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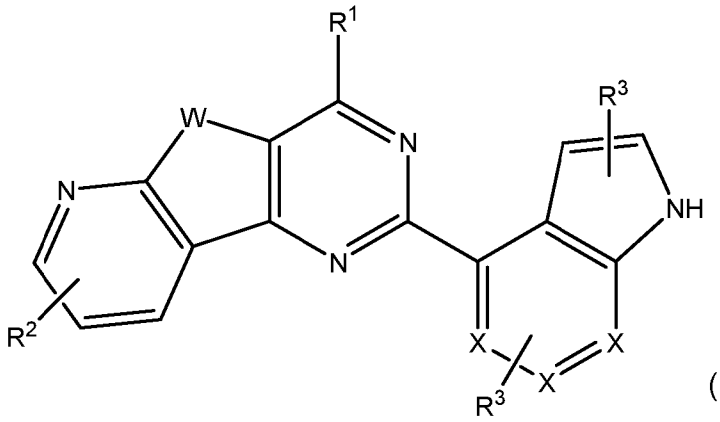
(54) **Title**: TRICYCLIC HETEROCYCLIC COMPOUNDS AS PHOSPHOINOSITIDE 3-KINASE INHIBITORS



(I)

(57) **Abstract**: 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 LY; each L is a direct bond, C_1 -C_{10} alkylene, C_2 -C_{10} alkenylene or C_2 -C_{10} alkynylene; Y is an optionally substituted fused, bridged or spirocyclic non-aromatic 5-12 membered heterocycle containing up to 4 heteroatoms selected from N or O; and each R^3 is independently H, C_1-C_{10} alkyl, halogen, fluoro C_1 -C_{10} alkyl, O- C_1 -C_{10} alkyl, NH-C_1 -C_{10} alkyl, S-C_1 -C_{10} alkyl, O- fluoro C_1 -C_{10} alkyl, NH-acyl, NH-C(O)-NH-C_1 -C_{10} alkyl, C(O)-NH-C_1 -C_{10} alkyl, aryl or heteroaryl, are useful as inhibitors of the class IA phosphoinositide 3- kinase enzyme, PI3K-p110δ, and therefore have potential utility in the therapy of cancer, immune and inflammatory diseases.

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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.

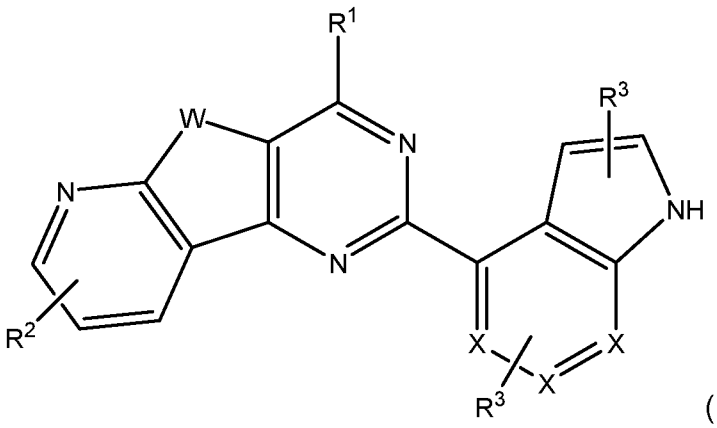
Compounds which are able to modulate p110δ activity have important therapeutic potential in cancer and immune and inflammatory disorders.

WO 2011/021038 describes compounds which act as inhibitors of PI3K-p110δ.

Summary of the Invention

The present invention relates to a selection of compounds having increased activity and/or bioavailability over the compounds described in WO 2011/021038. Without wishing to be bound by theory, this is believed to be owing to the provision of a bridged or spirocyclic non-aromatic group in the R^2 position.

Therefore, 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 selected independently for each occurrence from CH, CR^3, 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 L-Y;

each L is selected from the group consisting of a direct bond, C_1-C_{10} alkylene, C_2-C_{10} alkenylene and C_2-C_{10} alkynylene;

Y is an optionally substituted fused, bridged or spirocyclic non-aromatic heterocycle containing up to 4 heteroatoms (for example, one, two, three or four heteroatoms) each independently selected from N or O, and comprising 5 to 12 carbon or heteroatoms in total; and

each R^3 is independently H, C_1-C_{10} alkyl, halogen, fluoro C_1-C_{10} alkyl, O-C_1-C_{10} alkyl, -NH-C_1-C_{10} alkyl, S-C_1-C_{10} alkyl, O-fluoro C_1-C_{10} alkyl, NH-acyl, NH-C(O)-NH-C_1-C_{10} alkyl, C(O)-NH-C_1-C_{10} alkyl, aryl or heteroaryl.

Description of the Preferred Embodiments

Definitions

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, "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. They may also be substituted with halogen (e.g. F, Cl), NH_2, NO_2 or hydroxyl. Preferably, they may be substituted with up to 10 halogen atoms or more preferably up to 5 halogens. For example, they may be substituted by 1, 2, 3, 4 or 5 halogen atoms. Preferably, the halogen is fluorine. For example, they may be substituted with CF_3, CHF_2, CH_2CF_3, CH_2CHF_2 or CF_2CF_3.

As used herein, the term "fluoro C_1-C_{10} alkyl" means a C_1-C_{10} alkyl substituted with one or more fluorine atoms. Preferably, one, two, three, four or five fluorine atoms. Examples of "fluoro C_1-C_{10} alkyl" are CF_3, CHF_2, CH_2F, CH_2CF_3, CH_2CHF_2 or CF_2CF_3.

As used herein, "aryl" means a monocyclic, bicyclic, or tricyclic monovalent or divalent (as appropriate) 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 or divalent (as appropriate) aromatic radical containing up to four heteroatoms selected from oxygen, nitrogen and sulfur, such as thiazolyl, isothiazolyl, tetrazolyl, imidazolyl, oxazolyl, isoxazolyl, thienyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, triazolyl, thiadiazolyl, oxadiazolyl, 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 alkylsulfonyl, aminosulfonyl, mono C_1-C_3 alkyl aminosulfonyl and bis C_1-C_3-alkyl aminosulfonyl.

As used herein, the term "heterocycle" or "heterocycloalkyl" is a mono- or di-valent carbocyclic radical containing up to 4 heteroatoms selected from oxygen, nitrogen and sulfur. Preferably, it contains one or two heteroatoms. Preferably, at least one of the heteroatoms is nitrogen. It may be monocyclic or bicyclic. It is preferably saturated. Examples of heterocycles are piperidine, piperazine, thiomorpholine, morpholine, azetidine or oxetane. More preferably, the heterocycle is morpholine.

The heterocyclic ring may be mono- or di-unsaturated. 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, carboxy, C_1-C_3-haloalkyl (e.g. CF_3), 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.

