(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 February 2011 (24.02.2011)

PCT

(10) International Publication Number
WO 2011/021038 A1

(51) International Patent Classification:
C07D 495/14 (2006.01) ***A61K 31/519*** (2006.01)
C07D 519/00 (2006.01) ***A61P 35/02*** (2006.01)
C07D 491/147 (2006.01)

(21) International Application Number:
PCT/GB2010/051370

(22) International Filing Date:
19 August 2010 (19.08.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0914594.7 20 August 2009 (20.08.2009) GB
1005584.6 1 April 2010 (01.04.2010) GB

(71) Applicant *(for all designated States except US)*: **KARUS THERAPEUTICS LIMITED** [GB/GB]; Southampton Science Park, 2 Venture Road, Chilworth, Southampton, Hampshire SO16 7NP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SHUTTLEWORTH, Stephen Joseph** [GB/GB]; Karus Therapeutics Limited, Southampton Science Park, 2 Venture Road, Chilworth, Southampton Hampshire SO16 7NP (GB). **CECIL, Alexander Richard Liam** [GB/GB]; Karus Therapeutics Limited, Southampton Science Park, 2 Venture Road, Chilworth, Southampton Hampshire SO16 7NP (GB). **HILL, Thomas James** [GB/GB]; Karus Therapeutics Limited, Southampton Science Park, 2 Venture Road, Chilworth, Southampton Hampshire SO16 7NP (GB). **SILVA, Franck Alexandre** [FR/GB]; Karus Therapeutics Limited, Southampton Science Park, 2 Venture Road, Chilworth, Southampton Hampshire SO16 7NP (GB).

(74) Agent: PERRY, Robert Edward; Gill Jennings & Every LLP, Broadgate House, 7 Eldon Street, London, Greater London EC2M 7LH (GB).

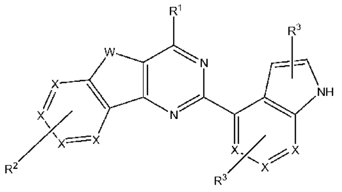
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

(54) Title: TRICYCLIC HETEROCYCLIC COMPOUNDS AS PHOSPHOINOSITIDE 3-KINASE INHIBITORS



(I)

(57) Abstract: Compounds of formula (I) or a pharmaceutically acceptable salt thereof, wherein: W is O, N-H, N-(C_1-C_{10} alkyl) or S; each X is independently CH or N; R^1 is a 5 to 7-membered saturated or unsaturated, optionally substituted heterocycle containing at least 1 heteroatom selected from N or O; R^2 is $(LQ)_mY$; and each R^3 is independently H, C_1-C_{10} alkyl, aryl or heteroaryl, are surprisingly found to be inhibitors of PI3K-p110δ, and therefore have utility in therapy.

TRICYCLIC HETEROCYCLIC COMPOUNDS AS PHOSPHOINOSITIDE 3-KINASE INHIBITORS

Field of the Invention

The present invention relates to novel compounds which act as inhibitors of the class IA phosphoinositide 3-kinase enzyme, PI3K-p110δ, for the treatment of cancer, immune and inflammatory diseases.

Background of the Invention

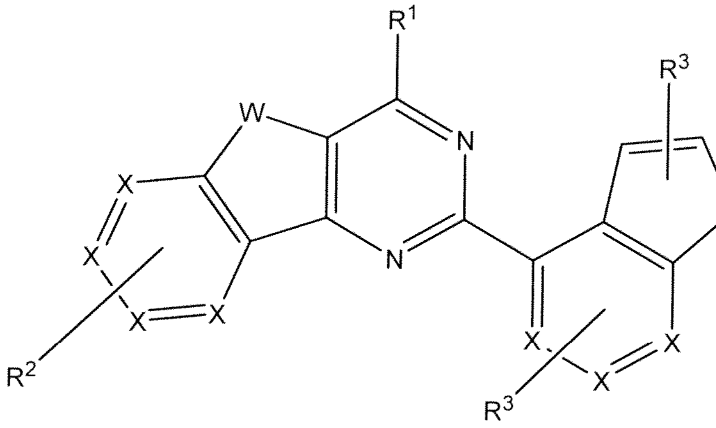
The phosphoinositide 3-kinases (PI3Ks) constitute a family of lipid kinases involved in the regulation of a network of signal transduction pathways that control a range of cellular processes. PI3Ks are classified into three distinct subfamilies, named class I, II, and III based upon their substrate specificities. Class IA PI3Ks possess a p110α, p110β, or p110δ catalytic subunit complexed with one of three regulatory subunits, p85α, p85β or p55δ. Class IA PI3Ks are activated by receptor tyrosine kinases, antigen receptors, G-protein coupled receptors (GPCRs), and cytokine receptors. The class IA PI3Ks primarily generate phosphatidylinositol-3,4,5-triphosphate ($PI(3,4,5)P_3$), a second messenger that activates the downstream target AKT. The consequences of biological activation of AKT include tumour cell progression, proliferation, survival and growth, and there is significant evidence suggesting that the PI3K/AKT pathway is dysregulated in many human cancers. Additionally, PI3K activity has been implicated in endocrinology, cardiovascular disease, immune disorders and inflammation. It has been established that PI3K-p110δ plays a critical role in the recruitment and activation of immune and inflammatory cells. PI3K-p110δ is also upregulated in a number of human tumours and plays a key role in tumour cell proliferation and survival.

Compounds which are able to modulate p110δ activity have important therapeutic potential in cancer and immune and inflammatory disorders.

WO2006/046035 describes fused pyrimidines, which have activity as inhibitors of PI3K. The compounds disclosed therein exhibit selectivity for class Ia PI3Ks, notably p110δ.

Summary of the Invention

The present invention is a compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

W is O, N-H, N-(C_1-C_{10} alkyl) or S;

each X is independently CH or N;

R^1 is a 5 to 7-membered saturated or unsaturated, optionally substituted heterocycle containing at least 1 heteroatom selected from N or O;

R^2 is $(LQ)_mY$;

each L is independently a direct bond, C_1-C_{10} alkylene, C_2-C_{10} alkenylene, C_2-C_{10} alkynylene, arylene or C_3-C_{10} cycloalkylene;

each Q is independently a direct bond, heteroarylene, a heterocycle linker, -O-, -NR^3-, -C(O)-, -C(O)NR_3-, -SO_2-, -SO_2-NR^3-, -N-C(O)-NR^3-, -N-SO_2-NR^3, halogen, -C(halogen)$_a$($R^3_{(2-a)}$)-, -NR^4R^5-, -C(O)NR^4R^5, where R^4 and R^5 together with the nitrogen to which they are attached form a 5 to 7-membered heterocycle linker;

m is from 0 to 5;

Y is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, aryl, C_3-C_{10} cycloalkyl, heterocycle, heteroaryl, -OR^3, -$N(R^3)_2$, -C(O)R^3, -C(O)OR_3, -C(O)$N(R^3)_2$, -$N(R^3)_2$, -SO_2-R^3, -SO_2-$N(R^3)_2$, -N-C(O)-$N(R^3)_2$, -N-SO_2-$N(R^3)_2$, halogen, -C(halogen)$_b$$R^3_{(3-b)}$, -CN, -$NR^4R^5$-, -C(O)$NR^4R^5$, where R^4 and R^5 together with the nitrogen to which they are attached form a 5- to 7-membered heterocycle;

b is from 1 to 3;

a is 1 or 2; and

each R^3 is independently H, C_1-C_{10} alkyl, aryl or heteroaryl.

It has been surprisingly found that these compounds are inhibitors of PI3K-p110δ. Some of the compounds disclosed herein may additionally inhibit PI3K-p110β.

Description of the Preferred Embodiments

As used herein, alkyl means a C_1-C_{10} alkyl group, which can be linear or branched. Preferably, it is a C_1-C_6 alkyl moiety. More preferably, it is a C_1-C_4 alkyl moiety. Examples include methyl, ethyl, n-propyl and t-butyl. It may be divalent, e.g. propylene.

As used herein, cycloalkyl contains from 3 to 10 carbon atoms. It may be monovalent or divalent.

As used herein, alkenyl means a C_2-C_{10} alkenyl group. Preferably, it is a C_2-C_6 alkenyl group. More preferably, it is a C_2-C_4 alkenyl group. The alkenyl radicals may be mono- or di-saturated, more preferably monosaturated. Examples include vinyl, allyl, 1-propenyl, isopropenyl and 1-butenyl. It may be divalent, e.g. propenylene

As used herein, alkynyl is a C_2-C_{10} alkynyl group which can be linear or branched. Preferably, it is a C_2-C_4 alkynyl group or moiety. It may be divalent.

Each of the C_1-C_{10} alkyl, C_2-C_{10} alkenyl and C_2-C_{10} alkynyl groups may be optionally substituted with each other, i.e. C_1-C_{10} alkyl optionally substituted with C_2-C_{10} alkenyl. They may also be optionally substituted with aryl, cycloalkyl (preferably C_3-C_{10}), aryl or heteroaryl.

As used herein, aryl means a monocyclic, bicyclic, or tricyclic monovalent or divalent aromatic radical, such as phenyl, biphenyl, naphthyl, anthracenyl, which can be optionally substituted with up to five substituents preferably selected from the group of C_1-C_6 alkyl, hydroxy, C_1-C_3 hydroxyalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, amino, C_1-C_3 mono alkylamino, C_1-C_3 bis alkylamino, C_1-C_3 acylamino, C_1-C_3 aminoalkyl, mono (C_1-C_3 alkyl) amino C_1-C_3 alkyl, bis(C_1-C_3 alkyl) amino C_1-C_3 alkyl, C_1-C_3-acylamino, C_1-C_3 alkyl sulfonylamino, halo, nitro, cyano, trifluoromethyl, carboxy, C_1-C_3 alkoxycarbonyl, aminocarbonyl, mono C_1-C_3 alkyl aminocarbonyl, bis C_1-C_3 alkyl aminocarbonyl, -SO_3H, C_1-C_3 alkylsulfonyl, aminosulfonyl, mono C_1-C_3 alkyl aminosulfonyl and bis C_1-C_3-alkyl aminosulfonyl.

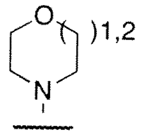
As used herein, heteroaryl means a monocyclic, bicyclic or tricyclic monovalent aromatic radical containing up to four heteroatoms selected from oxygen, nitrogen and sulfur, such as thiazolyl, tetrazolyl, imidazolyl, oxazolyl, isoxazolyl, thienyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, said radical being optionally substituted with up to three substituents preferably selected from the group of C_1-C_6 alkyl, hydroxy, C_1-C_3 hydroxyalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, amino, C_1-C_3 mono alkylamino, C_1-C_3 bis alkylamino, C_1-C_3 acylamino, C_1-C_3 aminoalkyl, mono (C_1-C_3 alkyl) amino C_1-C_3 alkyl , bis (C_1-C_3 alkyl) amino C_1-C_3 alkyl, C_1-C_3-acylamino, C_1-C_3 alkyl sulfonylamino, halo, nitro, cyano, trifluoromethyl, carboxy, C_1-C_3 alkoxycarbonyl, aminocarbonyl, mono C_1-C_3 alkyl aminocarbonyl, bis C_1-C_3 alkyl aminocarbonyl, -SO_3H, C_1-C_3 alkylsulphonyl, aminosulfonyl, mono C_1-C_3 alkyl aminosulfonyl and bis C_1-C_3-alkyl aminosulfonyl.

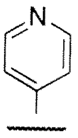
As used herein, heterocycle is a mono- or di-valent carbocyclic radical containing up to 4 heteroatoms selected from oxygen, nitrogen and sulphur. The word 'linker' has been used herein to mean di-valent. If the heterocycle is a di-valent linker, the heterocycle may be attached to neighbouring groups through a carbon atom, or through on of the heteroatoms, e.g. a N.

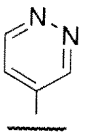
The heterocyclic ring may be mono- or di-saturated. The radical may be optionally substituted with up to three substituents independently selected from C_1-C_6 alkyl, hydroxy, C_1-C_3 hydroxyalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, amino, C_1-C_3 mono alkylamino, C_1-C_3 bis alkylamino, C_1-C_3 acylamino, C_1-C_3 aminoalkyl, mono (C_1-C_3 alkyl) amino C_1-C_3 alkyl , bis (C_1-C_3 alkyl) amino C_1-C_3 alkyl, C_1-C_3-acylamino, C_1-C_3 alkyl sulfonylamino, halo e.g. F, nitro, cyano, trifluoromethyl, carboxy, C_1-C_3 alkoxycarbonyl, aminocarbonyl, mono C_1-C_3 alkyl aminocarbonyl, bis C_1-C_3 alkyl aminocarbonyl, -SO_3H, C_1-C_3 alkylsulphonyl, aminosulfonyl, mono C_1-C_3 alkyl aminosulfonyl and bis C_1-C_3-alkyl aminosulfonyl.

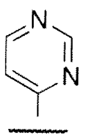
As used herein, the above groups can be followed by the suffix -ene. This means that the group is divalent, i.e. a linker group.

In a preferred embodiment R^1 is represented by any of the following structures:









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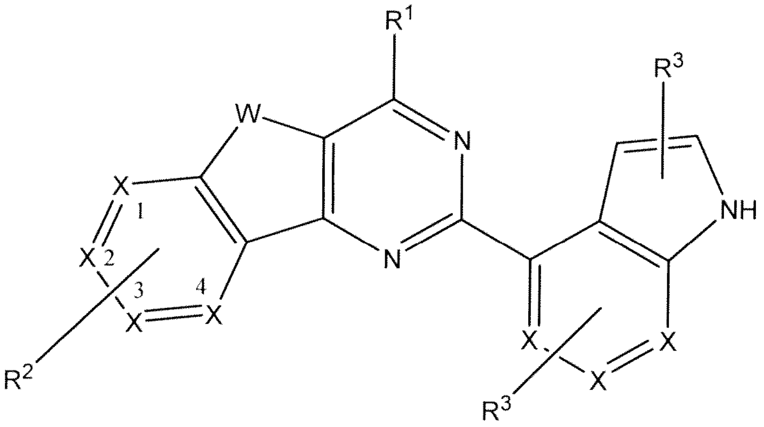
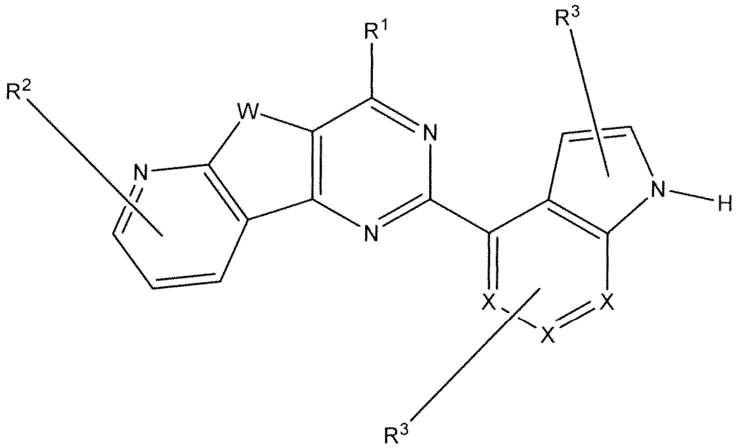
Preferably, W is S. More preferably, W is O.

R^2 may be attached to any suitable atom on the aryl group, as depicted in general formula I. Preferably, it is attached to atoms 2 or 3, as shown below:



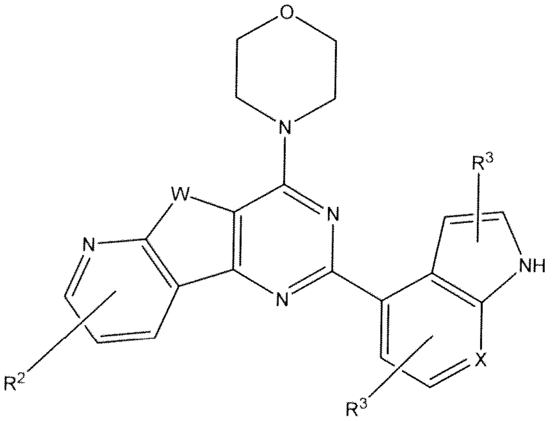
It may also be attached to atoms 1 or 4.

Preferably, a compound of the invention is of the structure:



As above, the placing of any of the R^2 and R^3 groups has no significance, other than the group must be attached to that particular aryl system. In other words, the R2 group has 4 possible bonding positions, the first R^3 group has only 2 possible positions of attachment, and the other R^3 group may be attached to one of 3 positions.

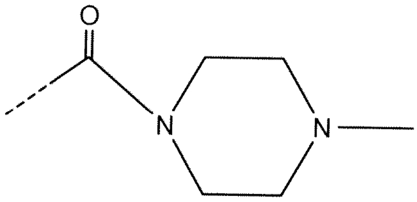
More preferably, a compound of the invention has the formula:



Preferably the 6,5-ring system in formula I is an indole. Alternatively, it may be a benzo-fused pyrrolo, a pyridyl-fused pyrrolo, a pyridazinyl-fused pyrrolo, a pyrazinyl-fused pyrrolo, or a pyrimidinyl-fused pyrrolo.

Preferably, both of the R^3 groups that are attached to the 6,5 ring system in formula I are H.

Preferably, at least one Q is –C(O)-NR^4R^5, where R^4 and R^5 together with the nitrogen to which they are attached form a 5 to 7-membered heterocycle linker. More preferably, Q is



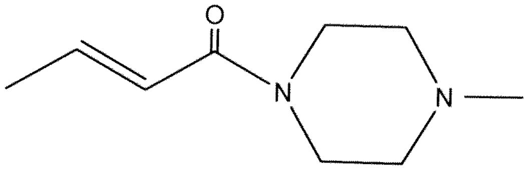
Preferably, at least one Q is -NR^3-

Preferably, at least one Q is a direct bond.

Preferably, at least one L is C_1-C_{10} alkylene or at least one L is C_2-C_{10} alkenylene, or at least one L is cyloalkylene.

Preferably Y is $N(R^3)_2$. More preferably, Y is a heteroaryl, such as an indolyl, or Y is a heterocycle.

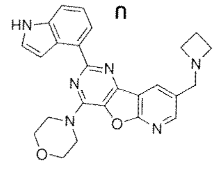
Preferably R^2 is H. Preferably R^2 is -(C_1-C_{10} alkylene)-$N(R^3)_2$. More preferably, R^2 is -CH_2-$N(CH_3)_2$. R^2 may also be –(C_2-C_{10} alkenylene)-C(O)-$N(R^4R^5)$-R^3, where R_4 and R_5 together with the nitrogen to which they are attached form a 5- to 7-membered heterocycle. More preferably, R^2 is



Still more preferably, R^2 comprises -(C_1-C_{10} alkylene)-NR^4R^5 or R^2 comprises -(C_1-C_{10} alkylene)-NR^3-(C_1-C_{10} alkylene)-cycloakyl, wherein R^2, R^4 and R^5 are as defined above.

Preferably m is 0, 1 or 2.

Examples of structures embodying the invention are: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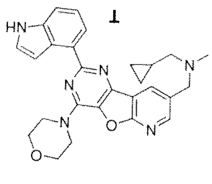
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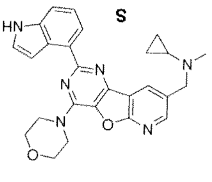
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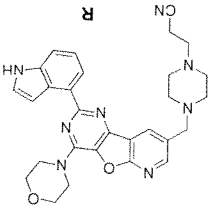
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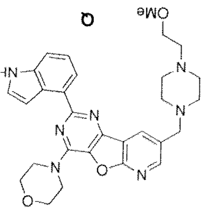
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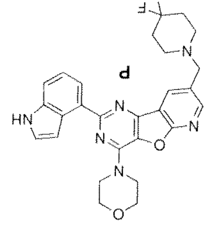
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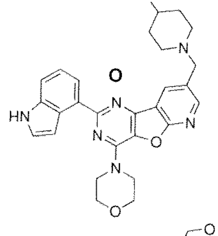
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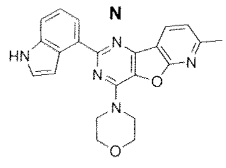
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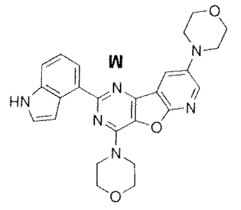
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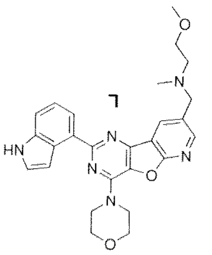
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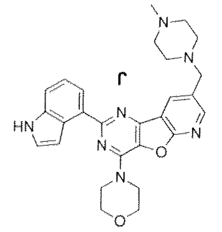
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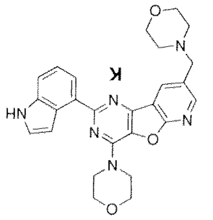
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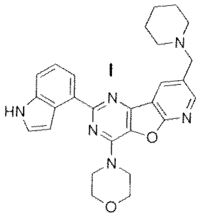
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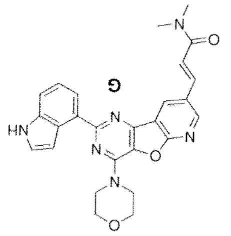
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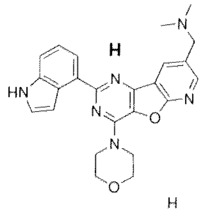
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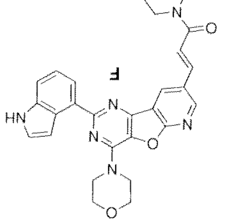
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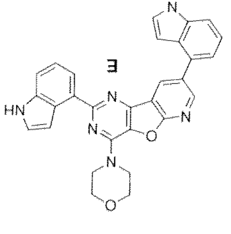
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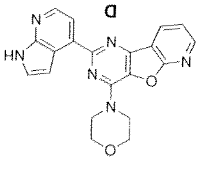
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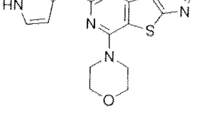
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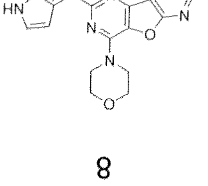
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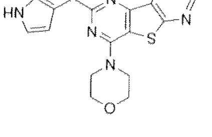

A

A pharmaceutical composition of the invention typically contains up to 85 wt% of a compound of the invention. More typically, it contains up to 50 wt% of a compound of the invention. Preferred pharmaceutical compositions are sterile and pyrogen-free. Further, the pharmaceutical compositions provided by the invention typically contain a compound of the invention which is a substantially pure optical isomer. Preferably, the pharmaceutical composition comprises a pharmaceutically acceptable salt form of a compound of the invention.

