-(4-(1-aminoethyl)phenyl)amino)-5-methylpyrimidin-4-yl)ethyl)phenyl)acetamide (34)
- 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)
- 25 2-(2-(2-(2-(4-(1-aminoethyl)phenylamino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (37)
- 2-(2-(2-(2-(3-(1-aminoethyl)phenyl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (38)
- 30 2-(2-(2-(2-(3-(1-acetamidoethyl)phenyl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (39)
- 2-(2-(2-(2-(6-(1-aminoethyl)pyridin-3-yl)amino)-5-chloropyrimidin-4-yl)ethyl)phenyl)acetamide (40)



or an isomer salt, solvate, protected form or prodrug thereof.

53. A process for the preparation of a compound according to any one of claims 1 to 52 or isomers, 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 or 13 and L^1 and L^2 are leaving groups.

54. A pharmaceutical agent comprising a compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52.

55. A composition comprising a compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, and a pharmaceutically acceptable carrier or diluents.

56. A compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55 for use in a method of therapy.

57. The use of a compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55 in the preparation of a medicament for treating a disease ameliorated by the inhibition of VEGFR3.

58. The use of a compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55 in the preparation of a medicament for treating cancer.

5 59. A compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55 for use in a method of treatment of a disease ameliorated by the inhibition of VEGFR3.

10 60. A compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 51, agent according to claim 53 or composition according to claim 54 for use in the method for treating cancer.

15 61. A compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55 for use in a method of treatment of the human or animal body.

20 62. A method of inhibiting VEGFR3 *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55.

63. The use of claim 58 or the compound or isomer, salt, solvate or prodrug thereof of claim 60, wherein the cancer is selected from melanoma, breast cancer and cancer of the head or neck.

25 64. An anti-cancer agent comprising a compound or an isomer, salt, solvate or prodrug thereof according to any one of claims 1 to 52, agent according to claim 54 or composition according to claim 55 and an anti-tumour agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2013/000912

A. CLASSIFICATION OF SUBJECT MATTER

**C07D 403/12 (2006.01) C07D 403/14 (2006.01) C07D 239/42 (2006.01) A61K 31/505 (2006.01) A61K 31/506 (2006.01)
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)

STN: Chemical Abstracts Registry and CAlus - structure search based on compounds of formula (I) and (II).

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	



Further documents are listed in the continuation of Box C



See patent family annex

* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
20 November 2013

Date of mailing of the international search report
20 November 2013

Name and mailing address of the ISA/AU

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/AU2013/000912
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2808540 A1 (MERCK PATENT GMBH) 23 February 2012 Page 4 lines 19-27, page 33 lines 30-32, Claims 1, 11 and 12.	1-4, 7, 8, 11-37, 42-47, 49-51, 54-61, 63, 64
A	CA 2463989 A1 (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.) 24 April 2003 Page 1 lines 5-14, Page 4 lines 4-24, Examples 37, 378, 401, Claim 1.	1-64
P,X	WO 2012/110773 A1 (CANCER THERAPEUTICS CRC PTY LIMITED) 23 August 2012 Page 6 lines 23-24, page 23 lines 11-19 Scheme A, page 31 lines 1-14 Scheme N, page 36 line 11 – page 37 line 10 Scheme X, page 38 line 23 – page 39 line 11, page 172 line 3 – page 177 line 11, Examples 1, 3-5, 8-11, 13, 14, 16-18, 20-33, 35, 36 and 38-40, Claim 25.	1, 11-14, 16-18, 27, 28, 31-33, 36-39, 42, 44, 45, 49, 50, 53-64

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 52
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See Supplemental Box

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2013/000912**Supplemental Box****Continuation of Box II**

Claim 52 does not comply with Rule 6.2(a) because it relies on references to the description and/or drawings.

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/AU2013/000912	
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
CA 2808540 A1	23 Feb 2012	AU 2011291110 A1	04 Apr 2013
		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
		WO 2012022408 A1	23 Feb 2012
CA 2463989 A1	24 Apr 2003	EP 1438053 A1	21 Jul 2004
		EP 1438053 B1	10 Sep 2008
		EP 2090571 A1	19 Aug 2009
		EP 2090571 B1	16 May 2012
		EP 2332924 A1	15 Jun 2011
		JP 2005509624 A	14 Apr 2005
		JP 4460292 B2	12 May 2010
		US 2003171359 A1	11 Sep 2003
		US 7173028 B2	06 Feb 2007
		US 2006100211 A1	11 May 2006
		US 7709480 B2	04 May 2010
		US 2010152167 A1	17 Jun 2010
		US 8420630 B2	16 Apr 2013
		UY 27487 A1	30 May 2003
		WO 03032997 A1	24 Apr 2003
WO 2012/110773 A1	23 Aug 2012	AU 2012216894 A1	05 Sep 2013
		CA 2827171 A1	23 Aug 2012
		CA 2827172 A1	23 Aug 2012
		US 2013017194 A1	17 Jan 2013
		US 2013022594 A1	24 Jan 2013
		WO 2012110773 A1	23 Aug 2012
		WO 2012110774 A1	23 Aug 2012
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			