In summary, each of the groups defined above, i.e., alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, heterocycloalkyl, may be 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, acyl, halo (e.g. fluoro), 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.

It should be noted that –NH-C_1-C_{10} alkyl, NH-acyl, NH-C(O)-NH-C_1-C_{10} alkyl and C(O)-NH-C_1-C_{10} alkyl can also be written as –N-C_1-C_{10} alkyl, N-acyl, N-C(O)-N-C_1-C_{10} alkyl and C(O)-N-C_1-C_{10} alkyl.

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.

As used herein, the term “fused” is intended to take its usual meaning within the art of organic chemistry. Fused systems, for example fused bicyclic systems, are those in which two rings share two and only two atoms.

As used herein, the term “bridged” is intended to take its usual meaning within the art of organic chemistry. Bridged compounds are compounds which contain interlocking rings. According to the invention, the atoms of the bridged non-aromatic group which form the bridgehead is either a tertiary carbon atom (when the remaining atom is hydrogen) or a quaternary carbon atom (when the remaining atom is not hydrogen). The bridge can be considered to be a chain of atoms (for example, alkyl) or a single atom (for example, O, S, N, C) connecting two bridgeheads.

As used herein, the term “spirocyclic” is intended to take its usual meaning within the art of organic chemistry. For example, a spirocyclic compound is a bicycle whose rings are attached though just one atom (known as a spiroatom). The rings may be different in size, or they may be the same size. Preferably, according to the invention, the two rings which are joined via the

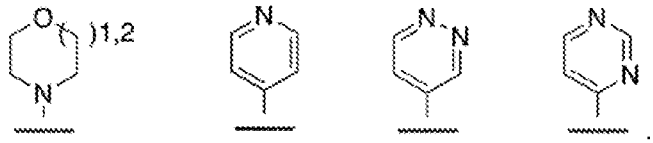
same atom are non-aromatic heterocycles, preferably heterocycloalkyls. For example, the spirocyclic non-aromatic group of Formula I may be a bicycle wherein both rings are heterocycloalkyl and are attached through the same atom, preferably a carbon atom.

Compounds with which the invention is concerned which may exist in one or more stereoisomeric form, because of the presence of asymmetric atoms or rotational restrictions, can exist as a number of stereoisomers with R or S stereochemistry at each chiral centre or as atropisomeres with R or S stereochemistry at each chiral axis. The invention includes all such enantiomers and diastereoisomers and mixtures thereof.

Preferred groups of the invention

Preferably, a compound of the invention is as defined in claim 1, but may additionally be a compound where at least one R^3 is NH_2.

Preferably, R^1 is represented by any of the following structures:



Most preferably, R^1 is morpholine.

In a preferred embodiment of the invention, W is oxygen or sulphur, preferably oxygen.

Preferably X is CH.

Preferably R^3 is H, C_1-C_{10} alkyl, halogen or fluoro C_1-C_{10} alkyl. More preferably R^3 is H.

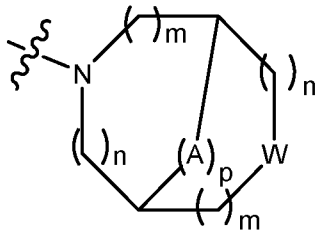
Preferably, the 6,5-ring system in Formula I is an indole. In other words, R^3 is hydrogen and X is CH.

R^2 may be attached to any suitable atom on the aryl group, as depicted in general formula I. However, it is preferred that R^2 is attached to the meta-position of the pyridine ring. For example, if the nitrogen atom of the pyridine is labelled as atom number 1, then R^2 is attached in the 3-position.

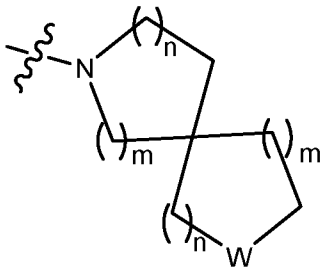
R^2 is LY. Preferably, L is C_1-C_{10} alkylene, preferably methylene.

Preferably, Y is a an optionally substituted bridged or spirocyclic heterocycloalkyl group containing up to 4 heteroatoms selected from N or O, and comprising 5 to 12 atoms in total.

Preferably, Y contains one or two heteroatoms, preferably two heteroatoms. More preferably, at least one of the heteroatoms is nitrogen and Y is bonded to L through the nitrogen atom, as depicted in the preferable Y groups below:



or



wherein:

A is selected from the group consisting of O, S, NR^4, optionally substituted C_1-C_3 alkylene, C_2-C_3 alkenylene and C_2-C_3 alkynylene;

W is selected from the group consisting of NR^4, O and CH_2;

wherein R^4 is selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl and C_1-C_3 halofluoroalkyl;

p is selected from 0, 1 or 2;

each m is independently selected from 0, 1 or 2; and

each n is independently selected from 1, 2 or 3.

Preferably, A is O or C_1-C_3 alkylene, most preferably methylene.

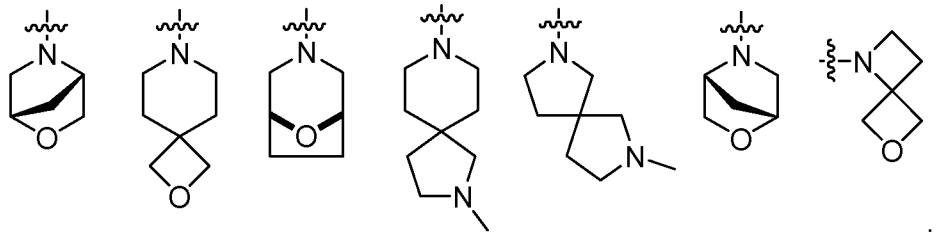
Preferably, W is O or CH_2, most preferably O.

When R^4 is present, it is preferably H, C_1-C_3 alkyl or C_1-C_3 halofluoroalkyl. More preferably, R^4 is H.

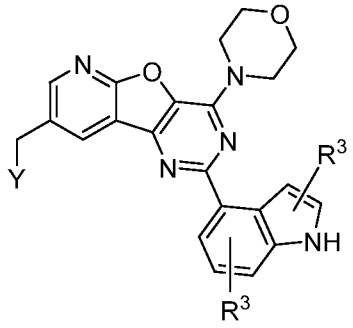
Preferably, each m and n is selected so as to form 5-, 6- or 7-membered nitrogen containing heterocycloalkyl groups. Preferably, p is 1. In particular, when A is O, S or NR^4, p is 1.

Y is preferably bicyclic, more preferably bridged bicyclic or spirocyclic bicyclic.