As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, salicylic, stearic, benzenesulphonic or *p*-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases such as alkyl amines, aryl amines or heterocyclic amines.

For the avoidance of doubt, the present invention also embraces prodrugs which react *in vivo* to give a compound of the present invention.

The compounds of the invention may be prepared by synthetic routes that will be apparent to those skilled in the art, e.g. based on the Examples.

The compounds of the invention and compositions comprising them may be administered in a variety of dosage forms. In one embodiment, a pharmaceutical composition comprising a compound of the invention may be formulated in a format suitable for oral, rectal, parenteral, intranasal or transdermal administration or administration by inhalation or by suppository. Typical routes of administration are parenteral, intranasal or transdermal administration or administration by inhalation.

The compounds of the invention can be administered orally, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. Preferred pharmaceutical compositions of the invention are compositions suitable for oral administration, for example tablets and capsules.

The compounds of the invention may also be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

The compounds of the invention may also be administered by inhalation. An advantage of inhaled medications is their direct delivery to the area of rich blood supply in comparison to many medications taken by oral route. Thus, the absorption is very rapid as the alveoli have an enormous surface area and rich blood supply and first pass metabolism is bypassed. A further advantage may be to treat diseases of the pulmonary system, such that delivering drugs by inhalation delivers them to the proximity of the cells which are required to be treated.

The present invention also provides an inhalation device containing such a pharmaceutical composition. Typically said device is a metered dose inhaler (MDI), which contains a pharmaceutically acceptable chemical propellant to push the medication out of the inhaler.

The compounds of the invention may also be administered by intranasal administration. The nasal cavity's highly permeable tissue is very receptive to medication and absorbs it quickly and efficiently, more so than drugs in tablet form. Nasal drug delivery is less painful and invasive than injections, generating less anxiety among patients. By this method absorption is very rapid and first pass metabolism is usually bypassed, thus reducing inter-patient variability. Further, the present invention also provides an intranasal device containing such a pharmaceutical composition.

The compounds of the invention may also be administered by transdermal administration. The present invention therefore also provides a transdermal patch containing a compound of the invention.

The compounds of the invention may also be administered by sublingual administration. The present invention therefore also provides a sub-lingual tablet comprising a compound of the invention.

A compound of the invention may also be formulated with an agent which reduces degradation of the substance by processes other than the normal metabolism of the patient, such as anti-bacterial agents, or inhibitors of protease enzymes which might be the present in the patient or in commensural or parasite organisms living on or within the patient, and which are capable of degrading the compound.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The compounds of the present invention can be used in both the treatment and prevention of cancer and can be used in a monotherapy or in a combination therapy. When used in a combination therapy, the compounds of the present invention are typically used together with small chemical compounds such as platinum complexes, anti-metabolites, DNA topoisomerase inhibitors, radiation, antibody-based therapies (for example herceptin and rituximab), anti-cancer vaccination, gene therapy, cellular therapies, hormone therapies or cytokine therapy.

In one embodiment of the invention a compound of the invention is used in combination with another chemotherapeutic or antineoplastic agent in the treatment of a cancer. Examples of such other chemotherapeutic or antineoplastic agents include platinum complexes including cisplatin and carboplatin, mitoxantrone, vinca alkaloids for example vincristine and vinblastine, anthracycline antibiotics for example daunorubicin and doxorubicin, alkylating agents for example chlorambucil and melphalan, taxanes for example paclitaxel, antifolates for example methotrexate and tomudex, epipodophyllotoxins for example etoposide, camptothecins for example irinotecan and its active metabolite SN38 and DNA methylation inhibitors for example the DNA methylation inhibitors disclosed in WO02/085400.

According to the invention, therefore, products are provided which contain a compound of the invention and another chemotherapeutic or antineoplastic agent as a combined preparation for simultaneous, separate or sequential use in alleviating a cancer. Also provided according to the invention is the use of compound of the invention in the manufacture of a medicament for use in the alleviation of cancer by coadministration with another chemotherapeutic or antineoplastic agent. The compound of the invention and the said other agent may be administrated in any order. In both these cases the compound of the invention and the other agent may be administered together or, if separately, in any order as determined by a physician.

The PI3K inhibitors of the present invention may also be used to treat abnormal cell proliferation due to insults to body tissue during surgery. These insults may arise as a result of a variety of surgical procedures such as joint surgery, bowel surgery, and cheloid scarring. Diseases that produce fibrotic tissue that may be treated using the PI3K inhibitors of the present invention include emphysema. Repetitive motion disorders that may be treated using the present invention include carpal tunnel syndrome. An example of a cell proliferative disorder that may be treated using the invention is a bone tumour.

Proliferative responses associated with organ transplantation that may be treated using PI3K inhibitors of the invention include proliferative responses contributing to potential organ rejections or associated complications. Specifically, these proliferative responses may occur during transplantation of the heart, lung, liver, kidney, and other body organs or organ systems.

Abnormal angiogenesis that may be treated using this invention include those abnormal angiogenesis accompanying rheumatoid arthritis, ischemic-reperfusion related brain edema and injury, cortical ischemia, ovarian hyperplasia and hypervascularity, polycystic ovary syndrome, endometriosis, psoriasis, diabetic retinopathy, and other ocular angiogenic diseases such as retinopathy of prematurity (retrolental fibroplastic), macular degeneration, corneal graft rejection, neuroscular glaucoma and Oster Webber syndrome.

Examples of diseases associated with uncontrolled angiogenesis that may be treated according to the present invention include, but are not limited to retinal/choroidal neovascularisation and corneal neovascularisation. Examples of diseases which include some component of retinal/choroidal neovascularisation include, but are not limited to, Best's diseases, myopia, optic pits, Stargart's diseases, Paget's disease, vein occlusion, artery occlusion, sickle cell anaemia, sarcoid, syphilis, pseudoxanthoma elasticum carotid apo structive diseases, chronic uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosus, retinopathy of prematurity, Eale's disease, diabetic retinopathy, macular degeneration, Bechet's diseases, infections causing a retinitis or chroiditis, presumed ocular histoplasmosis, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma and post-laser complications, diseases associated with rubesis (neovascularisation of the angle) and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy. Examples of corneal neovascularisation include, but are not limited to, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phylectenulosis, diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, Mooren ulcer, Terrien's marginal degeneration, marginal keratolysis, polyarteritis, Wegener sarcoidosis, Scleritis, periphigoid radial keratotomy, neovascular glaucoma and retrolental fibroplasia, syphilis, Mycobacteria infections, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, Herpes simplex infections, Herpes zoster infections, protozoan infections and Kaposi sarcoma.

Chronic inflammatory diseases associated with uncontrolled angiogenesis may also be treated using PI3K inhibitors of the present invention. Chronic inflammation depends on continuous formation of capillary sprouts to maintain an influx of inflammatory cells. The influx and presence of the inflammatory cells produce granulomas and thus maintains the chronic inflammatory state. Inhibition of angiogenesis using a PI3K inhibitor alone or in conjunction with other anti-inflammatory agents may prevent the formation of the granulosmas and thus alleviate the disease. Examples of chronic inflammatory diseases include, but are not limited to, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, psoriasis, sarcoidosis, and rheumatoid arthritis.

Inflammatory bowel diseases such as Crohn's disease and ulcerative colitis are characterised by chronic inflammation and angiogenesis at various sites in the gastrointestinal tract. For example, Crohn's disease occurs as a chronic transmural inflammatory disease that most commonly affects the distal ileum and colon but may also occur in any part of the gastrointestinal tract from the mouth to the anus and perianal area. Patients with Crohn's disease generally have chronic diarrhoea associated with abdominal pain, fever, anorexia, weight loss and abdominal swelling. Ulcerative colitis is also a chronic, nonspecific, inflammatory and ulcerative disease arising in the colonic mucosa and is characterised by the presence of bloody diarrhoea. These inflammatory bowel diseases are generally caused by chronic granulomatous inflammation throughout the gastrointestinal tract, involving new capillary sprouts surrounded by a cylinder of inflammatory cells. Inhibition of angiogenesis by these inhibitors should inhibit the formation of the sprouts and prevent the formation of granulomas. Inflammatory bowel diseases also exhibit extra intestinal manifestations, such as skin lesions. Such lesions are characterized by inflammation and angiogenesis and can occur at many sites other the gastrointestinal tract. Inhibition of angiogenesis by PI3K inhibitors according to the present invention can reduce the influx of inflammatory cells and prevent lesion formation.

Sarcoidosis, another chronic inflammatory disease, is characterized as a multisystem granulomatous disorder. The granulomas of this disease can form anywhere in the body. Thus, the symptoms depend on the site of the granulomas and whether the disease is active. The granulomas are created by the angiogenic capillary sprouts providing a constant supply of inflammatory cells. By using PI3K inhibitors according to the present invention to inhibit angiogenesis, such granulomas formation can be inhibited. Psoriasis, also a chronic and recurrent inflammatory disease, is characterised by papules and plaques of various sizes. Treatment using these inhibitors alone or in conjunction with other anti-inflammatory agents should prevent the formation of new blood vessels necessary to maintain the characteristic lesions and provide the patient relief from the symptoms.

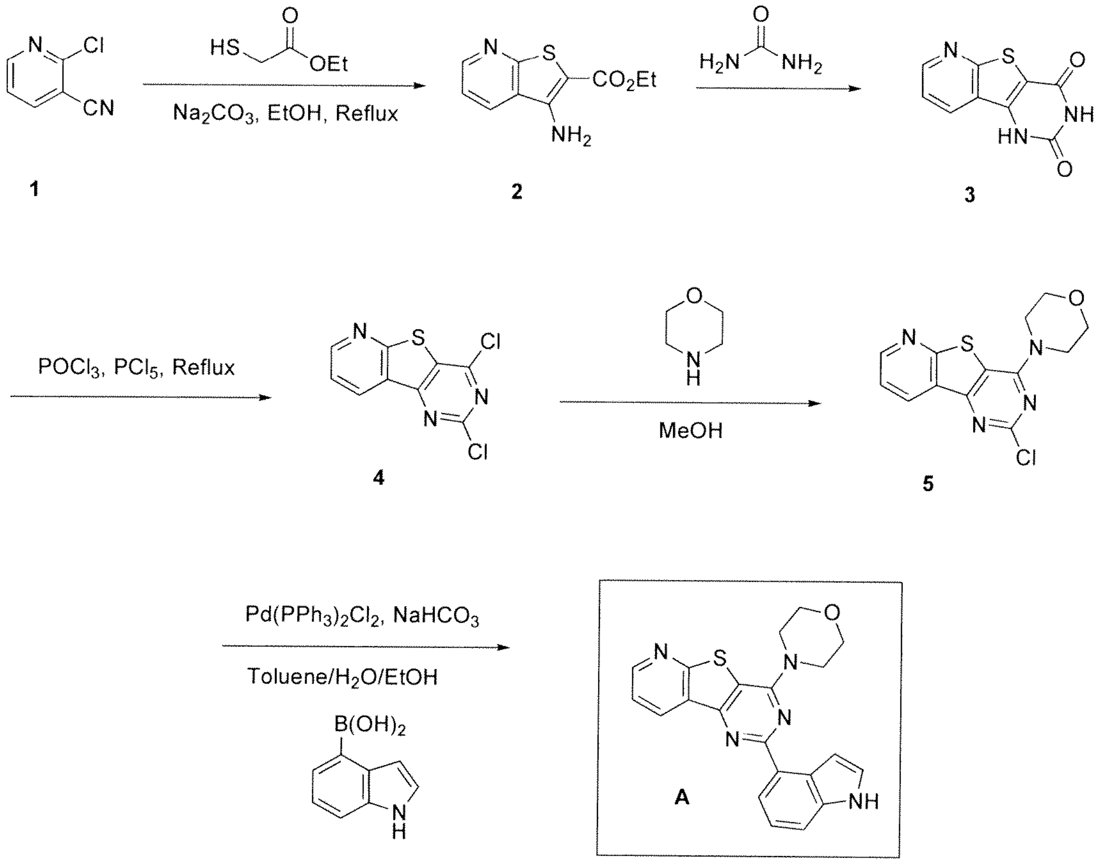
Rheumatoid arthritis (RA) is also a chronic inflammatory disease characterised by non-specific inflammation of the peripheral joints. It is believed that the blood vessels in the synovial lining of the joints undergo angiogenesis. In addition to forming new vascular networks, the endothelial cells release factors and reactive oxygen species that lead to pannus growth and cartilage destruction. The factors involved in angiogenesis may actively contribute to, and help maintain, the chronically inflamed state of rheumatoid arthritis. Treatment using PI3K inhibitors according to the present invention alone or in conjunction with other anti-RA agents may prevent the formation of new blood vessels necessary to maintain the chronic inflammation.

Preferably, the condition is cancer, notably leukaemias including chronic myelogenous leukaemia and acute myeloid leukaemia, lymphomas, solid tumours, and PTEN-negative tumours including PTEN-negative haematological, breast, lung, endometrial, skin, brain and prostrate cancers (where PTEN refers to "phosphatise and tensin homolog deleted on chromosome 10"). More preferably, the condition to be treated by a compound of the invention is rheumatoid arthritis, asthma, chronic obstructive pulmonary disease (COPD), multiple sclerosis, psoriasis and other inflammatory skin disorders, systemic lupus erythematosus, inflammatory bowel disease, and organ transplant rejection. More preferably,

The invention will now be illustrated by the following Examples.

Examples

Example A: 2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine



i. 3-Amino-thieno[2,3-b]pyridine-2-carboxylic acid ethyl ester, **2**

Under Ar(g), 2-chloro-3-pyridinecarbonitrile, **1**, (3.026g, 21.8mmol) and sodium carbonate (2.511g, 23.7mmol) were dissolved in dry ethanol (11.5mL). Ethyl-2-meracaptacetate (3.1mL, 28.3mmol) was then added, and the reaction mixture was heated at reflux for 4h 35 min. The reaction was then cooled to rt; water (140mL) was then added, at which point a precipitate formed, and the resulting reaction mixture was subsequently stirred for a further 30min. The precipitate was filtered, washed with water (2 x 15mL) and the resulting residue collected and dried under vacuum to furnish **2** (4.435g, 20mmol, 92%) as an orange solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.70 (dd, *J*=4.6, 1.44Hz, 1H), 7.96 (dd, *J*=8.1, 1.57Hz, 1H), 7.33 (dd, *J*=8.2, 4.6Hz, 1H), 5.92 (br. s, 2H), 4.38 (q, *J*=7.1Hz, 2H), 1.41 (t, *J*=7.2Hz, 3H).

MS (ES^+) 223.0 (100%, $[M+H]^+$).

ii. 1H-Pyrido[3',2':4,5]thieno[3,2-d]pyrimidine-2,4-dione, **3**

Under Ar(g), compound **2** (518mg, 2.33mmol) and urea (1.143g, 19.0mmol) were combined and heated to 190°C with stirring for 2.5h. The reaction mixture was then cooled, and 1M NaOH (10mL) was added while the mixture was warm; the resulting mixture was then stirred and filtered. The filtrate was acidified with 1M HCl, and a precipitate formed; the mixture was then filtered and the solid collected dried under vacuum to furnish **3** as an orange/brown solid (125mg, 0.574mmol, 25%).

^{1}H NMR (400MHz, DMSO-d_6) δ_H: 12.40 (s, 1H), 11.60 (s, 1H), 8.80-8.73 (m, 2H), 7.63 (dd, *J*=8.2, 4.6Hz, 1H).

MS (ES^-) 217.9 (100%, $[M-H]^-$).

iii. 2,4-Dichloro-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine, **4**

To compound **3** (15.2mg, 0.070mmol) and PCl_5 (592.2mg, 2.84mmol) under Ar(g) was added $POCl_3$ (2mL), and the resulting reaction mixture was then heated at reflux for 26h. The $POCl_3$ was then removed *in vacuo* to yield a solid residue which was slowly added to crushed ice (4g) with stirring. The aqueous phase was then extracted with $CHCl_3$, the layers were separated and the organic phase was washed with water to remove all the remaining phosphoric acid. The organic layer was subsequently dried ($MgSO_4$) and concentrated *in vacuo* to give **4** (3.8mg, 0.015mmol, 21%).

^{1}H NMR (300MHz, $CDCl_3$) δ_H: 8.93 (dd, *J*=4.7, 1.7Hz, 1H), 8.78 (dd, *J*=7.9, 1.5Hz, 1H), 7.61 (m, 1H).

MS (ES$^+$) 255.9 (100%, [M+H]$^+$).

iv. 2-Chloro-4-morpholin-4-yl-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine, **5**

To **4** (34.3mg, 0.14 mmol) in methanol (1.5mL) was added morpholine (25µL, 0.29mmol) dropwise, and the resulting reaction was stirred for 1h at rt. The mixture was then filtered, washed with water and then methanol, and the remaining solid was dissolved in CH_2Cl_2 and concentrated *in vacuo* to furnish **5** as a pale brown solid (30.1mg, 0.098mmol, 73%).

^{1}H NMR (300MHz, $CDCl_3$) δ_H: 8.83 (br. s, 1H), 8.72 (dd, *J*=8.0, 1.51Hz, 1H), 7.53 (m, 1H), 4.11-4.05 (m, 4H), 3.94-3.88 (m, 4H).

MS (ES$^+$) 307.0 (100%, [M+H]$^+$).

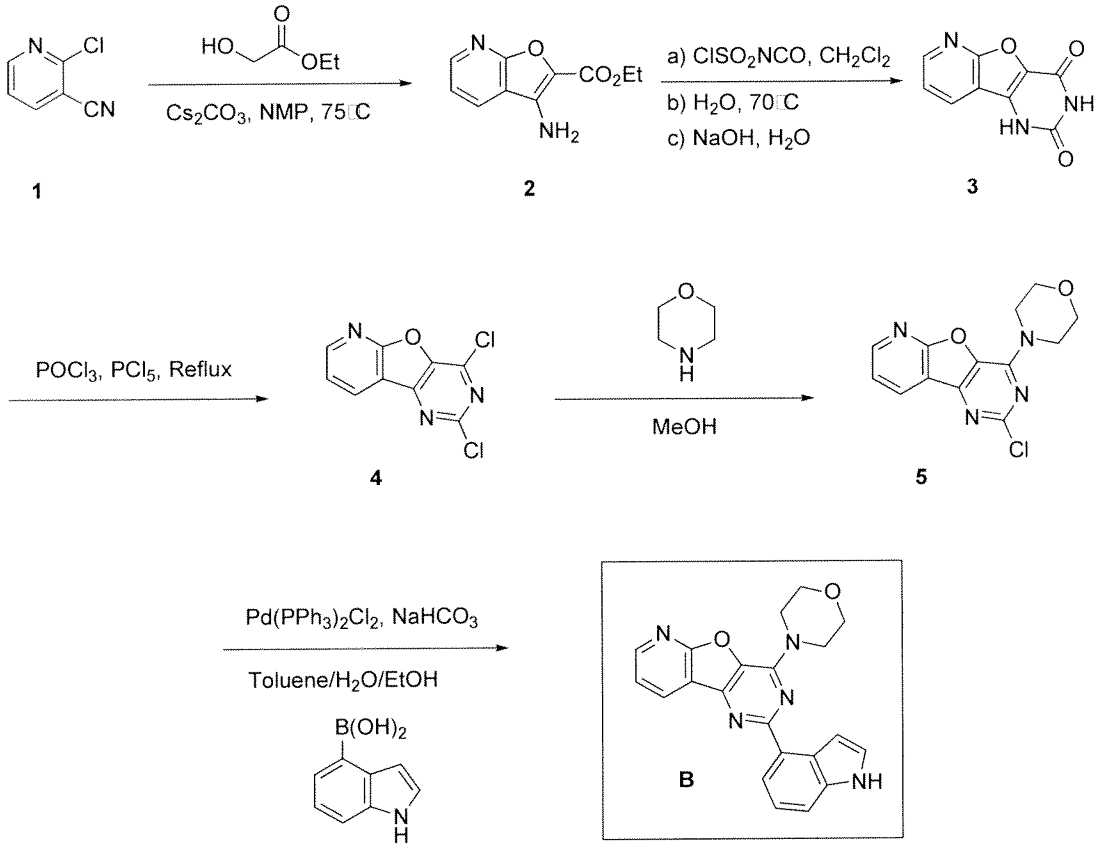
v. 2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine, **A**

Under Ar(g), to a mixture of compound **5** (14.97mg, 0.049mmol), indole-4-boronic acid (8.70mg, 0.054mmol), dichloro-bis(triphenylphosphine)palladium (II) (1.81mg, 0.0026mmol) and sodium hydrogen carbonate (12.50mg, 0.15mmol) was added ethanol (0.75mL) followed by toluene (1.25mL) and then water (0.35mL). The reaction was then heated in a microwave at 120°C (300W) for 1h. The reaction mixture was then cooled to rt, and was partitioned between CH_2Cl_2 and water, and the organic layer was then separated, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 0:1-1:99) MeOH/CH_2Cl_2) furnished **A** (1mg, 0.0026mol, 5%) as a white solid.

^{1}H NMR (300MHz, $CDCl_3$) δ_H: 8.91 (d, *J*=8.3Hz, 1H) 8.82 (dd, *J*=4.7, 1.7Hz, 1H) 8.40-8.33 (m, 2H), 7.72 (br. s, 1H), 7.54 (d, *J*=1.1Hz, 1H), 7.54 (dd, *J*=12.8, 4.9Hz, 1H), 7.42-7.32 (m, 2H), 4.19-4.11 (m, 4H), 4.01-3.93 (m, 4H).

MS (ES$^+$) 388.1 (100%, [M+H]$^+$).

Example B: 2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine



i. 3-Amino-furo[2,3-b]pyridine-2-carboxylic acid ethyl ester, **2**

2-Chloro-3-pyridinecarbonitrile, **1**, (4.00g, 28.9mmol), Cs_2CO_3 (28.2g, 86.6mmol) and ethyl glycolate (3mL, 31.7mmol) were placed in a flask under Ar(g). Dry NMP was added, and the suspension was heated at 75°C for 20h with vigorous stirring. The reaction mixture was cooled to rt, whereupon water (200 mL) and Et_2O (3 x 100mL) were added. The organic layers were combined, washed with water (3 x 15mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 15-40% EtOAc/Hex) gave **2** (2.41g, 11.7mmol, 40%) as a white solid.

^1H NMR (400MHz, $CDCl_3$) δ_H: 8.51 (dd, *J*=5.0, 2.0Hz, 1H), 7.96 (dd, *J*=8.0, 2.0Hz, 1H), 7.23-7.28 (m, 1H), 4.44 (q, *J*=7.0Hz, 2H), 4.01 (br. s., 2H), 1.44 (t, *J*=7.0Hz, 3H).

MS (ES^+) 229 (100%, $[M+Na]^+$).

ii. 1H-Pyrido[3',2':4,5]furo[3,2-d]pyrimidine-2,4-dione, **3**

Under Ar(g), and at 0°C, to a solution of compound **2** (1.189g, 5.77mmol) in CH_2Cl_2 (20mL) was added dropwise chlorosulfonyl isocyanate (0.55mL, 6.34mmol). The reaction mixture was allowed to warm to rt and after 4h it was concentrated *in vacuo*. Water (20mL) was added, and the suspension was stirred vigorously while heating to 70°C for 10min [MS analysis showed formation of the urea intermediate was complete]. The mixture was then cooled and filtered, washing with water. The resulting solid cake (0.87g) was subsequently suspended in water (61mL) and NaOH (3.15g) was added. After 1h stirring, LCMS analysis confirmed that the reaction had gone to completion. The mixture was then filtered, washing with water, to furnish **3** (460mg, 2.3mmol, 40%) as a white solid.

^{1}H NMR (400MHz, DMSO-d_6) δ_H: 12.06 (br. s., 1H), 11.49 (br. s., 1H), 8.60 (dd, *J*=5.0, 1.5Hz, 1H), 8.43 (dd, *J*=8.0, 2.0Hz, 1H), 7.56 (dd, *J*=8.0, 5.0Hz, 1H).

MS (ES$^-$) 202 (100%, [M-H]$^-$).

iii. 2,4-Dichloro-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **4**

To compound **3** (0.14g, 0.70mmol) and PCl_5 (2.4g, 2.84mmol) under Ar(g) was added $POCl_3$ (8mL), and the resulting reaction mixture was then heated at reflux for 20h. After the mixture had been cooled to rt it was poured onto crushed ice (200mL) with vigorous stirring. The aqueous phase was then extracted with CH_2Cl_2 (3 x 50mL). The combined organic layers were subsequently dried ($MgSO_4$) and concentrated *in vacuo* to give **4** (66mg, 0.28mmol, 40%) as an off-white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.80 (dd, *J*=5.0, 1.5Hz, 1H), 8.64 (dd, *J*=8.0, 2.0Hz, 1H), 7.61 (dd, *J*=7.5, 5.0Hz, 1H).

MS (ES$^+$) 240 (100%, [M+H]$^+$).

iv. 2-Chloro-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **5**

To a solution of **4** (64mg, 0.27mmol) in dry methanol (10mL) was added morpholine (55μL, 0.62mmol) dropwise, and the resulting reaction was stirred for 2h at rt. The resulting precipitate was then filtered, washed with water and then a mixture of 5:1 methanol/water, and the remaining solid was dried *in vacuo* to furnish **5** (50mg, 0.17mmol, 64%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.63 (dd, *J*=5.0, 2.0Hz, 1H), 8.52 (dd, *J*=7.5, 2.0Hz, 1H), 7.48 (dd, *J*=7.5, 5.0Hz, 1H), 4.10-4.23 (m, 4H), 3.86-3.91 (m, 4H). MS (ES^+) 291 (100%, $[M+H]^+$).

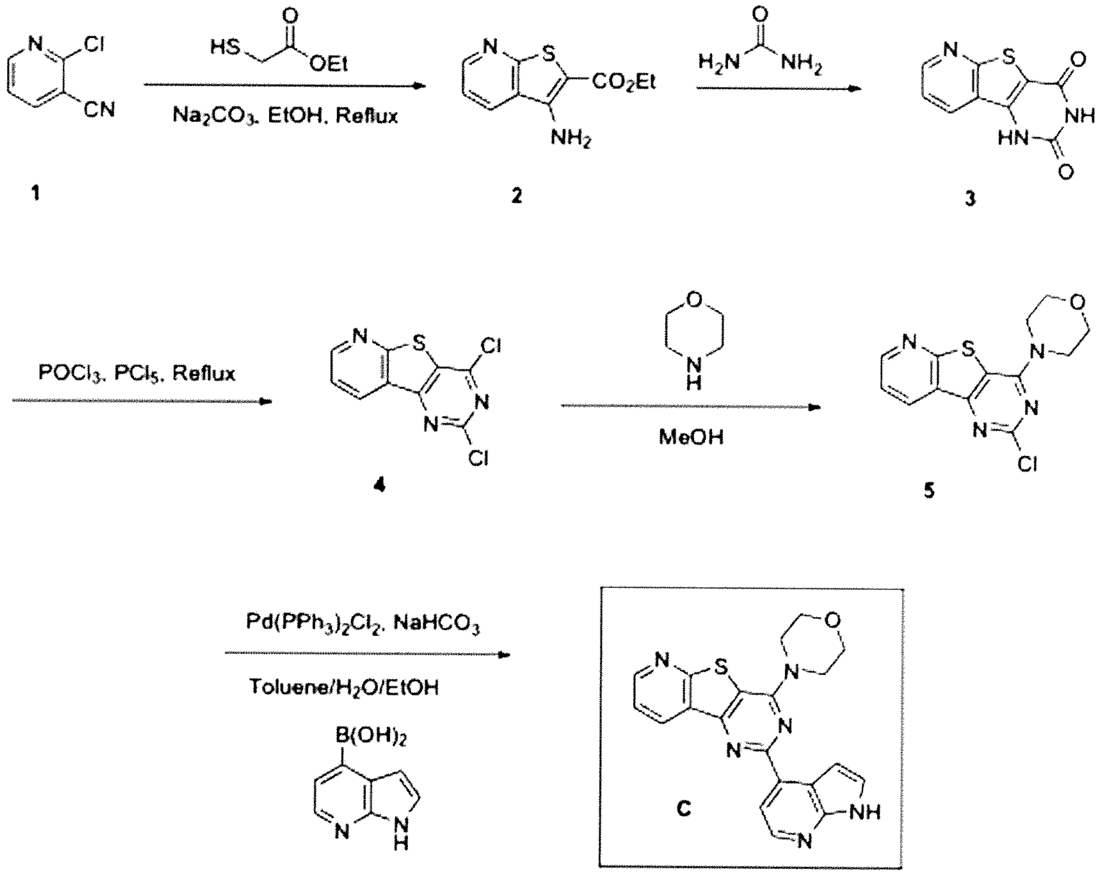
v. 2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **B**

Under Ar(g), to a mixture of compound **5** (25mg, 0.086mmol), indole-4-boronic acid (15.2mg, 0.095mmol), dichloro-bis(triphenylphosphine)palladium (II) (3mg, 0.004mmol) and sodium hydrogen carbonate (22mg, 0.26mmol) was added ethanol (1mL) followed by toluene (1.6mL) and then water (0.5mL). The reaction mixture was then heated in a microwave at 120°C (300W) for 45min, and was subsequently cooled to rt; the mixture was then partitioned between CH_2Cl_2 and water, and the organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 30-60% EtOAc/Hex) furnished **B** (24.5mg, 0.067mol, 77%) as an off-white solid.

^{1}H NMR (400MHz, 19:1 $CDCl_3/CD_3OD$) δ_H: 8.94 (br. s., 1H), 8.51 (dd, *J*=7.5, 2.0Hz, 1H), 8.40 (dd, *J*=5.0, 2.0Hz, 1H), 7.96 (d, *J*=7.5Hz, 1H), 7.26-7.35 (m, 3H), 7.08-7.18 (m, 2H), 4.02-4.11 (m, 4H), 3.71-3.79 (m, 4H). ^{13}C NMR (100MHz, 19:1 $CDCl_3/CD_3OD$) δ_C: 162.6, 161.7, 149.4, 148.9, 147.0, 137.0, 133.0, 132.3, 130.3, 126.6, 125.2, 121.6, 121.5, 120.4, 115.5, 113.2, 103.7, 67.0, 45.9.

MS (ES^+) 372 (100%, $[M+H]^+$).

Example C: 4-Morpholin-4-yl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl) - pyrido[3',2':4,5]thieno[3,2d]pyrimidine



i. 3-Amino-thieno[2,3-b]pyridine-2-carboxylic acid ethyl ester, **2**

2-Chloro-3-pyridinecarbonitrile, **1**, (3.026g, 21.8mmol) and sodium carbonate (2.511g, 23.7mmol) were dissolved in dry ethanol (11.5mL) under Ar(g). Ethyl-2-meracaptacetate (3.1mL, 28.3mmol) was then added, and the reaction mixture was heated at reflux for 4.5h. The reaction mixture was then cooled to rt; water (140mL) was added, at which point a precipitate formed, and the resulting reaction mixture was subsequently stirred for a further 30 min. The precipitate was filtered, washed with water (2 x 15mL) and the resulting residue collected and dried under vacuum to furnish **2** (4.435g, 20mmol, 92%) as an orange solid.

^{1}H NMR (400MHz, CDCl$_3$) δ_H: 8.70 (dd, *J*=4.6, 1.44Hz, 1H), 7.96 (dd, *J*=8.1, 1.57Hz, 1H), 7.33 (dd, *J*=8.2, 4.6Hz, 1H), 5.92 (br. s, 2H), 4.38 (q, *J*=7.1Hz, 2H), 1.41 (t, *J*=7.2Hz, 3H).

MS (ES$^+$) 223.0 (100%, [M+H]$^+$).

ii. 1H-Pyrido[3',2':4,5]thieno[3,2-d]pyrimidine-2,4-dione, **3**

Compound **2** (518mg, 2.33mmol) and urea (1.143g, 19.0mmol) were combined and heated to 190°C with stirring for 2.5h. The reaction mixture was then cooled, and 1M NaOH (10mL) was added while the mixture was warm; the resulting mixture was then stirred and filtered. The aqueous layer was acidified with 1M HCl, and a precipitate formed; the mixture was then filtered and the solid collected dried under vacuum to furnish **3** as an orange/brown solid (125mg, 0.574mmol, 25%).

^{1}H NMR (400MHz, DMSO-d_6) δ_H: 12.40 (s, 1H), 11.60 (s, 1H), 8.80-8.73 (m, 2H), 7.63 (dd, *J*=8.2, 4.6Hz, 1H).

MS (ES$^-$) 217.9 (100%, [M-H]$^-$).

iii. 2,4-Dichloro-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine, **4**

To compound **3** (15.2mg, 0.070mmol) and PCl_5 (592mg, 2.84mmol) under Ar(g) was added $POCl_3$ (2mL), and the resulting reaction mixture was then heated at reflux for 26h. The $POCl_3$ was then removed *in vacuo* to furnish a solid residue, which was slowly added to crushed ice (50g) with stirring. The aqueous phase was then extracted with CH_2Cl_2, the layers were separated and the organic phase was washed with water to remove all the remaining phosphoric acid. The organic layer was subsequently dried ($MgSO_4$) and concentrated *in vacuo* to give **4** (3.8mg, 0.015mmol, 21%).

^{1}H NMR (300MHz, $CDCl_3$) δ_H: 8.93 (dd, *J*=4.7, 1.7Hz, 1H), 8.78 (dd, *J*=7.9, 1.5Hz, 1H), 7.61 (m, 1H).

MS (ES$^+$) 255.9 (100%, [M+H]$^+$).

iv. 2-Chloro-4-morpholin-4-yl-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine, **5**

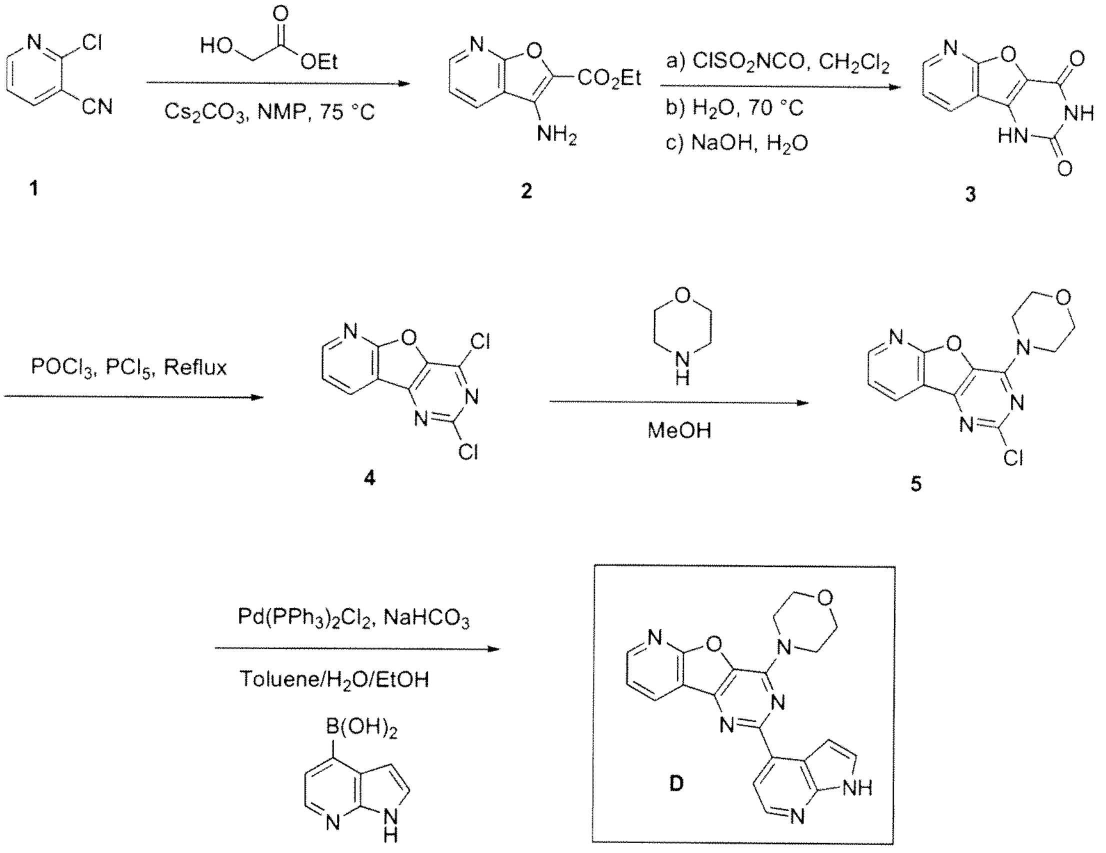
To compound **4** (34.3mg, 0.14mmol) in dry methanol (1.5mL) was added morpholine (25µL, 0.29mmol) in a dropwise fashion, and the resulting mixture was stirred for 1h at rt. The mixture was then filtered, washed with water and then methanol, and the remaining solid was dissolved in CH_2Cl_2 and concentrated *in vacuo* to furnish **5** as a pale brown solid (30.1mg, 0.098mmol, 73%).

^{1}H NMR (300MHz, $CDCl_3$) δ_H: 8.83 (br. s, 1H), 8.72 (dd, *J*=8.0, 1.51Hz, 1H), 7.53 (m, 1H), 4.11-4.05 (m, 4H), 3.94-3.88 (m, 4H).
MS (ES$^+$) 307.0 (100%, $[M+H]^+$).

v. 4-Morpholin-4-yl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-pyrido[3',2':4,5]thieno[3,2d]pyrimidine, **C**

To a mixture of compound **5** (16.0mg, 0.052mmol), 7-azaindole-4-boronic acid pinacol ester (14.3mg, 0.058mmol), sodium hydrogen carbonate (13.5mg, 0.16mmol) and dichloro-bis(triphenylphosphine)palladium (II) (2.2mg, 0.0031mmol) was added toluene (1.25mL) followed by ethanol (0.75mL) and then distilled water (0.35mL). The reaction mixture was then heated in a microwave at 120°C (300W) for 1h, and was subsequently cooled to rt; the mixture was then partitioned between CH_2Cl_2 (40mL) and water (40mL), and the organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 70-90% EtOAc/Hex) furnished **C** (4.81mg, 0.012mmol, 24%) as a pale green solid.
^{1}H NMR (400MHz, 19:1 $CDCl_3/CD_3OD$) δ_H: 8.84 (dd, *J*=8.0, 1.5Hz, 1H), 8.81 (dd, *J*=4.8, 1.8Hz, 1H), 8.36 (d, *J*=5.5Hz, 1H), 8.25 (d, *J*=5.0Hz, 1H), 7.50-7.60 (m, 3H), 4.09-4.16 (m, 4H), 3.92-3.98 (m, 4H).
MS (ES$^+$) 389 (100%, $[M+H]^+$).

Example D: 4-Morpholin-4-yl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-pyrido[3',2':4,5]furo[3,2-d]pyrimidine



i. 3-Amino-furo[2,3-b]pyridine-2-carboxylic acid ethyl ester, **2**

2-Chloro-3-pyridinecarbonitrile, **1**, (4.00g, 28.9mmol), Cs_2CO_3 (28.2g, 86.6mmol) and ethyl glycolate (3mL, 31.7mmol) were placed in a flask under Ar(g). Dry NMP was added, and the suspension was heated at 75°C for 20h with vigorous stirring. The reaction mixture was cooled to rt whereupon water (200mL) and Et_2O (3 x 100mL) were added. The organic layers were combined, washed with water (3 x 15mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 15-40% EtOAc/Hex) gave **2** (2.41g, 11.7mmol, 40%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.51 (dd, *J*=5.0, 2.0Hz, 1H), 7.96 (dd, *J*=8.0, 2.0Hz, 1H), 7.23-7.28 (m, 1H), 4.44 (q, *J*=7.0Hz, 2H), 4.01 (br. s., 2H), 1.44 (t, *J*=7.0Hz, 3H).

MS (ES$^+$) 229 (100%, [M+Na]$^+$).

ii. 1H-Pyrido[3',2':4,5]furo[3,2-d]pyrimidine-2,4-dione, **3**

Under Ar(g) and at 0°C to a solution of compound **2** (1.189g, 5.77mmol) in CH_2Cl_2 (20mL) was added dropwise chlorosulfonyl isocyanate (0.55mL, 6.34mmol). The reaction mixture was allowed to warm to rt, and after 4h it was concentrated *in vacuo*. Water (20mL) was added, and the suspension was stirred vigorously while heating to 70°C for 10min. The mixture was then cooled and filtered, washing with water. The resulting solid cake (0.87g) was subsequently suspended in water (61mL) and NaOH (3.15g) was added. After 1h stirring, LCMS analysis confirmed that the reaction had gone to completion. The mixture was then filtered, washing with water, to furnish **3** (460mg, 2.3mmol, 40%) as a white solid.