Even more preferably, Y is selected from one of the following groups:

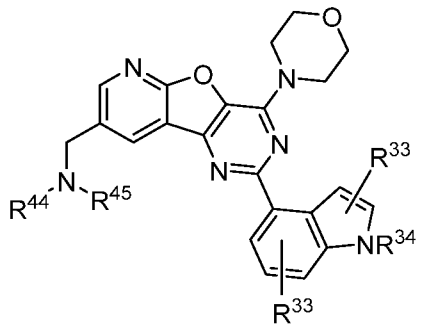


In certain embodiments, provided herein are compounds represented by:



, where Y and R^3 are defined above.

In another embodiment, provided herein are compounds represented by:



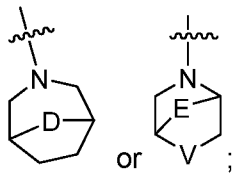
and pharmaceutically acceptable salts thereof, wherein:

R_{33} is independently selected for each occurrence from the group consisting of H, halogen, NH-C_{1-3}alkyl, NH_2, C_{1-6}alkyl and –O-C_{1-6}alkyl (wherein C_{1-6}alkyl for each occurrence is optionally substituted by one, two or three substituents selected from halogen and hydroxyl);

R^{34} is selected from H or C_{1-3}alkyl;

R^{44} and R^{45}, when taken together with the nitrogen to which they are attached form a 7 -10 membered bicyclic spirocycle or bridged heterocycle each having an additional heteroatom selected from O, S, or NR^{55}, wherein R^{55} is H or C_{1-3}alkyl.

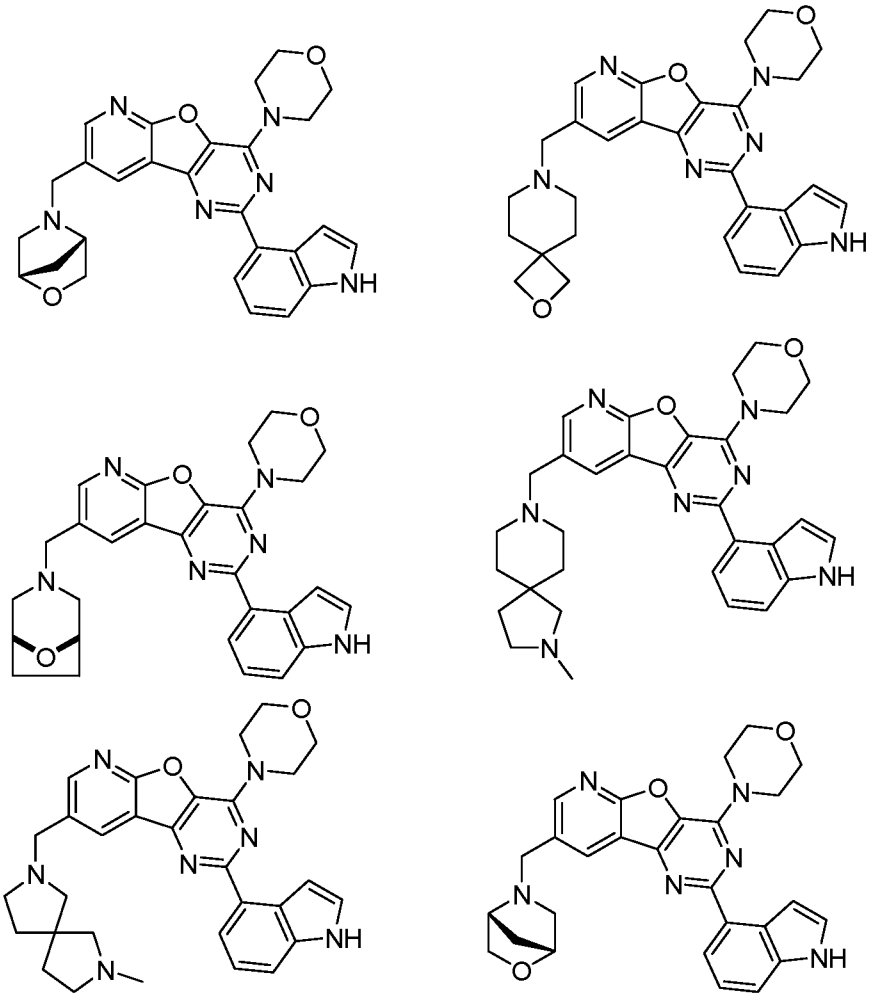
For example, R^{44} and R^{45}, when taken together with the nitrogen to which they are attached may form a 7 -8 membered bicyclic bridged heterocycle represented by:

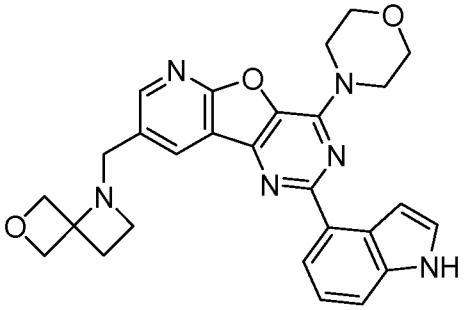


wherein D is O, S or NR^{55},; E is O or $(CH_2)_r$, wherein r is 1 or 2, and V is O or NR^{55}, wherein R^{55} is H or C_{1-3}alkyl.

In another exemplary embodiment, R^{44} and R^{45}, when taken together with the nitrogen to which they are attached form a 7 -10 membered spirocycle having one additional heteroatom selected from O or NR^{55}, wherein R^{55} is H or C_{1-3}alkyl. Alternatively, R^{44} and R^{45}, taken together with the nitrogen to which they are attached may be a Y substituent as described above.

Examples of structures embodying the invention are:





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. For example, contemplated herein is a pharmaceutically acceptable composition comprising a disclosed compound and a pharmaceutically acceptable excipient.

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. In some embodiments, disclosed compounds may have significantly higher oral bioavailability as compared to compounds having a non-spirocycle or non-bridged heterocyclic moiety, e.g., at R^2 above. .

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 in a human patient. 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.

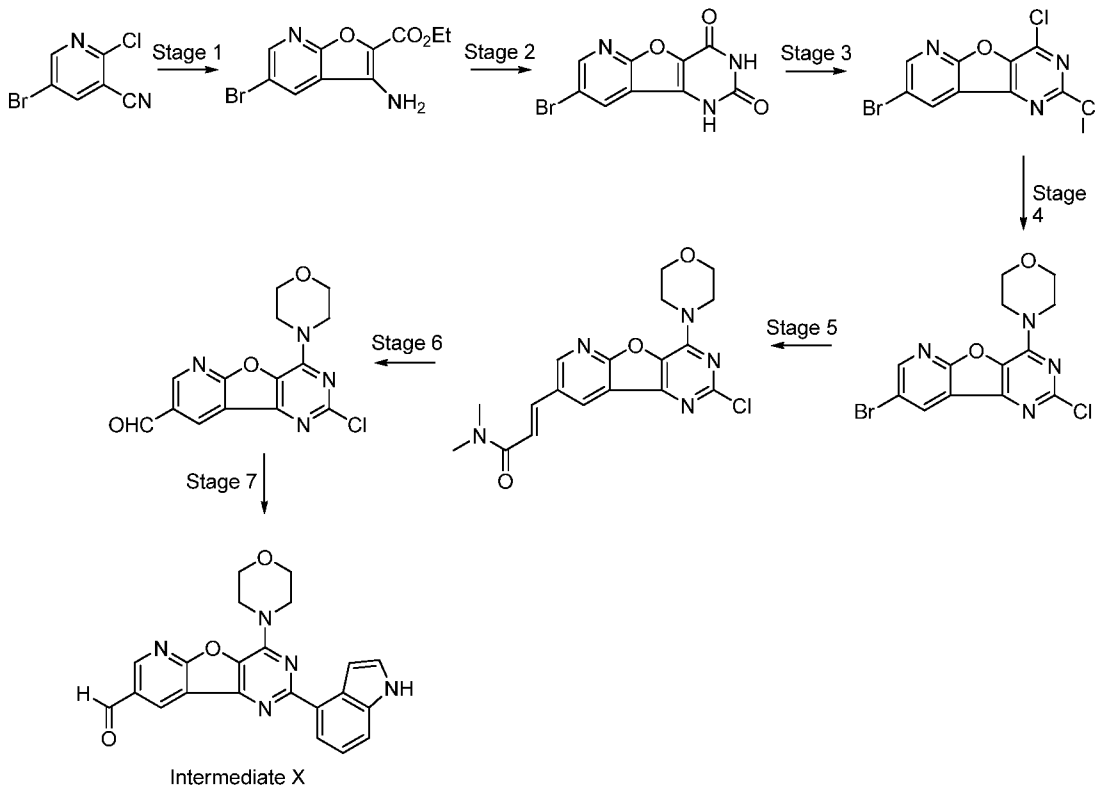
Preferably, the condition is cancer, notably leukaemias including chronic myelogenous leukaemia and acute myeloid leukaemia, lymphomas, solid tumours, and PTEN-negative tumours including PTEN-negative haematological, breast, lung, endometrial, skin, brain and prostate cancers (where PTEN refers to "phosphatise and tensin homolog deleted on chromosome 10"). More preferably, the condition to be treated in a patient in need theref by administering an effective amount of a disclosedcompound is a disorder selected from 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. For example, provided herein is a method of treating a patient suffering

a disorder selected from the group consisting leukaemias (including e.g., chronic myelogenous leukaemia and acute myeloid leukaemia), lymphoma, a solid tumour cancer such as breast, lung, or prostate cancer, PTEN-negative tumours including PTEN-negative haematological, breast, lung, endometrial, skin, brain and prostate cancers (where PTEN refers to "phosphatise and tensin homolog deleted on chromosome 10") comprising administering an effective amount of a disclosed compound.

The invention will now be illustrated by the following Examples.

EXAMPLES

Synthesis of Intermediate X (a precursor to the compounds of Formula I)



Intermediate X

Reagents and conditions: 1) K_2CO_3, ethyl glycolate, DMF, 115°C; 2) (i) chlorosulfonyl isocyanate, CH_2Cl_2, 0-10°C then rt (ii) water, 75°C (iii) NaOH max temp 40°C; 3) $POCl_3$, N,N-dimethylaniline, 107°C; 4) morpholine, MeOH, rt; 5) N,N,-dimethylacrylamide, $PdCl_2(PPh_3)_2$, NaOAc, DMF, 110°C; 6) $NaIO_4$, OsO_4,

THF, water, rt; 7) indole-4-boronic acid pinacol ester, $PdCl_2(PPh_3)_2$, sodium carbonate, dioxane, water, 102°C.

i. Ethyl-3-amino-5-bromofuro[2,3-b]pyridine-2-carboxylate

To a 10L flask under N_2(g) was added 5-bromo-2-chloropyridine-3-carbonitrile (435g, 2.0mol, 1eq), DMF (2790mL) and potassium carbonate (553g, 4.0mol, 2eq). This was followed by the addition of ethyl glycolate (208.2mL, 2.2mol, 1.1eq). The reaction mixture was heated to 115°C overnight. Upon completion, the reaction mixture was cooled to rt and water (13.1L) was added, this led to the formation of a precipitate. The mixture was stirred for 20mins, then filtered. The resulting brown solid was dried at 50°C, slurried in Et_2O:heptane (9:1, 2.8L) and filtered to give 405.6g. Further purification via soxhlet extraction using TBME (4.5L) yielded the product as a yellow solid (186g, 34%). This procedure was repeated twice.

^{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. 12-Bromo-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),10,12-tetraene-4,6-dione

To ethyl-3-amino-5-bromofuro[2,3-b]pyridine-2-carboxylate (239.0g, 0.84mol, 1eq) dissolved in CH_2Cl_2 (5.5L) was added chlorosulfonyl isocyanate (87.6mL, 1.0mol, 1.2eq) dropwise at 0-10°C. The resulting reaction was stirred for 30min, stripped to dryness and the resulting solid ground to a fine powder. Water (5.5L) was added to the solid and the suspension was heated at 75°C for 1h. After cooling to rt, solid NaOH (335g, 8.4mol, 10eq) was added allowing the reaction to exotherm (maximum temperature 40°C). The reaction was cooled to 0-10°C and the pH adjusted to 5-6 using 5M HCl (~1L). The reaction was stirred for 30mins, then filtered. The solid was washed with water (2.3L) and pulled dry. Further drying in a vacuum oven at 40°C yielded the product as a brown solid (193g, 76%). This procedure was repeated twice.

^{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%, $[M+H]^+$).

iii. 12-Bromo-4,6-dichloro-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3,5,10,12-hexaene

To 12-bromo-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),10,12-tetraene-4,6-dione (387g, 1.27mol, 1eq) was added $POCl_3$ (6070mL) and *N,N*-dimethylaniline (348mL, 2.8mol, 2.2eq). The mixture was heated at 107°C for 10h. Once cooled to rt, solvent was removed *in vacuo* azeotroping with toluene (3 x 3.9L). The resulting residue was partitioned between CH_2Cl_2 (12.76L) and water (3.9L) and the phases separated. The organic phase was washed with water (2 x 3.9L). The combined aqueous was back-extracted with CH_2Cl_2 (7.7L) and the combined organics dried over $MgSO_4$, filtered and stripped to yield the product as brown solid (429g, ~quant.).