^{1}H NMR (400MHz, DMSO-d_6) δ_H: 12.06 (br. s., 1H), 11.49 (br. s., 1H), 8.60 (dd, J=5.0, 1.5Hz, 1H), 8.43 (dd, J=8.0, 2.0Hz, 1H), 7.56 (dd, J=8.0, 5.0Hz, 1H).

MS (ES$^-$) 202 (100%, [M-H]$^-$).

iii. 2,4-Dichloro-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **4**

To compound **3** (0.14g, 0.70mmol) and PCl_5 (2.4g, 2.84mmol) under Ar(g) was added $POCl_3$ (8mL), and the resulting reaction mixture was then heated at reflux for 20h. After the mixture had been cooled to rt it was poured onto crushed ice (200mL) with vigorous stirring. The aqueous phase was then extracted with CH_2Cl_2 (3 x 50mL). The combined organic layers were subsequently dried ($MgSO_4$) and concentrated *in vacuo* to give **4** (66mg, 0.28mmol, 40%) as an off-white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.80 (dd, J=5.0, 1.5Hz, 1H), 8.64 (dd, J=8.0, 2.0Hz, 1H), 7.61 (dd, J=7.5, 5.0Hz, 1H).

MS (ES$^+$) 240 (100%, [M+H]$^+$).

iv. 2-Chloro-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **5**

To a solution of **4** (64mg, 0.27mmol) in dry methanol (10mL) was added morpholine (55μL, 0.62mmol) dropwise, and the resulting reaction was stirred for 2h at rt. The resulting precipitate was then filtered, washed with water and then a mixture of 5:1 methanol/water, and the remaining solid was dried *in vacuo* to furnish **5** (50mg, 0.17mmol, 64%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.63 (dd, J=5.0, 2.0Hz, 1H), 8.52 (dd, J=7.5, 2.0Hz, 1H), 7.48 (dd, J=7.5, 5.0Hz, 1H), 4.10-4.23 (m, 4H), 3.86-3.91 (m, 4H).

MS (ES$^+$) 291 (100%, $[M+H]^+$).

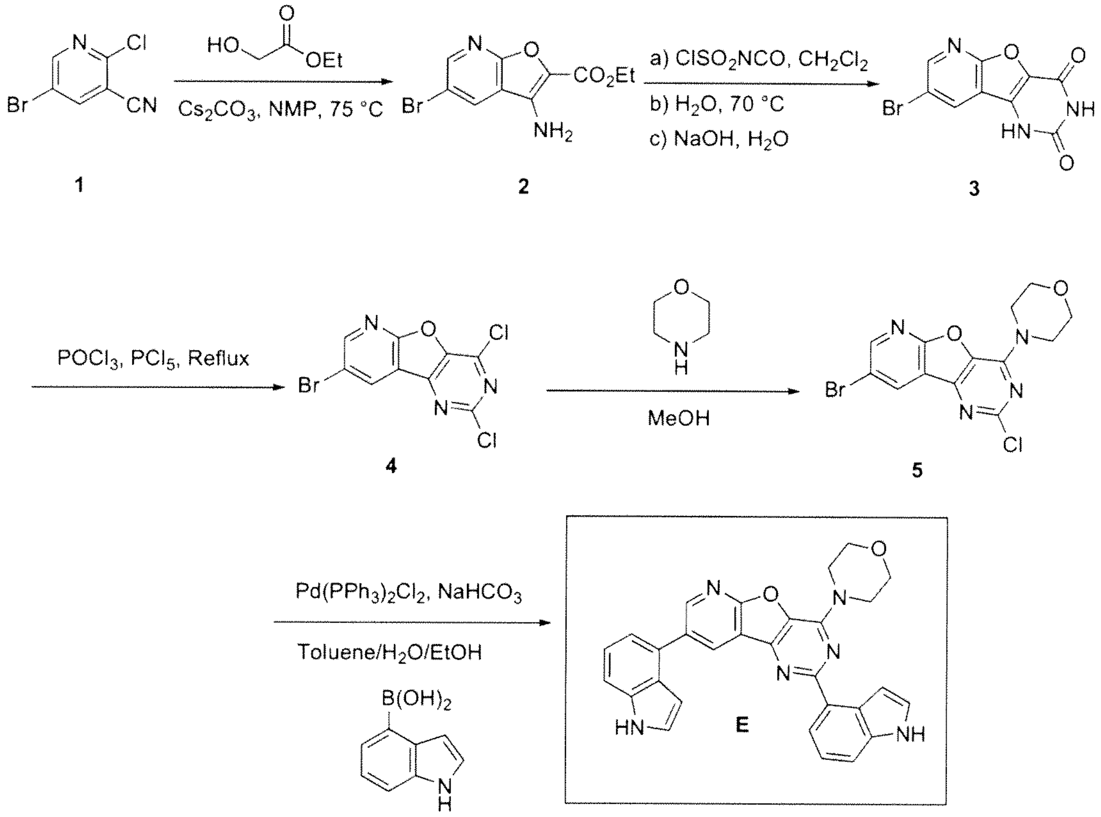
v. 4-Morpholin-4-yl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **D**

Under Ar(g) to a mixture of compound **5** (20mg, 0.069mmol), 7-azaindole-4-boronic acid pinacol ester (18.5mg, 0.076mmol), dichloro-bis(triphenylphosphine)palladium (II) (2.4mg, 0.003mmol) and sodium hydrogen carbonate (17.4mg, 0.21mmol) was added ethanol (1mL) followed by toluene (1.6mL) and then water (0.5mL). The reaction mixture was then heated in a microwave at 120°C (300W) for 1h, and was subsequently cooled to rt; the mixture was then partitioned between CH_2Cl_2 and water, and the organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 30-90% EtOAc/Hex) furnished **D** (20mg, 0.054mol, 78%) as an off-white solid.

^{1}H NMR (400MHz, 9:1 $CDCl_3/CD_3OD$) δ_H: 8.61 (dd, *J*=7.5, 1.5Hz, 1H), 8.54 (dd, *J*=5.0, 1.5Hz, 1H), 8.28 (d, *J*=5.0Hz, 1H), 8.00 (d, *J*=5.0Hz, 1H), 7.46 (dd, *J*=7.5, 5.0Hz, 1H), 7.41 (d, *J*=3.5Hz, 1H), 7.32 (d, *J*=3.5Hz, 1H), 4.15-4.24 (m, 4H), 3.84-3.92 (m, 4H).

MS (ES$^+$) 373 (100%, $[M+H]^+$).

Example E: 2,8-Bis-(1H-indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine



i. 3-Amino-5-bromo-furo[2,3-b]pyridine-2-carboxylic acid ethyl ester, **2**

5-Bromo-2-chloro-3-pyridinecarbonitrile, **1**, (4.802g, 22.08mmol), Cs_2CO_3 (21.6g, 66.2mmol) and ethyl glycolate (2.3mL, 24.3mmol) were placed in a flask under Ar(g). Dry NMP (50mL) was added, and the suspension was heated at 75°C for 20h with vigorous stirring. The reaction mixture was cooled to rt whereupon water (200mL) and Et_2O (3 x 100mL) were added. The organic layers were combined, washed with water (3 x 15mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 15-25% EtOAc/Hex) gave **2** (1.701g, 5.97mmol, 27%) as a yellow solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.53 (d, *J*=2.0Hz, 1H), 8.07 (d, *J*=2.0Hz, 1H), 5.00 (br. s., 2H), 4.44 (q, *J*=7.0Hz, 2H), 1.44 (t, *J*=7.0Hz, 3H).

MS (ES^+) 309 (100%, $[M+Na]^+$), 307 (100%, $[M+Na]^+$).

ii. 8-Bromo-1H-pyrido[3',2':4,5]furo[3,2-d]pyrimidine-2,4-dione, **3**

Under Ar(g) and at 0°C to a solution of compound **2** (1.701g, 5.97mmol) in CH_2Cl_2 (70mL) was added dropwise chlorosulfonyl isocyanate (0.62mL, 7.16mmol). The reaction mixture was allowed to warm to rt and after 2.5h it was concentrated *in vacuo*. Water (140mL) was added, and the suspension was stirred vigorously while heating to 70°C for 1h [MS analysis showed formation of the urea intermediate was complete]. The mixture was then cooled to rt whereupon NaOH (5.6g [to give a 1M solution]) was added. After 25 min a yellow/white precipitate had formed, 1M HCl was added to the suspension till pH 5 was achieved whereupon the mixture was filtered, washing with water, to furnish **3** (1.418g, 5.03mmol, 84%) as a yellow solid.

^{1}H NMR (400MHz, DMSO-d_6) δ_H: 12.01 (br. s., 1H), 11.58 (br. s, 1H), 8.72 (d, *J*=2.0Hz, 1H), 8.59 (d, *J*=2.0Hz, 1H).

MS (ES$^-$) 282 (100%, [M-H]$^-$), 280 (100%, [M-H]$^-$).

iii. 2,4-Dichloro-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **4**

To compound **3** (0.615g, 2.18mmol) and PCl_5 (7.2g, 34.6mmol) under Ar(g) was added $POCl_3$ (24mL), and the resulting reaction mixture was then heated at reflux for 24h. After the mixture had been cooled to rt it was poured onto crushed ice (400mL) with vigorous stirring. The aqueous phase was then extracted with CH_2Cl_2 (3 x 100mL). The combined organic layers were subsequently dried ($MgSO_4$) and concentrated *in vacuo* to give a 1:1 mixture of **4** and an impurity (0.532g) as an off-white solid that was used directly in the next step.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.78 (d, *J*=2.5Hz, 1H), 8.72 (d, *J*=2.5Hz, 1H), 8.71 (d, *J*=2.5Hz, 1H), 8.29 (d, *J*=2.5Hz, 1H).

iv. 8-Bromo-2-chloro-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **5**

To a solution of **4** (532mg) in dry methanol (25mL) was added morpholine (321μL, 3.7mmol) dropwise, and the resulting reaction was stirred for 1h at rt. The resulting precipitate was then filtered, washed with water and dried *in vacuo* to furnish **5** (251mg, 0.68mmol, 31%, 2 steps) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.66 (d, *J*=2.0Hz, 1H), 8.62 (d, *J*=2.0Hz, 1H), 4.07-4.21 (m, 4H), 3.85-3.91 (m, 4H).

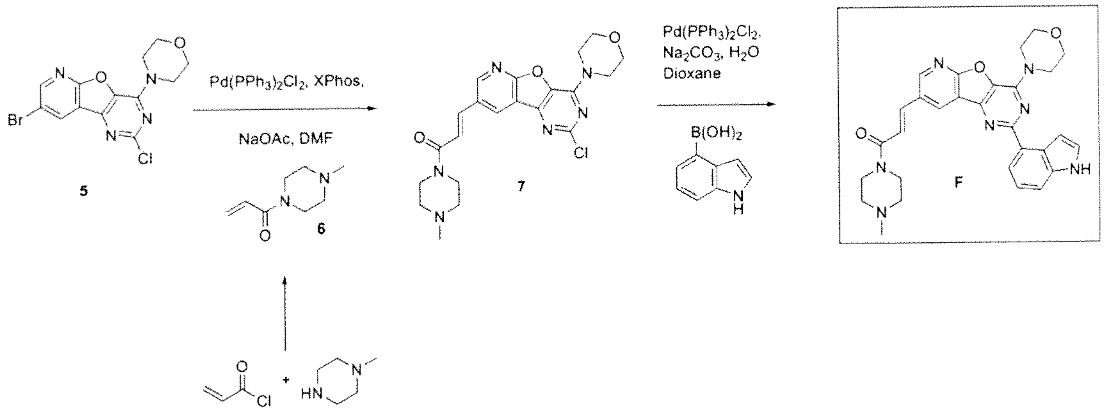
MS (ES$^+$) 393 (100%, [M+Na]$^+$), 391 (80%, [M+Na]$^+$).

v. 2,8-Bis-(1H-indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **E**

Under Ar(g) to a mixture of compound **5** (8mg, 0.022mmol), indole-4-boronic acid (10.5mg, 0.065mmol), dichloro-bis(triphenylphosphine)palladium (II) (1.5mg, 0.002mmol) and sodium hydrogen carbonate (8mg, 0.097mmol) was added ethanol (1mL) followed by toluene (1.6mL) and then water (0.5mL). The reaction mixture was then heated in a microwave at 120°C (300W) for 1h, and was subsequently cooled to rt; the mixture was then partitioned between CH_2Cl_2 and water, and the organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 20-40% EtOAc/Hex) furnished **E** (2.7mg, 0.005mol, 25%) as a yellow solid.

^{1}H NMR (400MHz, 9:1 $CDCl_3/CD_3OD$) δ_H: 9.08 (s, 1H), 8.88 (d, *J*=1.5Hz, 1H), 8.05 (d, *J*=7.5Hz, 1H), 7.49 (d, *J*=8.0Hz, 1H), 7.43 (d, *J*=7.5Hz, 1H), 7.17-7.33 (m, 6H), 6.66 (d, *J*=3.0Hz, 1H), 4.22-4.31 (m, *J*=4.5Hz, 4H), 3.85-3.95 (m, 4H). MS (ES$^+$) 487 (100%, $[M+H]^+$).

Example F: (E)-1-(4-Methyl-piperazin-1-yl)-3-[4-morpholin-4-yl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-yl]-propenone



i. 1-(4-Methyl-piperazin-1-yl)-propenone, **6**

At 0°C to a solution of N-methylpiperazine (3mL, 27mmol) in CH_2Cl_2 (15mL) was added acryloyl chloride (879mL, 10.8mmol) dropwise under Ar(g). After 2h water (20mL) was added. The organic layer was separated and washed with water (2 x 10mL), dried ($MgSO_4$), before being concentrated *in vacuo* to give **6** (463mg, 3mmol, 28%) as a pale yellow oil that required no further purification.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 6.56 (dd, J=16.6, 10.5Hz, 1H), 6.28 (dd, J=16.6, 2.0Hz, 1H), 5.61-5.75 (m, 1H), 3.54-3.79 (m, 4H), 2.38-2.49 (m, 4H), 2.33 (s, 3H).

MS (ES$^+$) 155 (100%, [M+H]$^+$).

ii. (E)-3-(2-Chloro-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-yl)-1-(4-methyl-piperazin-1-yl)-propenone, **7**

To a sealed tube was added **5** (as per *Example E* above, 50mg, 0.14mmol), **6** (20.9mg, 0.14mmol), dichloro-bis(triphenylphosphine)palladium (II) (2.9mg, 0.004mmol), XPhos (3.9mg, 0.008mmol) and NaOAc (33mg, 0.41mmol) followed by anhydrous DMF (4mL) under Ar(g). The lid was sealed and the tube was heated to 110°C for 16h whereupon it was cooled to rt and diluted with EtOAc (40mL). The organic layer was washed with water (2 x 20mL); the combined aqueous layers were then extracted with CH_2Cl_2 (3 x 60mL). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo*.

Purification by flash column chromatography on silica (eluant 2-6% MeOH/CH_2Cl_2) furnished **7** (44mg, 0.10mol, 71%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.62-8.76 (m, 2H), 7.82 (d, *J*=15.6Hz, 1H), 7.05 (d, *J*=15.6Hz, 1H), 4.07-4.23 (m, 4H), 3.85-3.92 (m, 4H), 3.68-3.84 (m, 4H), 2.47-2.61 (m, 4H), 2.39 (s, 3H).

MS (ES^+) 443 (100%, $[M+H]^+$).

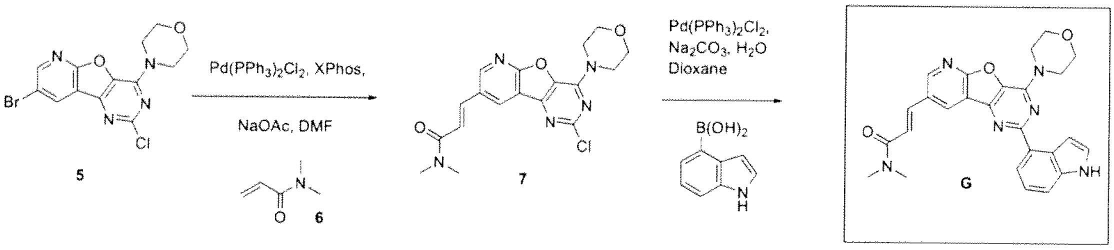
iii. (E)-1-(4-Methyl-piperazin-1-yl)-3-[4-morpholin-4-yl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-yl]-propenone, **F**

To a sealed tube was added **7** (20mg, 0.045mmol), indole-4-boronic acid (18mg, 0.11mmol), dichloro-bis(triphenylphosphine)palladium (II) (6.3mg, 0.009mmol) and Na_2CO_3 (9.6mg, 0.09mmol) followed by dioxane (2mL) and water (0.8mL) under Ar(g). The lid was sealed and the tube was heated to 88°C for 20h whereupon it was cooled to rt and diluted with EtOAc (30mL) and 50% brine (5mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 15mL). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 2-5% MeOH/CH_2Cl_2) furnished **F** (6.8mg, 0.013mol, 29%) as a white solid.

^{1}H NMR (400MHz, 5:1 $CDCl_3/CD_3OD$) δ_H: 8.74 (d, *J*=2.0Hz, 1H), 8.54 (d, *J*=2.0Hz, 1H), 7.89 (d, *J*=7.5Hz, 1H), 7.65 (d, *J*=15.1Hz, 1H), 7.40 (d, *J*=8.0Hz, 1H), 7.18-7.25 (m, 2H), 7.14 (t, *J*=7.7Hz, 1H), 7.05 (d, *J*=15.1Hz, 1H), 4.08-4.13 (m, 4H), 3.75-3.82 (m, 4H), 3.61-3.73 (m, 4H), 2.37-2.55 (m, 4H), 2.27 (s, 3H).

MS (ES^+) 524 (100%, $[M+H]^+$).

Example G: (E)-3-[2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-yl]-N,N-dimethylacrylamide



i. (E)-3-(2-Chloro-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-yl)-N,N-dimethylacrylamide, **7**

To a sealed tube was added **5** (as per *Example E* above, 50mg, 0.14mmol), dimethylacrylamide (**6**, 14mL, 0.14mmol), dichloro-bis(triphenylphosphine)palladium (II) (2.8mg, 0.004mmol), XPhos (3.9mg, 0.008mmol) and NaOAc (33mg, 0.41mmol) followed by anhydrous DMF (3.5mL) under Ar(g). The lid was sealed and the tube was heated to 110°C for 16h whereupon it was cooled to rt and diluted with EtOAc (40mL). The organic layer was washed with 50% brine (3 x 10mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 50-100% EtOAc/Hex then 1% MeOH) furnished **7** (44mg, 0.11mol, 84%) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.70 (s, 2H), 7.82 (d, *J*=15.6Hz, 1H), 7.07 (d, *J*=15.6Hz, 1H), 4.11-4.19 (m, 4H), 3.85-3.93 (m, 4H), 3.22 (s, 3H), 3.11 (s, 3H). MS (ES$^+$) 388 (100%, $[M+H]^+$).

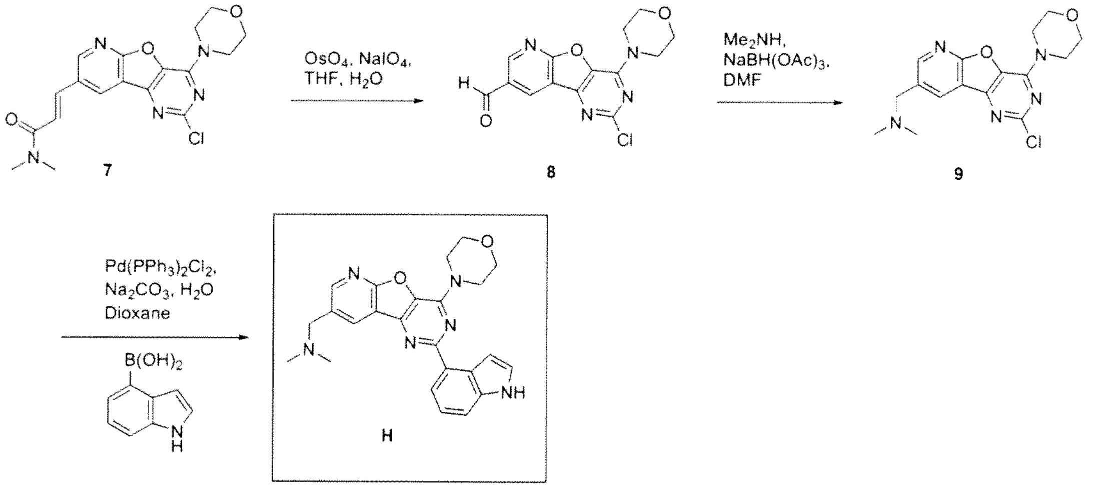
ii. (E)-3-[2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-yl]-N,N-dimethylacrylamide, **G**

To a sealed tube was added **7** (30mg, 0.077mmol), indole-4-boronic acid (31mg, 0.19mmol), dichloro-bis(triphenylphosphine)palladium (II) (13.6mg, 0.02mmol) and Na_2CO_3 (24.4mg, 0.23mmol) followed by dioxane (3mL) and water (1.2mL) under Ar(g). The lid was sealed and the tube was heated to 88°C for 20h whereupon it was cooled to rt and diluted with EtOAc (30mL) and 50% brine (3mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 5mL). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 1-3% MeOH/CH_2Cl_2) furnished **G** (6.9mg, 0.015mol, 19%) as an off white solid.

^1H NMR (400MHz, 5:1 $CDCl_3$/CD_3OD) δ_H: 8.77 (d, *J*=2.0Hz, 1H), 8.55 (d, *J*=2.0Hz, 1H), 7.88 (dd, *J*=7.5, 1.0Hz, 1H), 7.61 (d, *J*=15.6Hz, 1H), 7.40 (d, *J*=8.0Hz, 1H), 7.21 (d, *J*=3.0Hz, 1H), 7.10-7.17 (m, 2H), 7.04 (d, *J*=15.6Hz, 1H), 4.09 (s, 4H), 3.74-3.82 (m, 4H), 3.11 (s, 3H), 2.94 (s, 3H).

MS (ES^+) 469 (100%, $[M+H]^+$).

Example H: [2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl]-dimethyl-amine



i. 2-Chloro-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine-8-carbaldehyde, **8**

To a solution of (E)-3-(2-chloro-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-yl)-N,N-dimethylacrylamide (**7**, as per *Example G* above) (13mg, 0.034mmol) in THF (1.5mL) was added H_2O (0.5mL) followed by $NaIO_4$ (22mg, 0.10mmol) and a solution of OsO_4 (2.5% wt/v in ^{t}BuOH, 9mL, 0.0009mmol) under Ar(g). After stirring for 2 days at rt, EtOAc (25mL) and sodium thiosulfate (0.1M, 5mL) were added. The organic layer was separated and washed with brine (3mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 5-20% EtOAc/CH_2Cl_2) furnished **8** (8mg, 0.025mmol, 74%) as a white solid.

^{1}H NMR (9:1 $CDCl_3$/CD_3OD) δ_H: 10.13 (s, 1H), 9.04 (d, *J*=2.0Hz, 1H), 8.91 (d, *J*=2.0Hz, 1H), 3.99-4.13 (m, 4H), 3.73-3.84 (m, 4H).

LCMS (ES$^+$) 351 (100%, [M+MeOH+H]$^+$), 319 (40%, [M+H]$^+$).

ii. (2-Chloro-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl)-dimethyl-amine, **9**

To a suspension of **8** (7.8mg, 0.024mmol) in dry DMF (2.5mL) was added a solution of dimethylamine (2M in MeOH, 24mL, 0.049mmol) followed by $NaBH(OAc)_3$ (8mg, 0.037mmol) under Ar(g). After stirring at rt for 23h, a further quantity of dimethylamine (2M in MeOH, 35mL, 0.071mmol) and $NaBH(OAc)_3$ (6mg, 0.028mmol) were added. After 3 days the reaction was concentrated *in* *vacuo*. EtOAc (40mL) and 50% saturated brine (5mL) were added and the organic layer separated, re-extracting the aqueous with EtOAc (2 x 15mL). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 1-6% $MeOH/CH_2Cl_2$) furnished **9** (5mg, 0.014mmol, 60%) as a white solid.

^{1}H NMR ($CDCl_3$) δ_H: 8.65 (d, *J*=2.0Hz, 1H), 8.50 (d, *J*=2.0Hz, 1H), 4.08-4.23 (m, 4H), 3.82-3.93 (m, 4H), 3.75 (br. s., 2H), 2.38 (s, 6H).

MS (ES^+) 348 (100%, $[M+H]^+$).

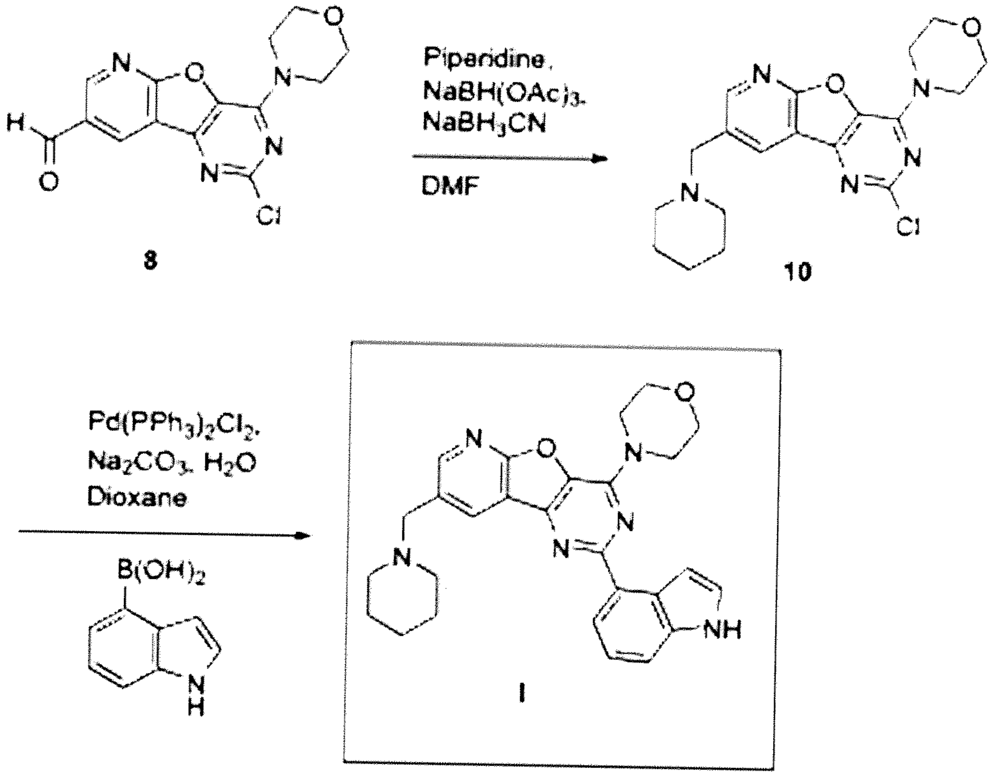
iii. [2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl]-dimethyl-amine, **H**

To a sealed tube was added **9** (5mg, 0.014mmol), indole-4-boronic acid (5.8mg, 0.036mmol), dichloro-bis(triphenylphosphine)palladium (II) (2.0mg, 0.0029mmol) and Na_2CO_3 (3.1mg, 0.029mmol) followed by dioxane (2mL) and water (0.8mL) under Ar(g). The lid was sealed and the tube was heated to 88°C for 18h whereupon it was cooled to rt and diluted with EtOAc (35mL) and 50% saturated brine (5mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 10mL). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 2-5% $MeOH/CH_2Cl_2$) furnished **H** (2mg, 0.005mmol, 32%) as an off-white solid.

^{1}H NMR (400MHz, 9:1 $CDCl_3/CD_3OD$) δ_H: 9.79 (br. s., 1H), 8.57 (br. s, 1H), 8.53 (br. s., 1H), 7.98 (d, *J*=7.5Hz, 1H), 7.45 (d, *J*=8.0Hz, 1H), 7.24-7.32 (m, 2H), 7.19 (t, *J*=8.0Hz, 1H), 4.13-4.19 (m, 4H), 3.81-3.87 (m, 4H), 3.78 (br. s, 2H), 2.36 (s, 6H).

MS (ES^+) 429 (100%, $[M+H]^+$).

Example I: 2-(1H-Indol-4-yl)-4-morpholin-4-yl-8-piperidin-1-ylmethyl-pyrido[3',2':4,5]furo[3,2d]pyrimidine



i. 2-Chloro-4-morpholin-4-yl-8-piperidin-1-ylmethyl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **10**

To compound **8** (as per *Example H* above) (19.7mg, 0.062mmol) in dry DMF (6.3mL) was added piperidine (12.2μL, 0.14mmol) followed by $NaBH(OAc)_3$ (20.05mg, 0.095mmol) and the reaction was stirred for 5h. After which time $NaBH_3CN$ (5.8mg, 0.092mmol) was added and the reaction was stirred for a further 48h. The DMF was removed *in vacuo*, EtOAc (50mL) was added along with 50% saturated brine (50mL), the layers separated, extracted with EtOAc (2 x 30mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 0:1-6:94) $MeOH/CH_2Cl_2$) furnished **10** (12.9mg, 0.033mmol, 54%) as a white solid.

^1H NMR (400MHz, $CDCl_3$) δ_H: 8.55 (d, *J*=2.0Hz, 1H), 8.49 (d, *J*=2.0Hz, 1H), 4.15 (br. s., 4H), 3.84-3.90 (m, 4H), 3.65 (s, 2H), 2.42 (m, 4H), 1.59 (quin, *J*=5.5Hz, 4H), 1.41-1.49 (m, 2H).

MS (ES^+) 388.2 (100%, $[M+H]^+$).

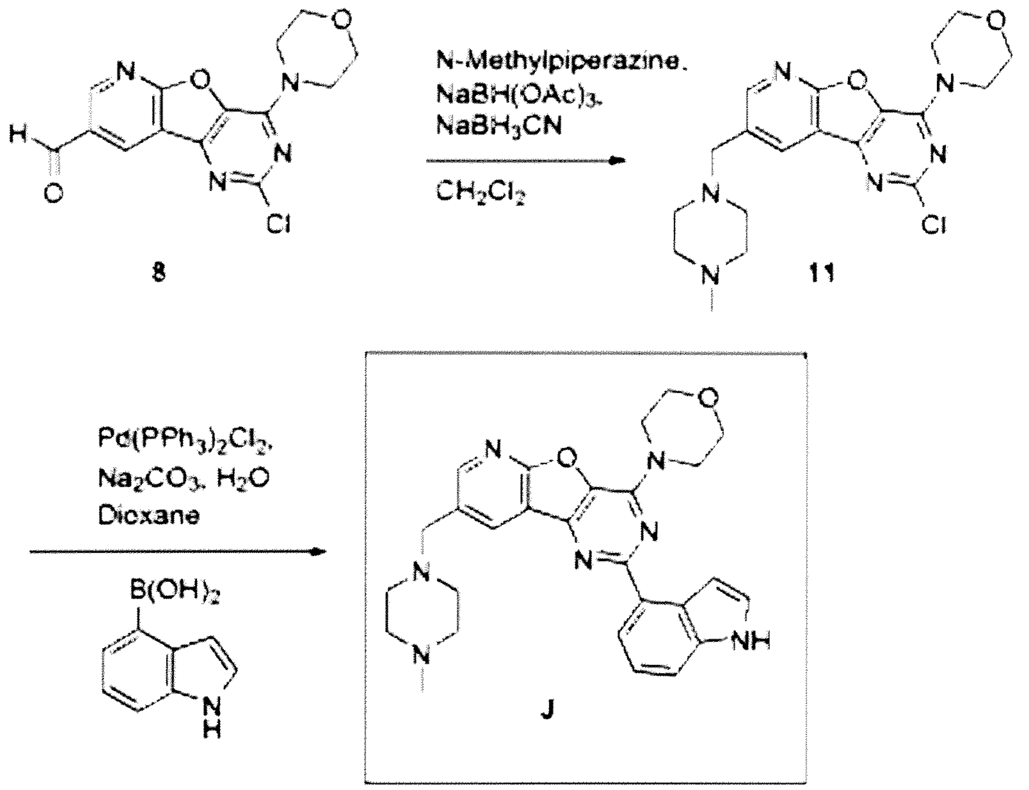
ii. 2-(1H-Indol-4-yl)-4-morpholin-4-yl-8-piperidin-1-ylmethyl-pyrido[3',2':4,5]furo [3,2d]pyrimidine, **I**

To indole-4-boronic acid (13.4mg, 0.083mmol), dichloro-bis(triphenylphosphine)palladium (II) (4.60mg, 0.0065mmol) and sodium carbonate (7.22 mg, 0.068mmol) was added compound **10** (12.9mg, 0.033mmol) dissolved in dioxane/water (2mL/0.8mL). The reaction was then heated in a sealed tube at 88°C for 16h. The reaction was cooled to rt where the reaction was partitioned between EtOAc/water (30mL/5mL) and the layers were separated, extracted with EtOAc (3 x 10mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 0:1-6:94) $MeOH/CH_2Cl_2$) give **I** (4mg, 0.0085mol, 26%) as a white solid.

^1H NMR (400MHz, 9.5:0.5 $CDCl_3/CD_3OD$) δ_H: 8.59 (d, *J*=2.0Hz, 1H), 8.50 (d, *J*=2.5Hz, 1H), 8.12 (d, *J*=7.5Hz, 1H), 7.49 (d, *J*=8.0Hz, 1H), 7.45-7.47 (m, 1H), 7.33 (d, *J*=3.0Hz, 1H), 7.25-7.30 (m, 2H), 4.22 (t, *J*=4.9Hz, 4H), 3.87-3.92 (m, 4H), 3.67 (s, 2H), 2.44 (m, 4H), 1.54-1.62 (m, 4H), 1.39-1.46 (m, 2H).

MS (ES^+) 469.2 (100%, $[M+H]^+$).

Example J: 2-(1H-Indol-4-yl)-8-(4-methyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine



i. 2-Chloro-8-(4-methyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **11**

To compound **8** (as per *Example H* above) (19.13mg, 0.060mmol) in dry CH_2Cl_2 (6.6mL) was added N-methylpiperazine (13.3μL, 0.12mmol) followed by $NaBH_3CN$ (4.6mg, 0.073mmol) and the reaction mixture was stirred for 21h. $NaBH(OAc)_3$ (11.3mg, 0.053mmol) was then added and the reaction mixture was stirred for a further 6.5h. EtOAc (50mL) was added along with 50% saturated brine (50mL); the layers were separated, extracted with EtOAc (2 x 30mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 0:1-1:9 $MeOH/CH_2Cl_2$) furnished **11** (8.48mg, 0.021mmol, 35%) as a white solid.

^1H NMR (400MHz, 9:1 $CDCl_3/CD_3OD$) δ_H: 8.49 (d, J=2.5Hz, 1H), 8.45 (d, J=2.0Hz, 1H), 4.10 (br. s., 4H), 3.82 (t, J=4.8Hz, 4H), 3.65 (s, 2H), 2.49 (br. s., 8H), 2.27 (s, 3H). MS (ES^+) 403.1 (100%, $[M+H]^+$).

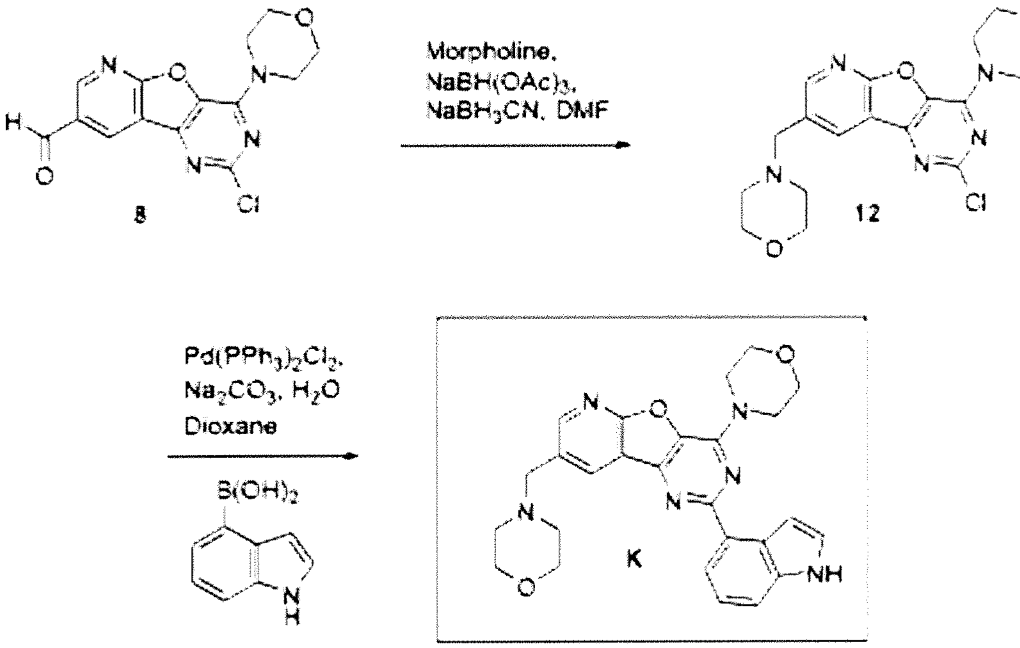
ii. 2-(1H-Indol-4-yl)-8-(4-methyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **J**

To indole-4-boronic acid (14.1mg, 0.088mmol), dichloro-bis(triphenylphosphine)palladium (II) (4.77mg, 0.0068mmol) and sodium carbonate (7.47mg, 0.070mmol) was added compound **11** (13.1mg, 0.032mmol) dissolved in dioxane/water (2mL/0.8mL). The resulting reaction mixture was then heated in a sealed tube at 88°C for 16h. The mixture was then cooled to rt, and was partitioned between EtOAc/water (30mL/5mL); the layers were subsequently separated, extracted with EtOAc (2 x 10mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 0:1-1:9) $MeOH/CH_2Cl_2$) furnished compound **J** (3.97mg, 0.0082mol, 25%) as a white solid.

^1H NMR (400MHz, 9:1 $CDCl_3/CD_3OD$) δ_H.: 8.59 (d, *J*=2.0Hz, 1H), 8.48 (d, *J*=2.0Hz, 1H), 8.06-8.12 (m, 1H), 7.48 (d, *J*=8.0Hz, 1H), 7.42 (d, *J*=3.0Hz, 1H), 7.32 (d, *J*=3.0Hz, 1H), 7.25 (s, 1H), 4.20 (t, *J*=4.8Hz, 4H), 3.88 (m, *J*=4.8Hz, 4H), 3.67 (s, 2H), 2.51 (br. s., 8H), 2.25 (s, 3H).

MS (ES^+) 484.2 (100%, $[M+H]^+$).

Example K: 2-(1H-Indol-4-yl)-4-morpholin-4-yl-8-morpholin-4-ylmethyl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine



i. 2-Chloro-4-morpholin-4-yl-8-morpholin-4-ylmethyl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **12**

To compound **8** (as per *Example H* above) (19.7mg, 0.062mmol) in dry DMF (3mL) was added morpholine (11µL, 0.13mmol) followed by NaBH(OAc)$_3$ (20mg, 0.095mmol) under Ar(g) and the reaction mixture was stirred for 3 days. NaBH$_3$CN (5mg, 0.07mmol) was then added, and the reaction mixture was stirred for a further 5h. The DMF was then removed *in vacuo*, and EtOAc (40mL) was added along with 50% saturated brine (5mL); the resulting layers were separated, extracted with EtOAc (2 x 15mL), dried (MgSO$_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 1-2.5% MeOH/CH$_2$Cl$_2$) furnished **12** (15mg, 0.038mmol, 61%) as a white solid.

^{1}H NMR (CDCl$_3$) δ_H: 8.56 (s, 1H), 8.53 (s, 1H), 4.08-4.21 (m, 4H), 3.83-3.91 (m, 4H), 3.65-3.79 (m, 6H), 2.43-2.59 (m, 4H).

MS (ES$^+$) 390 (100%, [M+H]$^+$).

ii. 2-(1H-Indol-4-yl)-4-morpholin-4-yl-8-morpholin-4-ylmethyl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **K**

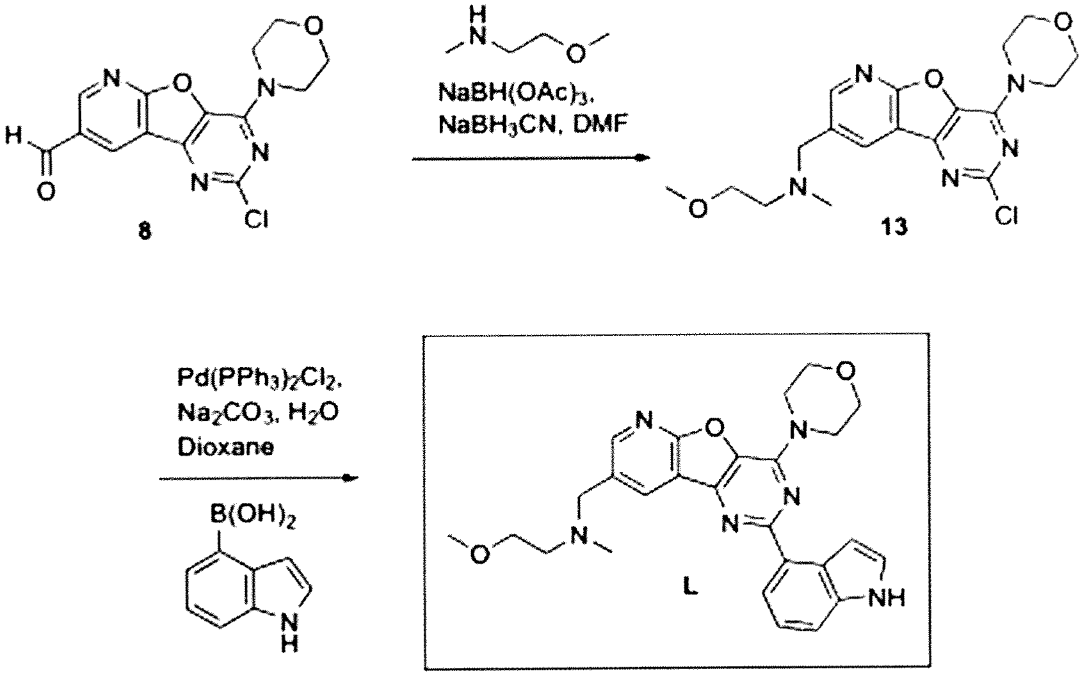
To a sealed tube was added compound **12** (15mg, 0.038mmol), indole-4-boronic acid (15.5mg, 0.1mmol), dichloro-bis(triphenylphosphine)palladium (II)

(5.4mg, 0.008mmol) and Na_2CO_3 (8.2mg, 0.077mmol), followed by dioxane (2mL) and water (0.8mL) under Ar(g). The tube was heated to 88°C for 18h whereupon it was cooled to rt, and diluted with EtOAc (35mL) and 50% saturated brine (5mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 10mL). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 1-3% MeOH/CH_2Cl_2) furnished **K** (6.7mg, 0.014mmol, 37%) as an off-white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.63 (d, *J*=2.0Hz, 1H), 8.58 (br. s., 1H), 8.39 (br. s., 1H), 8.24 (dd, *J*=7.5, 1.0Hz, 1H), 7.58-7.67 (m, 1H), 7.53 (d, *J*=8.0Hz, 1H), 7.38 (t, *J*=2.5Hz, 1H), 7.34 (t, *J*=8.0Hz, 1H), 4.19-4.33 (m, 4H), 3.90-4.01 (m, 4H), 3.67-3.84 (m, 6H), 2.45-2.67 (m, 4H).