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

iv. 12-bromo-4-chloro-6-(morpholin-4-yl)-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3,5,10,12-hexaene

To 12-bromo-4,6-dichloro-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3,5,10,12-hexaene (419.3g, 1.32mol, 1eq) in MeOH (8588mL) was added Morpholine (259mL, 2.90mol, 2.2eq) at rt. After stirring for 2h, water (0.8L) was added. It was then cooled to 0-5°C and stirred for an additional 30mins. The resulting solid was filtered, washed with water (5.2L) and pulled dry. Further purification by silica gel column chromatography with CH_2Cl_2/EtOAc (1:0-9:1) yielded the desired product (419g, 84%).

^1H 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. (2E)-3-[4-Chloro-6-(morpholin-4-yl)-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3,5,10,12-hexaen-12-yl]-N,N-dimethylprop-2-enamide

To 12-bromo-4-chloro-6-(morpholin-4-yl)-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3,5,10,12-hexaene (60g, 0.15mol, 1eq) was added *N,N*-dimethylacrylamide (16.7mL, 0.15mol, 1eq), $PdCl_2(PPh_3)_2$ (3.4g,

4.5mmol, 0.03eq) and NaOAc (40g, 0.45mol, 3eq) in DMF (1.2L). The reaction was heated at 110°C for 7h. This process was repeated 3 times and batches combined. Once cooled down to rt, solvent was removed *in vacuo* and the resulting residue was partitioned between CH_2Cl_2 (6.5L) and water (5.5L). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 4L). The combined organics were washed with brine (2 x 4L), dried over $MgSO_4$, filtered and stripped. The resulting solid was slurried in EtOAc/heptane (1:1, 0.8L) for 30mins, filtered, washed and washed with EtOAc/heptane (1:1, 2 x 450mL). Further drying in a vacuum oven at 40°C yielded the desired product as an orange solid (203.0g, 86%).

^{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%, $[M+H]^+$).

vi. 4-Chloro-6-(morpholin-4-yl)-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3,5,10,12-hexaene-12-carbaldehyde

(2E)-3-[4-chloro-6-(morpholin-4-yl)-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3,5,10,12-hexaen-12-yl]-N,N-dimethylprop-2-enamide (124.0g, 0.39mol, 1eq) was dissolved in THF (12.4L) at 65°C. Once cooled to 35°C, water (4.1L), $NaIO_4$ (205.4g, 1.17mol, 3eq) and OsO_4 (2.5wt% in ^{t}BuOH, 80.3mL, 2%) were added. The reaction was stirred at rt for 60h. The reaction was cooled to 0-5°C, stirred for 30mins then filtered. The solid was washed with water (545mL) and pulled dry. The crude product was combined with two further batches (2 x 118.3g scale) and slurried in water (6.3L) for 30mins at rt. The solids were filtered, washed with water (1.6L) and pulled dry. Further drying in a vacuum oven yielded the desired product as a pink solid (260g, 88%)

^{1}H NMR (400MHz, $CDCl_3$:MeOD, 9:1) 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).

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

vii. 4-(1H-Indol-4-yl)-6-(morpholin-4-yl)-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2,4,6,10,12-hexaene-12-carbaldehyde

To 4-chloro-6-(morpholin-4-yl)-8-oxa-3,5,10-triazatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7),3,5,10,12-hexaene-12-carbaldehyde (164.4g, 0.52mol, 1eq) was added indole-4-boronic acid pinacol ester (376.0g, 1.55mol, 3eq), $PdCl_2(PPh_3)_2$ (72.0g, 0.10mol, 2eq) and sodium carbonate (110.2g, 1.04mol, 2eq) in dioxane (16.4L) / water (5.8L). Reaction mixture was refluxed for 1h. It was then cooled to 60-70°C. Water (9.8L), brine (4.9L) and EtOAc (9.5L) were added. The phases were separated and the aqueous phase extracted with EtOAc (3 x 9.5L) at 60-65°C. The combined organics were dried over $MgSO_4$, filtered and stripped. The resulting solid was slurried in CH_2Cl_2 (4.75L) for 30mins, filtered, washed with CH_2Cl_2 (3 x 238mL) and pulled dry. Further drying in a vacuum oven at 40°C yielded **Intermediate X** as a yellow solid (135.7g, 66%).

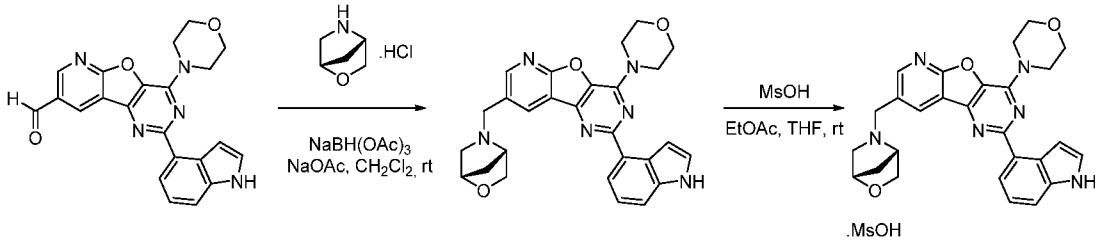
^{1}H NMR (300MHz, $CDCl_3$) δ_H: 11.27 (br. s, 1H), 10.26 (s, 1H), 9.16 (d, *J*=2.3Hz, 1H), 9.11 (d, *J*=2.3Hz, 1H), 8.18 (d, *J*=7.5Hz, 1H), 7.58-7.67 (m, 2H), 7.49 (t, *J*=2.8Hz, 1H), 7.23 (t, *J*=7.7Hz, 1H), 4.08-4.16 (m, 4H), 3.83-3.90 (m, 4H).

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

Synthesis of Examples of the present invention

Example A:

4-(1H-Indol-4-yl)-6-(morpholin-4-yl)-12-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-ylmethyl]-8-oxa-3,5,10-triazatricyclo[7.4.0.$0^{2,7}$]trideca-1(13),2(7),3,5,9,11-hexaene



A

To a suspension of intermediate **X** (7.00g, 17.53mmol, 1eq), (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (7.13g, 52.58mmol, 3eq) and NaOAc (4.31g, 52.58mmol, 3eq) in anhydrous CH_2Cl_2 (150mL) was added $NaBH(OAc)_3$ (7.43g, 35.06mmol, 2eq). The reaction mixture was stirred at rt overnight. Then,

it was partitioned with 1N NaOH (100mL) and extracted with CH_2Cl_2 (3 x 200mL). The combined organic extracts were washed with brine (50mL) then dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel column chromatography with EtOAc/MeOH (1:0-7:1) yielded the product **A** as a white solid (6.02g, 71%).