MS (ES$^+$) 471 (100%, $[M+H]^+$).

Example L: [2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl]-(2-methoxy-ethyl)-methyl-amine



i. (2-Chloro-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl)-(2-methoxy-ethyl)-methyl-amine, **13**

To compound **8** (as per *Example H* above) (23mg, 0.072mmol) in dry CH_2Cl_2 (5mL), MeOH (2mL) was added 3Å molecular sieves, (2-methoxyethyl)methylamine (12µL, 0.11mmol) followed by $NaBH(OAc)_3$ (46mg,0.22mmol) and $NaBH_3CN$ (4.5mg, 0.07mmol) under Ar(g). After 18h, the reaction mixture was filtered, washing through with CH_2Cl_2 (30mL). 50% saturated brine (5mL) was then added to the filtrate and the layers were separated, extracting with CH_2Cl_2 followed by EtOAc, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by first flash column chromatography on silica (eluant 1-4% $MeOH/CH_2Cl_2$) followed by ion exchange column chromatography (SCX-3, MeOH-0.5M NH_3 in MeOH) furnished **13** (11mg, 0.028mmol, 39%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.60 (d, *J*=2.0Hz, 1H), 8.49 (d, *J*=2.0Hz, 1H), 4.10-4.19 (m, 4H), 3.84-3.90 (m, 4H), 3.80 (br. s., 2H), 3.57 (t, *J*=5.5Hz, 2H), 3.37 (s, 3H), 2.71 (t, *J*=5.5Hz, 2H), 2.31 (s, 3H).

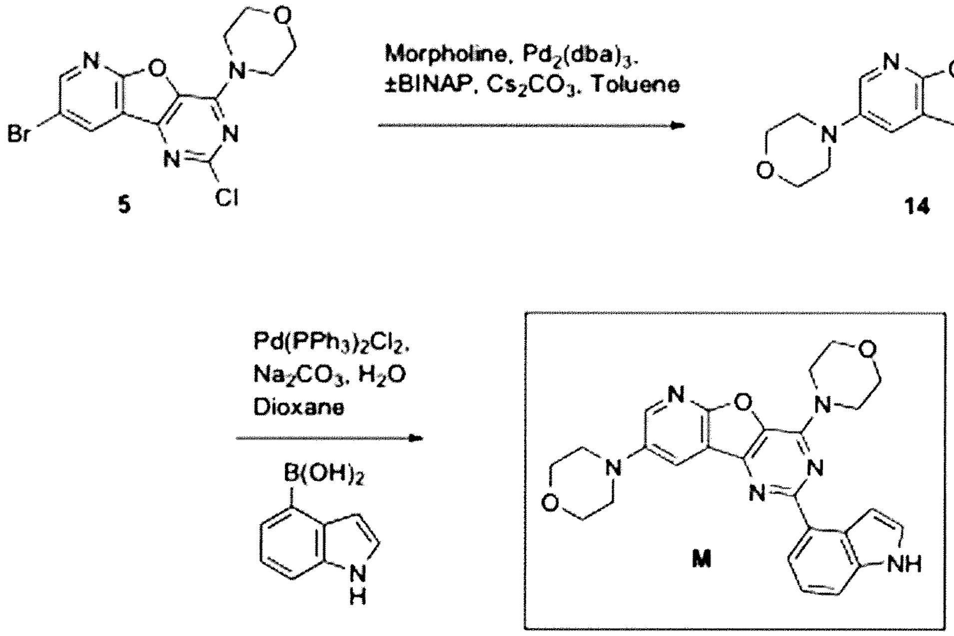
MS (ES$^+$) 392 (100%, [M+H]$^+$).

ii. [2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl]-(2-methoxy-ethyl)-methyl-amine, **L**

To a sealed tube was added compound **13** (11mg, 0.028mmol), indole-4-boronic acid (11.3mg, 0.07mmol), dichloro-bis(triphenylphosphine)palladium (II) (4mg, 0.006mmol) and Na_2CO_3 (6mg, 0.056mmol) followed by dioxane (2mL) and water (0.8mL) under Ar(g). The tube was heated to 88°C for 18h whereupon it was cooled to rt and diluted with EtOAc (35mL) and 50% saturated brine (5mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 10mL). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 1-3% MeOH/CH_2Cl_2) furnished **L** (4.5mg, 0.01mmol, 34%) as an off-white solid.

^{1}H NMR (400MHz, 9:1 $CDCl_3/CD_3OD$) δ_H: 9.80 (br. s., 1H), 8.56 (s, 1H), 8.49 (br. s., 1H), 7.98 (d, *J*=7.5Hz, 1H), 7.44 (d, *J*=8.0Hz, 1H), 7.31 (br. s., 1H), 7.24-7.28 (m, 1H), 7.18 (t, *J*=7.5Hz, 1H), 4.10-4.20 (m, 4H), 3.76-3.87 (m, 4H), 3.51 (t, *J*=5.0Hz, 2H), 3.27 (s, 3H), 3.22-3.26 (m, 2H), 2.59-2.75 (m, 2H), 2.29 (s, 3H).
MS (ES$^+$) 473 (100%, $[M+H]^+$).

Example M: 2-(1H-Indol-4-yl)-4,8-di-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine



i. 2-Chloro-4,8-di-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **14**

To a sealed tube was added compound **5** (as per *Example E* above, 20mg, 0.054mmol), $Pd_2(dba)_3$ (1.5mg, 0.0016mmol), ±BINAP (2mg, 0.0032mmol) and Cs_2CO_3 (26mg, 0.081mmol) followed by dry toluene (2mL) and morpholine (5.7mL, 0.065mmol) under Ar(g). The tube was heated at 90°C for 18h. After cooling to rt, EtOAc (35mL) and 50% saturated brine (5mL) were added. The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 10mL). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 0.5-2% MeOH/CH_2Cl_2) furnished **14** (10mg, 0.027mmol, 49%) as a yellow solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.34 (d, *J*=3.0Hz, 1H), 7.94 (d, *J*=3.0Hz, 1H), 4.07-4.23 (m, 4H), 3.90-3.97 (m, 4H), 3.81-3.89 (m, 4H), 3.18-3.28 (m, 4H).

MS (ES$^+$) 376 (100%, [M+H]$^+$).

ii. 2-(1H-Indol-4-yl)-4,8-di-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **M**

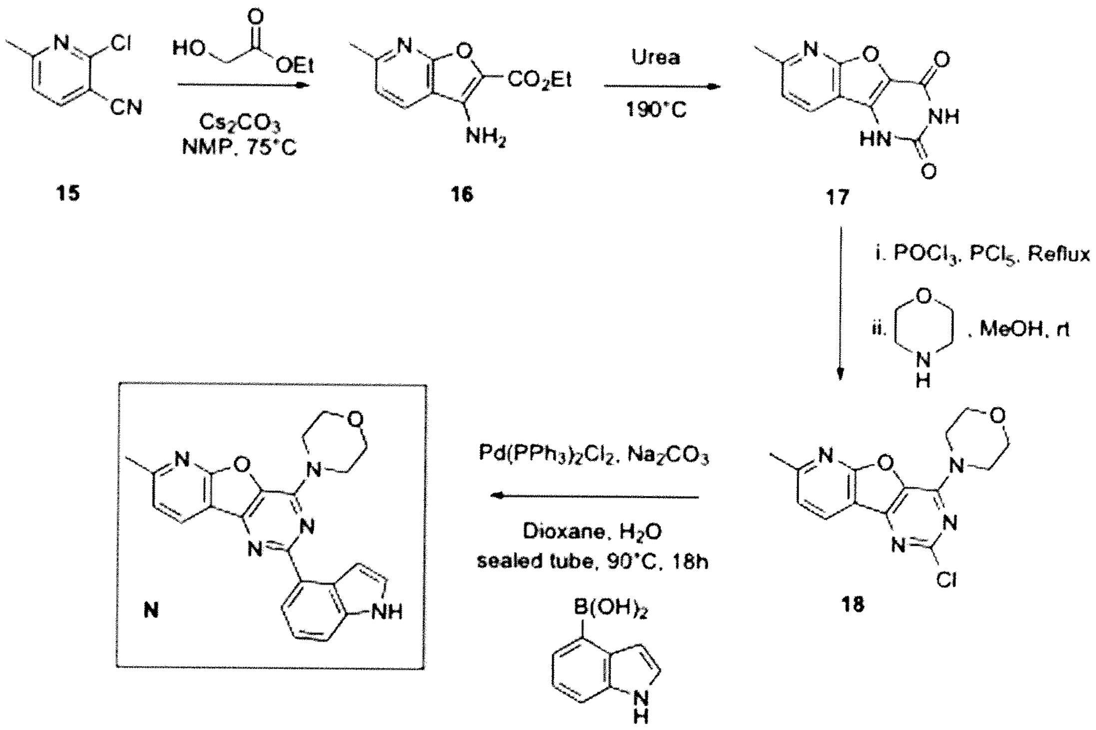
To a sealed tube was added compound **14** (10mg, 0.027mmol), indole-4-boronic acid (10.9mg, 0.068mmol), dichloro-bis(triphenylphosphine)palladium (II)

(3.7mg, 0.005mmol) and Na_2CO_3 (5.7mg, 0.054mmol) followed by dioxane (2mL) and water (0.8mL) under Ar(g). The tube was heated to 88°C for 18h whereupon it was cooled to rt and diluted with EtOAc (35mL) and 50% saturated brine (5mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 10mL). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by first flash column chromatography on silica (eluant 0.5-1.5% MeOH/CH_2Cl_2) followed by ion exchange column chromatography (SCX-3, MeOH-0.5M NH_3 in MeOH) furnished **M** (3.2mg, 0.007mmol, 26%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.39 (br. s., 1H), 8.35 (d, *J*=2.5Hz, 1H), 8.21 (d, *J*=7.5Hz, 1H), 7.33-7.58 (m, 3H), 7.19-7.31 (m, 2H), 4.19-4.37 (m, 4H), 3.85-4.02 (m, 8H), 3.25-3.37 (m, 4H).

LCMS (ES$^+$) 457 (100%, [M+H]$^+$).

Example N: 2-(1H-Indol-4-yl)-7-methyl-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine



i. 3-Amino-6-methyl-furo[2,3-b]pyridine-2-carboxylic acid ethyl ester, **16**

To a suspension of 2-chloro-3-cyano-6-methylpyridine, **15** (2.0g, 13.1mmol, 1eq) and cesium carbonate (12.8g, 39.3mmol, 3eq) in anhydrous NMP (20mL) was added at rt ethyl glycolate (1.36mL, 14.4mmol, 1.1eq) under Ar(g). The reaction mixture was heated up at 75°C overnight; once cooled down, it was partitioned with H_2O (200mL) and extracted with EtOAc (3 x 70mL). The combined organics were thoroughly washed with H_2O (3 x 75mL), then dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was further purified by silica gel column chromatography with hexane/EtOAc (4:1-1:3) to yield **16** as a pale yellow solid (1.30 g, 45%).

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 7.84 (d, J=8.0Hz, 1H), 7.12 (d, J=8.0Hz, 1H), 4.41 (q, J=7.0Hz, 2H), 4.26 (br. s., 2H), 2.66 (s, 3H), 1.42 (t, J=7.0Hz, 3H).

MS (ES$^+$) 221.0 (50%, [M+H]$^+$), 243.0 (50%, [M+Na]$^+$).

ii. 7-Methyl-1H-pyrido[3',2':4,5]furo[3,2-d]pyrimidine-2,4-dione, **17**

A round-bottomed flask was loaded up with 3-amino-6-methyl-furo[2,3-b]pyridine-2-carboxylic acid ethyl ester, **16** (926mg, 4.20mmol, 1eq) and urea (2.52g, 42.0mmol, 10eq). The mixture was heated up at 190°C for 3h until no more ammonia release was observed. H_2O (10mL) was added, and the reaction mixture was stirred for 30 min vigorously; it was then filtered, and the solid was washed with H_2O (3 x 10mL) before drying to furnish the product as a pale brown solid (1.60 g, quant.)

^{1}H NMR (400MHz, DMSO-d_6) δ_H: 8.24 (d, *J*=7.5Hz, 1H), 7.40 (d, *J*=8.0Hz, 1H), 7.16 (br. s., 1H), 5.41 (br. s., 1H), 2.61 (s, 3H).

MS (ES$^+$) 240.0 (100%, [M+Na]$^+$).

iii. 2-Chloro-7-methyl-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **18**

To a mixture of 7-methyl-1H-pyrido[3',2':4,5]furo[3,2-d]pyrimidine-2,4-dione (1.6g, 4.20 mmol, 1eq) **17**, and PCl_5 (10.5 g, 50 mmol, 12eq) was added at rt $POCl_3$ (33.5mL, 357mmol, 85eq) under Ar(g). The reaction mixture was refluxed at 115°C overnight. Once cooled down to rt, the mixture was poured dropwise very slowly onto stirred crushed ice over 2h, then warmed up to rt for 1h. The resulting aqueous was extracted with EtOAc (3 x 100mL) and CH_2Cl_2 (4 x 100mL). The combined organics were dried over $MgSO_4$ and the solvent was removed *in vacuo*. To this residue in dry MeOH (50 mL) was added at rt morpholine (0.92mL, 10.5mmol, 2.5eq) under Ar(g). The reaction mixture was stirred for 3h, then the solvent was removed *in vacuo*. The residue was further purified by silica gel column chromatography with hexane/EtOAc (1:1-0:1) to yield the product as a pale brown solid (384mg, 30%).

^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.38 (d, *J*=8.0Hz, 1H), 7.34 (d, *J*=8.0Hz, 1H), 4.10-4.19 (m, 4H), 3.84-3.89 (m, 4H), 2.74 (s, 3H).

MS (ES$^+$) 305.0 (90%, [M+H]$^+$).

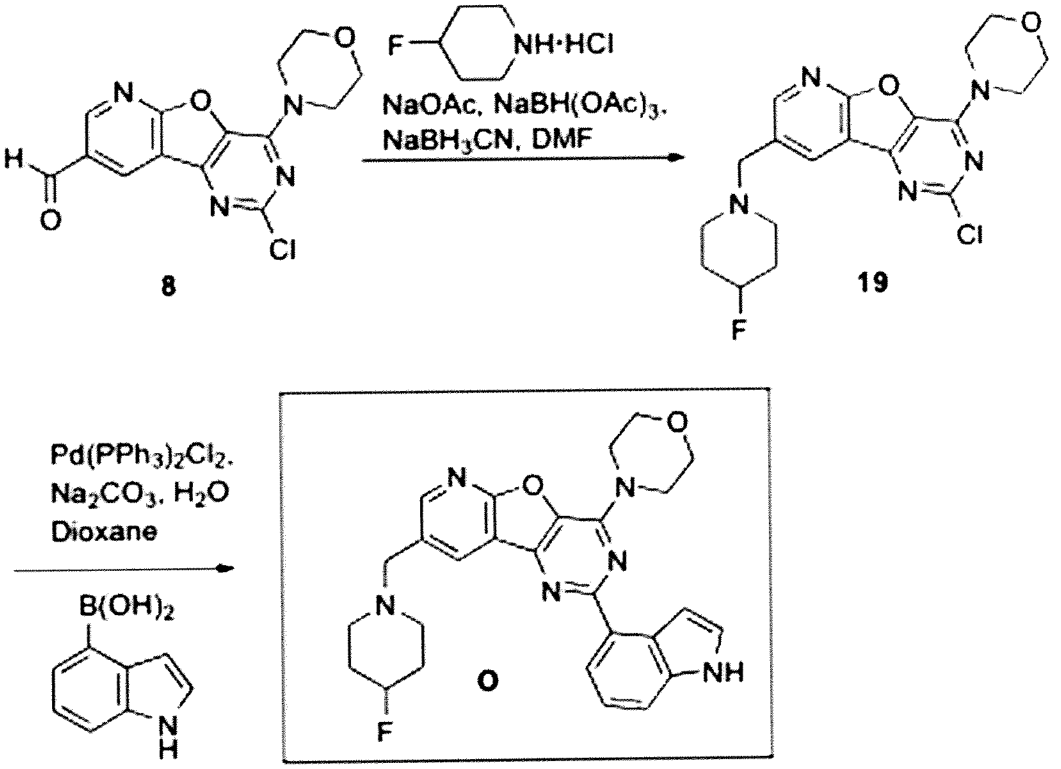
iv. 2-(1H-Indol-4-yl)-7-methyl-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **N**

To a solution of 2-chloro-7-methyl-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **18** (27mg, 0.09mmol, 1eq), indole-4-boronic acid (43mg, 0.27mmol, 3eq) and $PdCl_2(PPh_3)_2$ (12.4mg, 0.02mmol, 20mol%) in a mixture of dioxane (2mL) and H_2O (1.0mL) was added Na_2CO_3 (19mg, 0.18mmol, 2eq) under Ar(g). The reaction mixture was then heated in a pressure tube for 18h at 90°C. Once cooled down, the mixture was partitioned with H_2O (10mL) and extracted with CH_2Cl_2 (2 x 10mL) and EtOAc (2 x 10mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was further purified by SCX-3 cartridge eluting with CH_2Cl_2/MeOH (1:0-0:1 then + 1M NH_3) followed by silica gel column chromatography with hexane/EtOAc (3:1-0:1) to yield **N** as a pale brown solid (5.4 mg, 16%).

^{1}H NMR (400MHz, $CDCl_3$ + 10% MeOD) δ_H: 8.38 (d, *J*=8.0Hz, 1H), 7.82 (d, *J*=7.5Hz, 1H), 7.35 (d, *J*=8.0Hz, 1H), 7.19 (d, *J*=7.5Hz, 1H), 7.16 (d, *J*=3.0Hz, 1H), 7.12 (m, *J*=1.0Hz, 1H), 7.08 (t, *J*=7.5Hz, 1H), 4.03-4.09 (m, 4H), 3.70-3.76 (m, 4H), 2.54 (s, 3H).

MS (ES$^+$) 386.1 (100%, [M+H]$^+$).

Example O: 8-(4-Fluoro-piperidin-1-ylmethyl)-2-(1H-indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine



i. 2-Chloro-8-(4-fluoro-piperidin-1-ylmethyl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **19**

To compound **8** (as per *Example H* above) (80mg, 0.25mmol) in dry DMF (12mL) was added 4-fluoropiperidine hydrochloride (70 mg, 0.5mmol) and NaOAc (41mg, 0.5mmol) under Ar(g). After 20 minutes $NaBH(OAc)_3$ (106mg, 0.5mmol) and $NaBH_3CN$ (16mg, 0.25mmol) were added and the suspension was stirred for 16h. The DMF was then removed *in vacuo*, EtOAc (45mL) was added along with 50% saturated brine (7mL), the layers separated, extracted with EtOAc (2 x 15mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 1-2% $MeOH/CH_2Cl_2$) furnished **9** (58mg, 0.014mmol, 57%) as a white solid.

^1H NMR (300MHz, $CDCl_3$) δ_H: 8.55 (d, J=1.8Hz, 1H), 8.51 (d, J=1.8Hz, 1H), 4.58-4.86 (m, 1H), 4.06-4.23 (m, 4H), 3.82-3.92 (m, 4H), 3.69 (s, 2H), 2.54-2.68 (m, 2H), 2.38-2.52 (m, 2H), 1.81-2.00 (m, 4H).

LCMS (ES^+) 406 (100%, $[M+H]^+$).

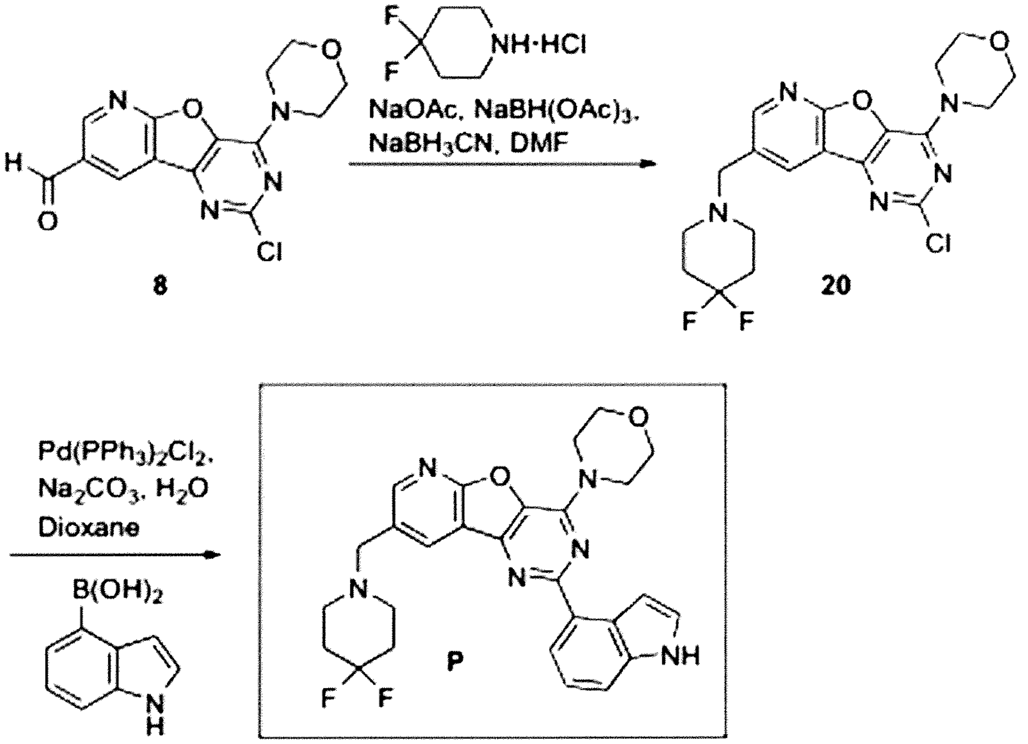
ii. 8-(4-Fluoro-piperidin-1-ylmethyl)-2-(1H-indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **O**

To a sealed tube was added **19** (55mg, 0.136mmol), indole-4-boronic acid (55mg, 0.34mmol), dichloro-bis(triphenylphosphine)palladium (II) (19mg, 0.027mmol) and Na_2CO_3 (29mg, 0.27mmol) followed by dioxane (3.5mL) and water (1.4mL) under Ar(g). The tube was heated to 88°C for 18h whereupon it was cooled to rt and diluted with EtOAc (45mL) and 50% saturated brine (7mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 10mL). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 1-3% MeOH/CH_2Cl_2) furnished **O** (30mg, 0.06mmol, 45%) as a brown solid.

^{1}H NMR (300MHz, $CDCl_3$) δ_H: 8.62 (d, *J*=2.2Hz, 1H), 8.55 (d, *J*=2.2Hz, 1H), 8.34 (br. s., 1H), 8.24 (d, *J*=7.0Hz, 1H), 7.59-7.68 (m, 1H), 7.54 (d, *J*=8.1Hz, 1H), 7.31-7.41 (m, 2H), 4.57-4.88 (m, 1H), 4.20-4.34 (m, 4H), 3.89-4.00 (m, 4H), 3.72 (s, 2H), 2.57-2.74 (m, 2H), 2.39-2.54 (m, 2H), 1.81-2.04 (m, 4H).

LCMS (ES$^+$) 487 (100%, $[M+H]^+$).

Example P: 8-(4,4-Difluoro-piperidin-1-ylmethyl)-2-(1H-indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine



i. 8-(4,4-Difluoro-piperidin-1-ylmethyl)-2-(1H-indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **20**

To compound **8** (as per *Example H* above) (80mg, 0.25mmol) in dry DMF (12mL) was added 4,4-difluoropiperidine hydrochloride (79mg, 0.5mmol) and NaOAc (41mg, 0.5mmol) under Ar(g). After 20 minutes $NaBH(OAc)_3$ (106mg, 0.5mmol) and $NaBH_3CN$ (16mg, 0.25mmol) were added and the suspension was stirred for 16h. The DMF was then removed *in vacuo*, EtOAc (45mL) was added along with 50% saturated brine (7mL), the layers separated, extracted with EtOAc (2 x 15mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 1-2% $MeOH/CH_2Cl_2$) furnished **20** (41mg, 0.097mmol, 39%) as a white solid.

^{1}H NMR (300MHz, $CDCl_3$) δ_H: 8.55 (d, *J*=2.0Hz, 1H), 8.51 (d, *J*=2.0Hz, 1H), 4.08-4.23 (m, 4H), 3.82-3.93 (m, 4H), 3.74 (s, 2H), 2.54-2.66 (m, 4H), 1.92-2.12 (m, 4H).

LCMS (ES^+) 424 (100%, $[M+H]^+$).

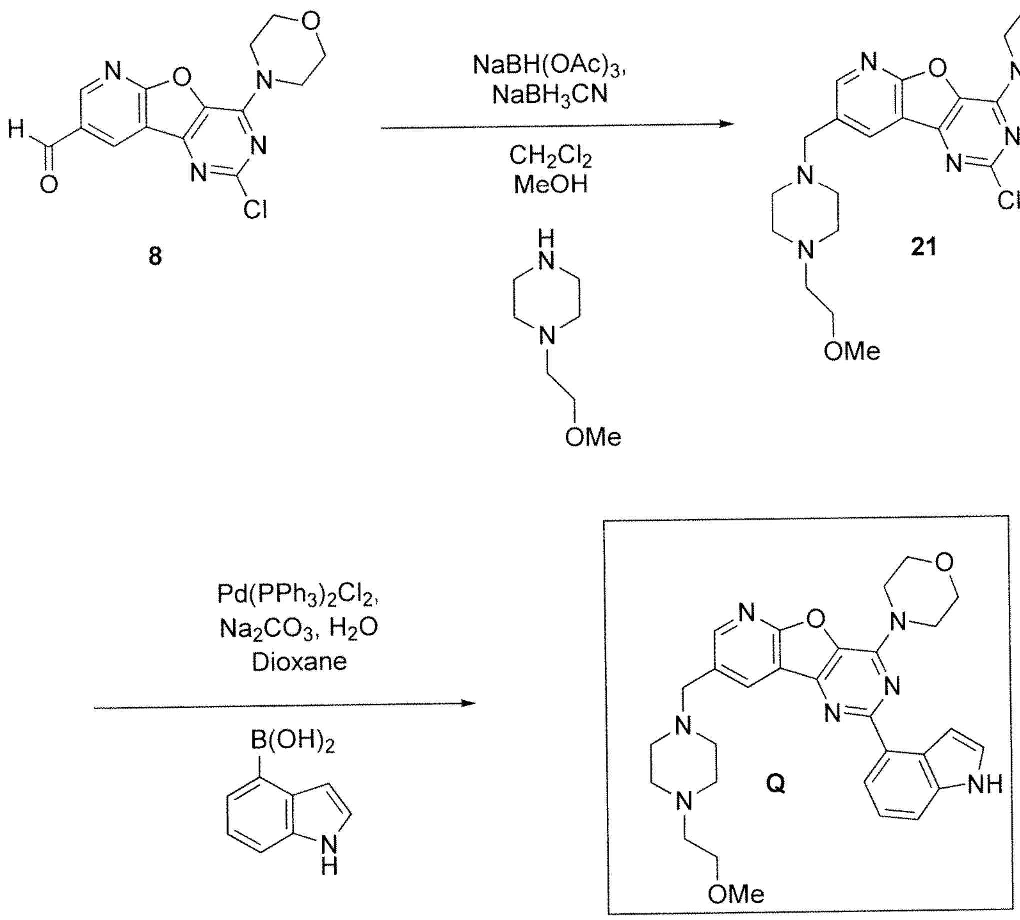
ii. [2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl]-(2-methoxy-ethyl)-methyl-amine, **N**

To a sealed tube was added **20** (41mg, 0.097mmol), indole-4-boronic acid (39mg, 0.24mmol), dichloro-bis(triphenylphosphine)palladium (II) (13.6mg, 0.02mmol) and Na_2CO_3 (21mg, 0.19mmol) followed by dioxane (3.5mL) and water (1.4mL) under Ar(g). The tube was heated to 88°C for 18h, and the reaction mixture was then cooled to rt, and diluted with EtOAc (45mL) and 50% saturated brine (7mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 10mL). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 0.5-2% $MeOH/CH_2Cl_2$) furnished **P** (7.4mg, 0.015mmol, 15%) as a white solid.

^1H NMR (300MHz, $CDCl_3$) δ_H: 8.61 (d, *J*=2.3Hz, 1H), 8.54 (d, *J*=2.3Hz, 1H), 8.38 (br. s., 1H), 8.24 (dd, *J*=7.5, 0.8Hz, 1H), 7.58-7.65 (m, 1H), 7.53 (d, *J*=7.9Hz, 1H), 7.37-7.40 (m, 1H), 7.34 (t, *J*=7.9Hz, 1H), 4.21-4.32 (m, 4H), 3.91-3.99 (m, 4H), 3.76 (s, 2H), 2.56-2.70 (m, 4H), 1.95-2.14 (m, 4H).

LCMS (ES^+) 505 (100%, $[M+H]^+$).

Example Q: 2-(1H-Indol-4-yl)-8-[4-(2-methoxy-ethyl)-piperazin-1-ylmethyl]-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine



i. 2-Chloro-8-[4-(2-methoxy-ethyl)-piperazin-1-ylmethyl]-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **21**

To compound **8** (as per *Example H* above) (22.2mg, 0.070mmol) in dry CH_2Cl_2/MeOH (5mL/2mL) was added 1-(2-methoxyethyl) piperazine (13µL, 0.093mmol) and the reaction was stirred for 1h. $NaBH(OAc)_3$ (45.8mg, 0.022mmol) was then added, followed by $NaBH_3CN$ (4.4mg, 0.070mmol), and the reaction mixture was stirred for 48h. EtOAc (30 mL) was added along with water/saturated brine (10mL/5mL); the layers were separated, extracted with EtOAc (2 x 30mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 2:98-6:94 MeOH/CH_2Cl_2) furnished **21** (10mg, 0.022mmol, 32%) as a white solid.

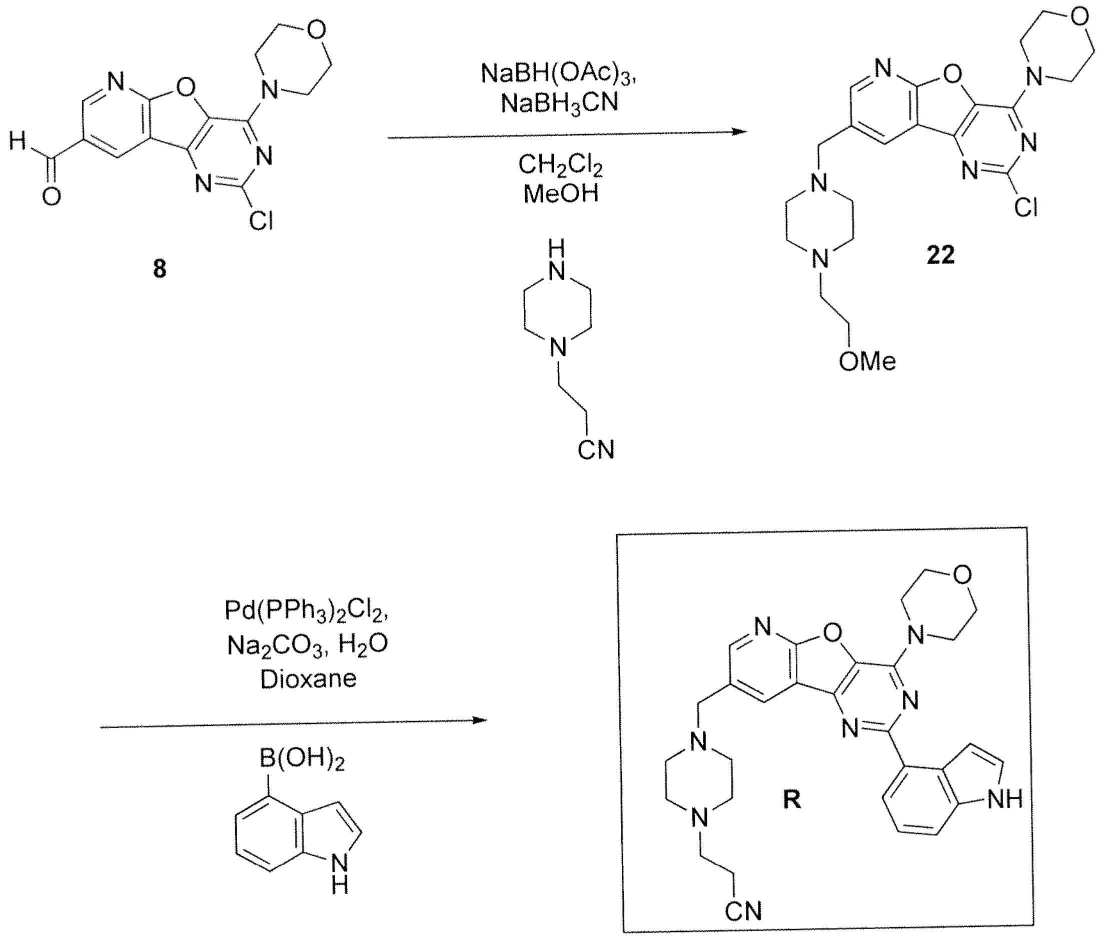
^{1}H NMR (300MHz, 9.5:0.5 $CDCl_3$/CD_3OD) δ_H 8.53 (d, *J*=1.9Hz, 1H), 8.47-8.52 (m, 1H), 4.14 (br. s., 4H), 3.83-3.93 (m, 4H), 3.68 (s, 2H), 3.48-3.57 (m, 2H), 3.34 (s, 3H), 2.47-2.66 (m, 10H). MS (ES$^+$) 447.2 (100%, [M+H]$^+$).

ii. 2-(1H-Indol-4-yl)-8-[4-(2-methoxy-ethyl)-piperazin-1-ylmethyl]-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine, **Q**

To indole-4-boronic acid (8.6mg, 0.053mmol), dichloro-bis(triphenylphosphine)palladium (II) (3.0mg, 0.0043mmol) and sodium carbonate (4.7 mg, 0.045mmol) was added compound **21** (10.0mg, 0.022mmol) dissolved in dioxane/water (2mL/0.8mL). The reaction was then heated in a sealed tube at 88°C for 16h, and was subsequently cooled to rt; it was then partitioned between EtOAc/water (30mL/5mL), the layers separated, extracted with EtOAc (2 x 30mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 0:1-2:98 MeOH/CH_2Cl_2) furnished **Q** (1.09mg, 0.0021mol, 9%) as a white solid.

LCMS (ES$^+$) 528.3 (100%, [M+H]$^+$).

Example R: 3-{4-[2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl]-piperazin-1-yl}-propionitrile



i. 3-[4-(2-Chloro-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl)-piperazin-1-yl]-propionitrile, **22**

To compound **8** (as per *Example H* above) (24.2mg, 0.076mmol) in dry CH_2Cl_2/MeOH (5mL/2mL) was added 3-(1-piperazinyl) propionitrile (15μL, 0.11mmol) and the reaction mixture was stirred for 15 mins. $NaBH(OAc)_3$ (47.8mg, 0.023mmol) was then added, and the resulting mixture was stirred for 17h. $NaBH_3CN$ (4.8mg, 0.076mmol) was added, and following additional stirring for a further 5h, the reaction mixture was partitioned between EtOAc/water/saturated brine (30mL/10mL/5mL), the layers separated, extracted with EtOAc (2 x 30mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification using an SCX-2 column with MeOH/CH_2Cl_2 (1:9-1:1-1:1+ 0.2M NH_3 in MeOH) followed by flash column chromatography on silica (eluant 1:9 MeOH/CH_2Cl_2) furnished **22** (15.1mg, 0.034mmol, 45%) as a white solid.

^{1}H NMR (400MHz, 9:1 $CDCl_3$/CD_3OD) δ_H 8.43 (d, *J*=2.0Hz, 1H), 8.38 (d, *J*=2.0Hz, 1H), 4.04 (br. s., 4H), 3.76 (t, 4H, *J*=5.0Hz), 3.60 (s, 2H), 2.57-2.64 (m, 2H), 2.40-2.51 (m, 10H).

MS (ES$^+$) 442.1 (100%, [M+H]$^+$).

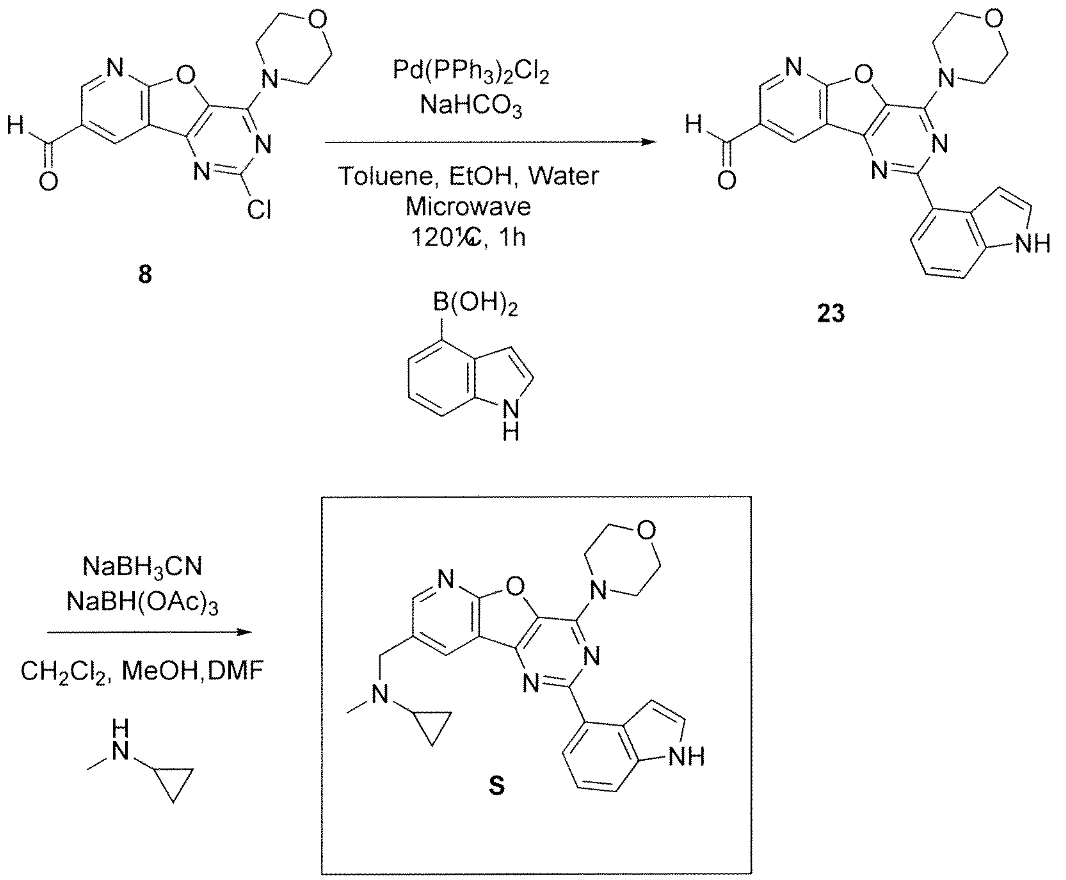
ii.3-{4-[2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl]-piperazin-1-yl}-propionitrile, **R**

To indole-4-boronic acid (14.6mg, 0.091mmol), dichloro-bis(triphenylphosphine)palladium (II) (4.7mg, 0.0066mmol) and sodium carbonate (7.5mg, 0.071mmol) was added **22** (15.1mg, 0.034mmol) dissolved in dioxane/water (2mL/0.8mL). The reaction mixture was heated in a sealed tube at 88°C for 16h, was subsequently cooled to rt, and was then partitioned between EtOAc/water (30mL/5mL). The layers were separated, extracted with EtOAc (2 x 30mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 2:98-4:96-6:94) MeOH/CH_2Cl_2) furnished **R** (6.8mg, 0.013mol, 38%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ_H 8.60 (s, 1H), 8.54 (s, 1H), 8.40 (br. s., 1H), 8.24 (dd, *J*=7.5, 1.0Hz, 1H), 7.60-7.63 (m, 1H), 7.53 (d, *J*=8.0Hz, 1H), 7.38 (br. s., 1H), 7.34 (t, *J*=7.8Hz, 1H), 4.26 (t, *J*=4.3Hz, 4H), 3.94 (t, *J*=4.5Hz, 4H), 3.72 (s, 2H), 2.69-2.75 (m, 2H), 2.48-2.65 (m, 10H).