^{1}H NMR (300MHz, $CDCl_3$) δ_H: 8.65 (d, *J*=2.1 Hz, 1H), 8.58 (d, *J*=2.1 Hz, 1H), 8.37 (br. s., 1H), 8.24 (dd, *J*=7.5, 0.9 Hz, 1H), 7.62 (td, *J*=2.6, 0.8 Hz, 1H), 7.53 (d, *J*=8.1 Hz, 1H), 7.37-7.41 (m, 1H), 7.31-7.37 (m, 1H), 4.47 (s, 1H), 4.22-4.30 (m, 4H), 4.18 (d, *J*=8.1 Hz, 1H), 3.98 (d, *J*=2.3 Hz, 2H), 3.91-3.97 (m, 4H), 3.70 (dd, *J*=7.9, 1.7 Hz, 1H), 3.53 (s, 1H), 2.94 (dd, *J*=10.0, 1.5 Hz, 1H), 2.64 (d, *J*=10.2 Hz, 1H), 1.97 (dd, *J*=9.8, 1.9 Hz, 1H), 1.80 (dt, *J*=9.8, 1.1 Hz, 1H).

MS (ES^+) 483.1 (100%, $[M+H]^+$).

4-(1H-Indol-4-yl)-6-(morpholin-4-yl)-12-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-ylmethyl]-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),3,5,9,11-hexaene; methanesulfonic acid

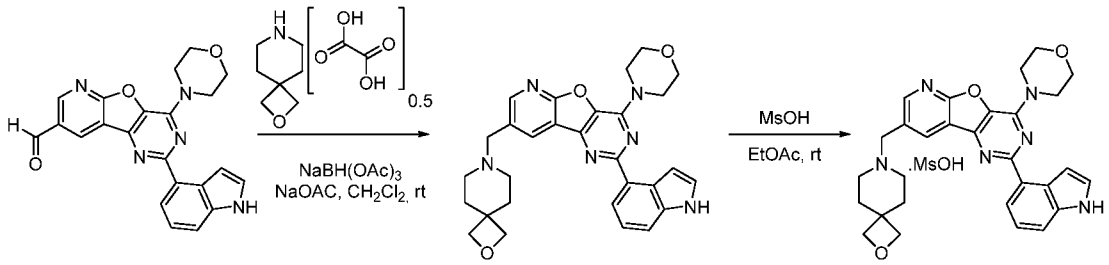
A (5.98g, 12.38mmol, 1eq) was dissolved in hot EtOAc (1L) and THF (200mL). Once cooled down to rt, a solution of MsOH (884µL, 13.6mmol, 1.1eq) in EtOAc (5mL) was added slowly. An instant yellow precipitate formed. The suspension was shaken vigorously for 10s then left to stand at rt overnight. As solid settled, excess supernatant was decanted off (200mL), then EtOAc was added (200mL). The suspension was shaken again and left to stand for 1h. This operation was repeated twice, then the solvent was removed *in vacuo*. The salt form of **A** was obtained as a yellow solid (6.50g, 91%).

^{1}H NMR (300MHz, DMSO-d_6) δ_H: 11.33 (br. s., 1H), 9.69-10.24 (m, 1H), 9.05 (d, *J*=2.1 Hz, 1H), 8.79-8.93 (m, 1H), 8.19 (d, *J*=7.5 Hz, 1H), 7.54-7.62 (m, 2H), 7.50 (t, *J*=2.7 Hz, 1H), 7.24 (t, *J*=7.7 Hz, 1H), 4.64-4.89 (m, 2H), 4.47-4.61 (m, 2H), 4.14 (m, 4H), 3.94-4.00 (m, 2H), 3.83-3.91 (m, 4H), 3.72-3.83 (m, 1H), 3.29-3.46 (m, 2H), 2.33 (s, 4H), 2.02-2.15 (m, 1H).

MS (ES^+) 483.1 (100%, $[M-MsOH+H]^+$).

Example B:

4-(1H-Indol-4-yl)-6-(morpholin-4-yl)-12-{2-oxa-7-azaspiro[3.5]nonan-7-ylmethyl}-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),3,5,9,11-hexaene



B

To a suspension of intermediate **X** (3.108g, 7.78mmol 1eq), 2-oxa-7-azaspiro[3.5]nonane hemioxalate (4.02g, 23.3mmol, 3eq) and NaOAc (1.91g, 23.3mmol, 3eq) in anhydrous CH_2Cl_2 (280mL) was added $NaBH(OAc)_3$ (3.30g, 15.6mmol, 2eq). The reaction mixture was stirred at rt overnight. Then, it was partitioned with 1N NaOH (150mL) and extracted with CH_2Cl_2 (2 x 100mL). The combined organic extracts were washed with 50% brine (100mL) then dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel column chromatography with EtOAc/MeOH (1:0-8:1) yielded the product **B** as an off-white solid (3.154g, 79%).

^1H NMR (300MHz, $CDCl_3$) δ_H: 8.59 (d, *J*=2.1 Hz, 1H), 8.53 (d, *J*=1.9 Hz, 1H), 8.41 (br. s., 1H), 8.24 (dd, *J*=7.4, 0.8 Hz, 1H), 7.61 (t, *J*=2.3 Hz, 1H), 7.53 (d, *J*=8.1 Hz, 1H), 7.37-7.41 (m, 1H), 7.34 (t, *J*=7.9 Hz, 1H), 4.43 (s, 4H), 4.22-4.30 (m, 4H), 3.86-4.00 (m, 4H), 3.68 (s, 2H), 2.23-2.59 (m, 4H), 1.83-2.00 (m, 4H).
MS (ES^+) 511.1 (100%, $[M+H]^+$).

4-(1H-Indol-4-yl)-6-(morpholin-4-yl)-12-{2-oxa-7-azaspiro[3.5]nonan-7-ylmethyl}-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),3,5,9,11-hexaene; methanesulfonic acid

To a solution of **B** (2.987g, 5.854mmol, 1eq) in EtOAc (1.2L, heat to 70°C for 5 min to dissolve) at rt was added a solution of MsOH (590 μL, 6.14mmol, 1.05eq) in EtOAc (16mL). A yellow precipitate formed instantly. The suspension was shaken vigorously for 20s then left to stand at rt overnight. The excess supernatant was decanted off (600mL), then EtOAc was added (500mL). The suspension was shaken again and left to stand for 1h before another 500mL of

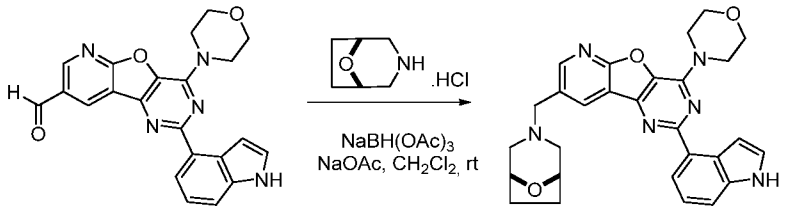
excess supernatant was decanted off. The solvent was removed *in vacuo* to give the salt form of **F** as a yellow solid (3.230g, 91%).

^{1}H NMR (300MHz, DMSO-d_6) δ_H: 11.33 (br. s., 1H), 9.45 (br. s., 1H), 8.90 (d, *J*=1.9 Hz, 1H), 8.72 (d, *J*=1.9 Hz, 1H), 8.19 (d, *J*=7.3 Hz, 1H), 7.41-7.69 (m, 3H), 7.23 (t, *J*=7.8 Hz, 1H), 4.58 (d, *J*=3.8 Hz, 2H), 4.39 (s, 2H), 4.29 (s, 2H), 4.03-4.22 (m, 4H), 3.81-3.97 (m, 4H), 3.40 (d, *J*=12.1 Hz, 2H), 2.88-3.13 (m, 2H), 2.33 (s, 3H), 2.26 (d, *J*=13.9 Hz, 2H), 1.69-1.91 (m, 2H).

MS (ES$^+$) 511.1 (100%, [M-MsOH+H]$^+$).

Example C:

4-(1H-Indol-4-yl)-6-(morpholin-4-yl)-12-{8-oxa-3-azabicyclo[3.2.1]octan-3-ylmethyl}-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),3,5,9,11-hexaene



C

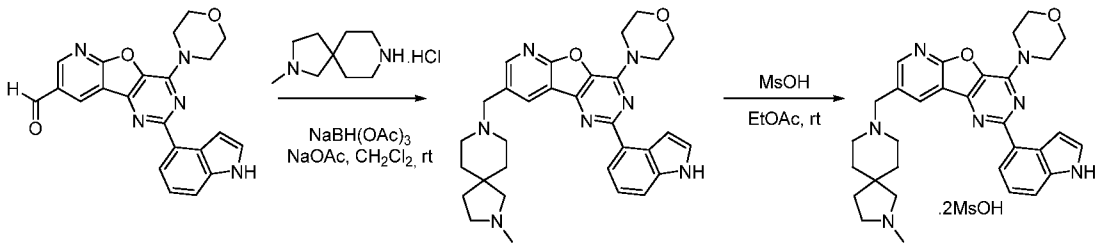
To a suspension of intermediate **X** (100mg, 0.25mmol, 1eq), 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (112mg, 0.75mmol, 3eq) and NaOAc (62mg, 0.75mmol, 3eq) in anhydrous CH_2Cl_2 (10mL) was added $NaBH(OAc)_3$ (106mg, 0.50mmol, 2eq). The reaction mixture was stirred at rt overnight. Then, it was partitioned with 1N NaOH (10mL), extracted with CH_2Cl_2 (3 x 10mL). The combined organic extracts were washed with brine (10mL) then dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel column chromatography with EtOAc/MeOH (1:0-49:1) yielded the product **C** as an off white solid (116mg, 93%).

^{1}H NMR (300MHz, $CDCl_3$) δ_H: 8.56 (d, *J*=3.6 Hz, 2H), 8.35 (br. s., 1H), 8.24 (d, *J*=7.5 Hz, 1H), 7.58-7.66 (m, 1H), 7.51-7.57 (m, 1H), 7.31-7.44 (m, 2H), 4.30-4.38 (m, 2H), 4.23-4.30 (m, 4H), 3.89-4.01 (m, 4H), 3.68 (s, 2H), 2.61 (d, *J*=10.7 Hz, 2H), 2.40-2.52 (m, 2H), 1.96-2.09 (m, 2H), 1.83-1.95 (m, 2H).

MS (ES^+) 497.1 (100%, $[M+H]^+$).

Example D:

4-(1H-Indol-4-yl)-12-({2-methyl-2,8-diazaspiro[4.5]decan-8-yl}methyl)-6-(morpholin-4-yl)-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),3,5,9,11-hexaene



D

To a suspension of intermediate **X** (1.02g, 2.55mmol, 1eq), 2-methyl-2,8-diazaspiro[4.5]decane hydrochloride (1.46g, 7.66mmol, 3eq) and NaOAc (628mg, 7.66mmol, 3eq) in anhydrous CH_2Cl_2 (100mL) was added $NaBH(OAc)_3$ (1.08g, 5.1mmol, 2eq). The reaction mixture was stirred at rt overnight. Then, it was partitioned with 1N NaOH (30mL) and extracted with CH_2Cl_2 (3 x 50mL). The combined organic extracts were washed with brine (10mL) then dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel column chromatography with CH_2Cl_2/MeOH (0:1-4:1) yielded the product **D** as a white solid (890mg, 65%).

^1H NMR (300MHz, $CDCl_3$) δ_H: 8.60 (d, *J*=2.1 Hz, 1H), 8.54 (d, *J*=2.1 Hz, 1H), 8.39 (br. s., 1H), 8.24 (dd, *J*=7.4, 0.8 Hz, 1H), 7.62 (t, *J*=2.3 Hz, 1H), 7.53 (d, *J*=8.1 Hz, 1H), 7.38 (t, *J*=2.8 Hz, 1H), 7.30-7.37 (m, 1H), 4.21-4.31 (m, 4H), 3.89-3.99 (m, 4H), 3.69 (s, 2H), 2.59 (t, *J*=6.8 Hz, 2H), 2.38-2.50 (m, 5H), 2.35 (s, 3H), 1.54-1.73 (m, 7H).

MS (ES^+) 538.2 (100%, $[M+H]^+$).

4-(1H-Indol-4-yl)-12-({2-methyl-2,8-diazaspiro[4.5]decan-8-yl}methyl)-6-(morpholin-4-yl)-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),3,5,9,11-hexaene; bis(methanesulfonic acid)

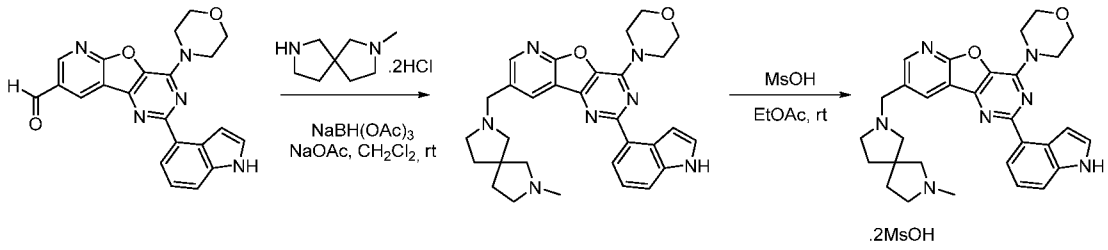
Compound **D** (821mg, 1.52mmol, 1eq) was dissolved in hot EtOAc (400mL). Once cooled down to rt, a solution of MsOH (218μL, 3.36mmol, 2.2eq) in EtOAc (5mL) was added slowly. An instant yellow precipitate formed. The suspension was shaken vigorously for 10s then left to stand at rt overnight. As solid settled, excess supernatant was decanted off (200mL), then EtOAc was added (200mL). The suspension was shaken again and left to stand for 1h. This operation was repeated twice, then the solvent was removed *in vacuo*. The salt form of **D** was obtained as a yellow solid (1.037g, 93%).