MS (ES$^+$) 523.2 (100%, [M+H]$^+$).

Example S: Cyclopropyl-[2-(1H-indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl]-methyl-amine



i. 2-(1H-Indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine-8-carbaldehyde, **23**

To compound **8** (as per *Example H* above) (40mg, 0.13mmol, 1eq), indole-4-boronic acid (61mg, 0.38mmol, 3eq) and $PdCl_2(PPh_3)_2$ (18.0mg, 0.03mmol, 20mol%) in a mixture of toluene (2.5mL), ethanol (1.5mL) and H_2O (0.8mL) was added $NaHCO_3$ (32mg, 0.38mmol, 3eq) under Ar(g). The reaction mixture was heated in a microwave for 1h at 120°C. Once cooled down, the mixture was partitioned with H_2O (10mL) and extracted with CH_2Cl_2 (2 x 10mL) and EtOAc (2 x 10mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The resulting residue was further purified by silica gel column chromatography with CH_2Cl_2/MeOH (1:0-19:1) to yield the product, **23**, as a pale yellow solid (33.0mg, 65%).

^{1}H NMR (300MHz, DMSO-d_6) δ_H: 11.27 (br. s, 1H), 10.26 (s, 1H), 9.16 (d, *J*=2.3Hz, 1H), 9.11 (d, *J*=2.3Hz, 1H), 8.18 (d, *J*=7.5Hz, 1H), 7.58-7.67 (m, 2H), 7.49 (t, *J*=2.8Hz, 1H), 7.23 (t, *J*=7.7Hz, 1H), 4.08-4.16 (m, 4H), 3.83-3.90 (m, 4H).

MS (ES$^+$) 432.0 (100%, [M+H+MeOH]$^+$).

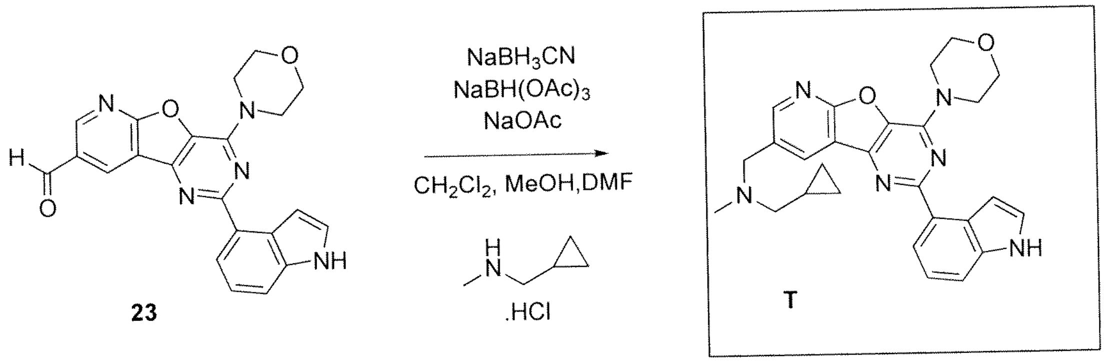
ii. Cyclopropyl-[2-(1H-indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl]-methyl-amine, **S**

To a solution of compound **23** (19mg, 0.048mmol, 1eq), $NaBH_3CN$ (6.0mg, 0.096mmol. 2eq), $NaBH(OAc)_3$ (31mg, 0.144mmol, 3eq) in a mixture of anhydrous CH_2Cl_2 (2mL), MeOH (2mL) and DMF (0.5mL) was added cyclopropyl-methyl-amine (19µL, 0.19mmol, 4eq) under Ar(g). The reaction mixture was stirred at rt overnight, and the solvents were removed *in vacuo*. The resulting residue was then partitioned with H_2O (10mL) and extracted with CH_2Cl_2 (3 x 10mL) and EtOAc (2 x 10mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was further purified by silica gel column chromatography with CH_2Cl_2/MeOH (1:0-24:1) to furnish the product, **S**, as a white solid (9.56mg, 44%).

^{1}H NMR (300MHz, $CDCl_3$) δ_H: 8.55 (d, *J*=2.3Hz, 1H), 8.50 (d, *J*=2.3Hz, 1H), 8.33 (br. s., 1H), 8.23 (dd, *J*=7.5, 0.8Hz, 1H), 7.58-7.63 (m, 1H), 7.50-7.56 (m, 1H), 7.37-7.40 (m, 1H), 7.30-7.37 (m, 1H), 4.22-4.30 (m, 4H), 3.91-3.98 (m, 4H), 3.89 (s, 2H), 2.33 (s, 2H), 1.76-1.84 (m, 1H), 0.43-0.58 (m, 4H).

MS (ES$^+$) 455.1 (100%, [M+H]$^+$).

Example T: Cyclopropylmethyl-[2-(1H-indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidin-8-ylmethyl]-methyl-amine

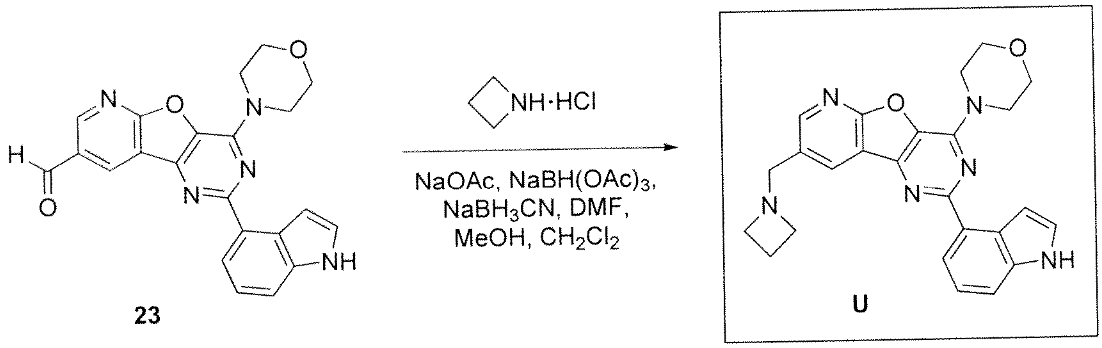


To a solution of compound **23** (as per *Example S* above) (19mg, 0.048mmol, 1eq), $NaBH_3CN$ (6.0mg, 0.096mmol. 2eq), $NaBH(OAc)_3$ (31mg, 0.144mmol, 3eq), NaOAc (15.7mg, 0.19mmol, 4eq) in a mixture of anhydrous CH_2Cl_2 (2mL), MeOH (2mL) and DMF (0.5mL) was added cyclopropylmethyl-methyl-amine hydrochloride (23mg, 0.19mmol, 4eq) under Ar(g). The reaction mixture was stirred at rt overnight. Solvents were removed *in vacuo*. Then, the residue was partitioned with H_2O (10mL) and extracted with CH_2Cl_2 (3 x 10mL) and EtOAc (2 x 10mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was further purified by silica gel column chromatography with CH_2Cl_2/MeOH (1:0-47:3) to yield the product, **T**, as a white solid (8.35mg, 37%).

^1H NMR (300MHz, $CDCl_3$ + 10% CD_3OD) δ_H: 8.57 (d, J=2.3Hz, 1H), 8.49 (d, J=2.3Hz, 1H), 8.05 (dd, J=7.5, 1.1Hz, 1H), 7.47 (d, J=8.3Hz, 1H), 7.37 (dd, J=3.4, 0.8Hz, 1H), 7.30 (d, J=3.4Hz, 1H), 7.19-7.26 (m, 1H), 4.16-4.22 (m, 4H), 3.84-3.90 (m, 4H), 3.75 (s, 2H), 2.32 (d, J=6.8Hz, 2H), 2.29 (s, 3H), 0.46-0.54 (m, 2H), 0.04-0.12 (m, 2H).

MS (ES^+) 469.1 (100%, $[M+H]^+$).

Example U: 8-Azetidin-1-ylmethyl-2-(1H-indol-4-yl)-4-morpholin-4-yl-pyrido[3',2':4,5]furo[3,2-d]pyrimidine



To compound **23** (as per *Example S* above) (17mg, 0.04mmol) in a mixture of dry DMF (2mL), CH_2Cl_2 (0.5mL) and MeOH (0.2mL) was added azetidine hydrochloride (16mg, 0.17mmol) and NaOAc (14mg, 0.17mmol) under Ar(g). After 5 minutes $NaBH(OAc)_3$ (27mg, 0.13mmol) and $NaBH_3CN$ (5.4mg, 0.09mmol) were added and the reaction mixture was stirred for 16h. EtOAc (45mL) was added along with 50% saturated brine (5mL); the layers were separated, extracted with EtOAc (3 x 10mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica (eluant 2-8% MeOH/CH_2Cl_2) furnished **U** (5.4mg, 0.012mmol, 28%) as an off-white solid.

^{1}H NMR (300MHz, 9:1 $CDCl_3/CD_3OD$) δ_H: 8.52 (d, *J*=2.3Hz, 1H), 8.43 (d, *J*=2.3Hz, 1H), 8.02 (dd, *J*=7.5, 1.1Hz, 1H), 7.47 (d, *J*=7.9Hz, 1H), 7.34 (dd, *J*=3.4, 0.8Hz, 1H), 7.29 (d, *J*=3.0Hz, 1H), 7.22 (t, *J*=7.8Hz, 1H), 4.15-4.21 (m, 4H), 3.83-3.89 (m, 4H), 3.73 (s, 2H), 3.20-3.33 (m, 4H), 2.01-2.15 (m, 2H). LCMS (ES$^+$) 441 (100%, $[M+H]^+$).

Biological Data

1) PI3K Isoform Biochemical Data

Compound	IC_{50} (nM) PI3K			
	p110α	p110β	p110δ	p110γ
A	54	137	15	873
B	159	19	6	317
D	104	57	33	103
E	88	69	7	627
F	127	109	6	269
G	223	83	5	1655
H	398	63	6	213
I	508	503	10	4946
J	680	277	26	1039
K	355	64	6	2612
L	604	111	21	1820
M	96	25	10	219
R	597	131	22	2536

2) Anti-Inflammatory Activity: Inhibition of the Production of Pro-Inflammatory Cytokines from Stimulated Human Peripheral Blood Mononuclear Cells (hPBMCs)

Compounds were tested at a concentration of 1uM for cytokine release inhibition in hPBMCs stimulated with LPS (TNFα), PHA (IFNγ) and anti-CD3 (IL-17A, IL-17F, IL-21, IL-23):

Compound	% Inhibition of Proinflammatory Cytokine Production at 1uM					
	TNFα	IFNγ	IL-17A	IL-17F	IL-21	IL-23
B	26	73	99	96	96	94
F	74	67	77	74	82	93

H	75	87	99	96	96	93
I	61	80	95	95	96	90

3) *In Vitro* Inhibition of Rheumatoid Arthritis Synovial Fibroblast (RASF) Proliferation

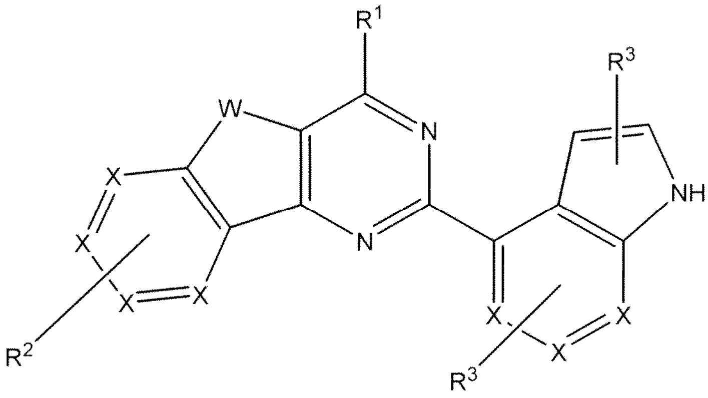
Compound	IC_{50} (nM) RASF Proliferation
A	1347
B	817
F	2237
H	1901
I	5722
K	3020
M	1610

4) *In Vitro* Inhibition of Tumour Cell Proliferation

Compound	IC_{50} (nM)		
	PC3 (Prostate Tumour)	MCF7 (Breast Tumour)	A549 (Lung Tumour)
A	3013	331	151
B	1339	145	229
F	7294	215	1152
G	3770	127	186
H	3030	165	466
K	3336	352	682
L	3244	119	1605

CLAIMS

1. A compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

W is O, N-H, N-(C_1-C_{10} alkyl) or S;

each X is independently CH or N;

R^1 is a 5 to 7-membered saturated or unsaturated, optionally substituted heterocycle containing at least 1 heteroatom selected from N or O;

R^2 is $(LQ)_mY$;

each L is independently a direct bond, C_1-C_{10} alkylene, C_2-C_{10} alkenylene, C_2-C_{10} alkynylene, arylene or C_3-C_{10} cycloalkylene;

each Q is independently a direct bond, heteroarylene, a heterocycle linker, -O-, -NR^3-, -C(O)-, -C(O)NR_3-, -SO_2-, -SO_2-NR^3-, -N-C(O)-NR^3-, -N-SO_2-NR^3, halogen, -C(halogen)$_a$($R^3_{(2-a)}$)-, -NR^4R^5-, -C(O)NR^4R^5, where R^4 and R^5 together with the nitrogen to which they are attached form a 5 to 7-membered heterocycle linker;

m is from 0 to 5;

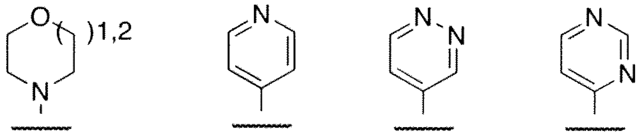
Y is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, aryl, C_3-C_{10} cycloalkyl, heterocycle, heteroaryl, -OR^3, -N(R^3)$_2$, -C(O)R^3, -C(O)OR_3, -C(O)N(R^3)$_2$, -N(R^3)$_2$, -SO_2-R^3, -SO_2-N(R^3)$_2$, -N-C(O)-N(R^3)$_2$, -N-SO_2-N(R^3)$_2$, halogen, -C(halogen)$_b$$R^3_{(3-b)}$, -CN, -$NR^4R^5$-, -C(O)$NR^4R^5$, where R^4 and R^5 together with the nitrogen to which they are attached form a 5- to 7-membered heterocycle;

b is from 1 to 3;

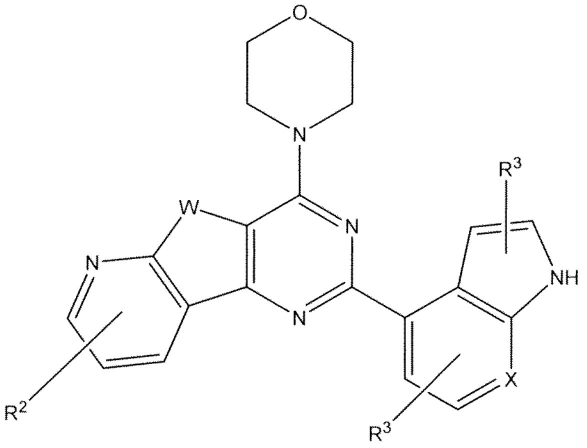
a is 1 or 2; and

each R^3 is independently H, C_1-C_{10} alkyl, aryl or heteroaryl.

2. A compound according to claim 1, wherein R^1 is represented by any of the following structures:



3. A compound according to claim 1 or claim 2, with the structure



4. A compound according to any preceding claim, wherein W is O.

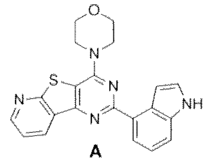
5. A compound according to any of claims 1 to 3, wherein W is S.

6. A compound according to any preceding claim, wherein both of the R^3 groups that are attached to the 6,5-ring system in formula I are H.

7. A compound according to any preceding claim, wherein R^2 comprises $-(C_1\text{-}C_{10}$ alkylene$)\text{-}NR^4R^5$ or R^2 comprises $-(C_1\text{-}C_{10}$ alkylene$)\text{-}NR^3\text{-}(C_1\text{-}C_{10}$ alkylene$)$-cycloakyl, wherein R^2, R^4 and R^5 are as defined in claim 1.

8. A compound according to any preceding claim, wherein m is 0, 1 or 2.

9. A compound according to any preceding claim, which is of any of the structures shown below:



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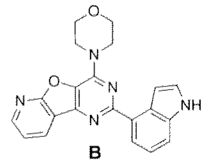

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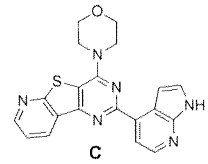

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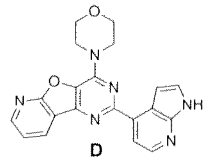

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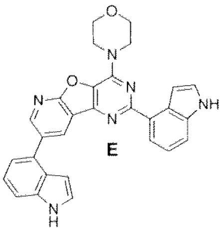

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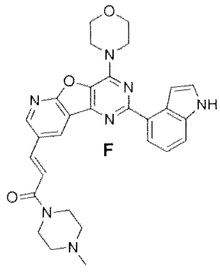

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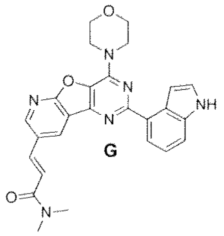

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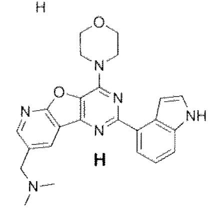
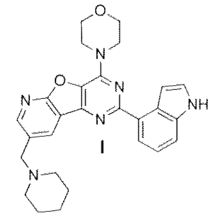


H



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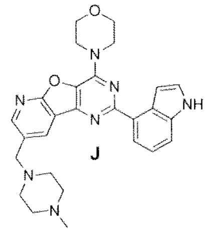

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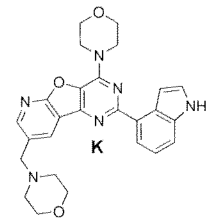

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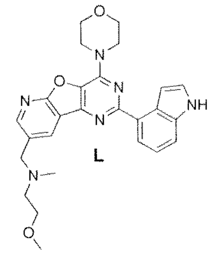
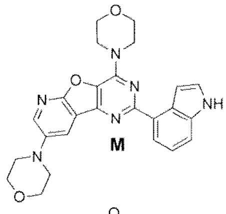
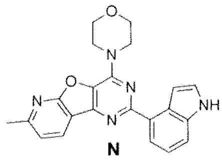


L



M



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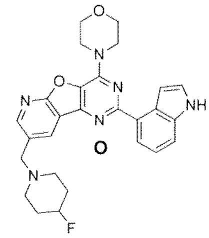

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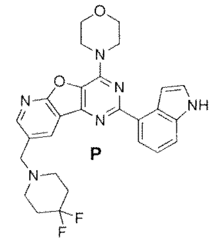

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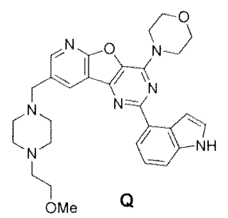

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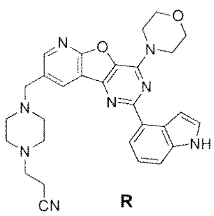

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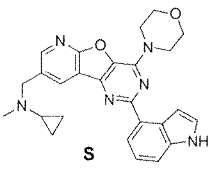

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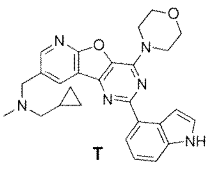
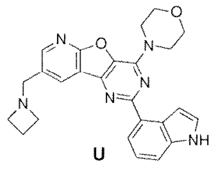


T



U

10. A pharmaceutical composition comprising a compound according to any preceding claim, and a pharmaceutically acceptable excipient.

11. A compound or composition according to any preceding claim, for use in therapy.

12. A compound or composition according to claim 11, wherein the therapy is of cancer, an immune disorder or an inflammatory disorder.

13. A compound or composition according to claim 12, wherein the cancer is a leukaemia or a PTEN-negative solid tumour.

14. A compound according to claim 11 or claim 12, wherein the therapy is of rheumatoid arthritis.

15. A compound or composition according to claim 11, for use in anti-rejection therapy following an organ transplant.

16. Use of a compound or composition as defined in any of claims 1 to 10, for the manufacture of a medicament for use in therapy.

17. Use according to claim 16, wherein the therapy is as defined in any of claims 12 to 14.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/051370

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/14 C07D519/00 C07D491/147 A61K31/519 A61P35/02
ADD.

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	M. HAYAKAWA ET. AL.: "Synthesis and biological evaluation of pyrido[3',2':4,5]furo[3,2-d]pyrimidine derivatives as novel PI3K p110alpha inhibitors." BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 17, no. 9, 15 February 2007 (2007-02-15), pages 2438-2442, XP002602756 paragraph [0008]; tables 1-3	1-17
Y	US 2002/151544 A1 (HAYAKAWA ET. AL.) 17 October 2002 (2002-10-17) page 1, paragraph 2 - paragraph 8; claims; examples	1-17

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

☒ See patent family annex.

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search
28 October 2010

Date of mailing of the international search report
09/11/2010

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

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Helps, Ian

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/051370

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/127183 A1 (GENETECH INC.) 8 November 2007 (2007-11-08) page 1, paragraph 6 - page 3, paragraph 18; claims; examples 113-120,154, 246 -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2010/051370

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