^{1}H NMR (300MHz, DMSO-d_6) δ_H: 11.32 (br. s., 1H), 9.46-10.03 (m, 2H), 8.93 (d, *J*=2.1 Hz, 1H), 8.76 (d, *J*=1.7 Hz, 1H), 8.19 (dd, *J*=7.4, 0.7 Hz, 1H), 7.53-7.60 (m, 2H), 7.50 (t, *J*=2.6 Hz, 1H), 7.24 (t, *J*=7.8 Hz, 1H), 4.63 (br. s., 2H), 4.10-4.20 (m, 4H), 3.82-3.91 (m, 5H), 3.54-3.77 (m, 2H), 3.36-3.51 (m, 2H), 3.05-3.25 (m, 3H), 2.89-3.03 (m, 1H), 2.80-2.89 (m, 3H), 2.36 (s, 6H), 2.02-2.17 (m, 1H), 1.65-1.95 (m, 4H).

MS (ES$^+$) 538.2 (100%, [M-2MsOH+H]$^+$).

Example E:

4-(1H-Indol-4-yl)-12-({7-methyl-2,7-diazaspiro[4.4]nonan-2-yl}methyl)-6-(morpholin-4-yl)-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),3,5,9,11-hexaene



E

To a suspension of intermediate **X** (250mg, 0.63mmol, 1eq), 2-methyl-2,7-diazaspiro[4,4]nonane dihydrochloride (400mg, 1.87mmol, 3eq) and NaOAc (305mg, 3.70mmol, 6eq) in anhydrous CH_2Cl_2 (20mL) was added $NaBH(OAc)_3$ (265mg, 1.25mmol, 2eq). The reaction mixture was stirred at rt overnight. Then, it was partitioned with 1N NaOH (10mL), extracted with CH_2Cl_2 (3 x 10mL) and EtOAc (10mL). The combined organic extracts were washed with brine (10mL)

then dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel column chromatography with CH_2Cl_2/MeOH (0:1-4:1) yielded the product **E** as a white solid (169mg, 52%).

^{1}H NMR (300MHz, $CDCl_3$) δ_H: 8.58 (d, *J*=2.1 Hz, 1H), 8.53 (d, *J*=2.1 Hz, 1H), 8.48 (br. s., 1H), 8.23 (dd, *J*=7.4, 0.8 Hz, 1H), 7.63 (t, *J*=2.2 Hz, 1H), 7.53 (d, *J*=7.9 Hz, 1H), 7.39 (t, *J*=2.7 Hz, 1H), 7.29-7.36 (m, 1H), 4.21-4.30 (m, 4H), 3.89-3.99 (m, 4H), 3.72-3.85 (m, 2H), 2.49-2.83 (m, 8H), 2.45 (s, 3H), 1.81-2.06 (m, 4H).

MS (ES^+) 524.1 (100%, $[M+H]^+$).

4-(1H-Indol-4-yl)-12-({7-methyl-2,7-diazaspiro[4.4]nonan-2-yl}methyl)-6-(morpholin-4-yl)-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),3,5,9,11-hexaene; bis(methanesulfonic acid)

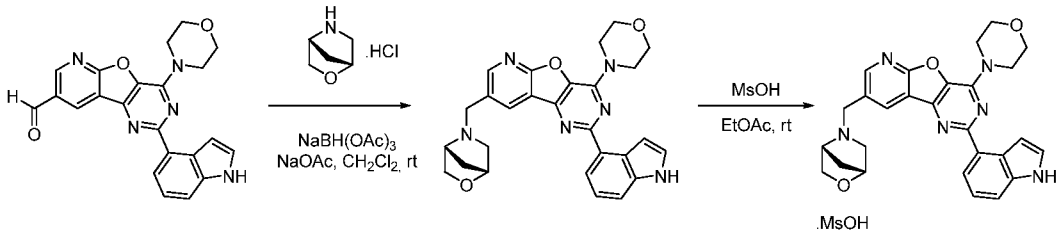
Compound **E** (129mg, 0.25mmol, 1eq) was dissolved in hot EtOAc (50mL). Once cooled down to rt, a solution of MsOH (35μL, 0.54mmol, 2.2eq) in EtOAc (2mL) was added slowly. An instant yellow precipitate formed. The suspension was shaken vigorously for 10s then left to stand at rt overnight. As solid settled, excess supernatant was decanted off (20mL), then EtOAc was added (20mL). The suspension was shaken again and left to stand for 1h. This operation was repeated twice, then the solvent was removed *in vacuo*. The salt form of **E** was obtained as a yellow solid (173mg, 98%).

^{1}H NMR (300MHz, DMSO-d_6) δ_H: 11.33 (br. s., 1H), 10.39 (br. s., 1H), 9.72-10.12 (m, 1H), 8.73-9.09 (m, 2H), 8.19 (d, *J*=7.5 Hz, 1H), 7.41-7.63 (m, 3H), 7.24 (t, *J*=7.8 Hz, 1H), 4.53-4.87 (m, 2H), 4.10-4.22 (m, 4H), 3.79-3.93 (m, 4H), 3.32-3.77 (m, 6H), 2.99-3.29 (m, 2H), 2.78-2.89 (m, 3H), 2.36 (s, 6H), 1.87-2.22 (m, 3H).

MS (ES^+) 524.5 (100%, $[M-2MsOH+H]^+$).

Example F:

4-(1H-Indol-4-yl)-6-(morpholin-4-yl)-12-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-ylmethyl]-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),3,5,9,11-hexaene



F

To a suspension of intermediate **X** (200mg, 0.50mmol, 1eq), (1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (204mg, 1.50mmol, 3eq) and NaOAc (123mg, 1.5mmol, 3eq) in anhydrous CH_2Cl_2 (10mL) was added $NaBH(OAc)_3$ (160mg, 0.76mmol, 2eq). The reaction mixture was stirred at rt overnight. Then, it was partitioned with 1N NaOH (20mL) and extracted with CH_2Cl_2 (3 x 20mL). The combined organic extracts were passed through a phase separator and the solvent was removed *in vacuo*. Purification by silica gel column chromatography with EtOAc/MeOH (1:0-9:1) yielded the product **F** as a white solid (141.1mg, 59%).

^1H NMR (400MHz, $CDCl_3$) δ_H: 8.64 (d, *J*=2.1 Hz, 1H), 8.57 (d, *J*=2.1 Hz, 1H), 8.35 (br. s., 1H), 8.23 (dd, *J*=7.5, 0.9 Hz, 1H), 7.62 (m, 1H), 7.53 (d, *J*=8.1 Hz, 1H), 7.36-7.39 (m, 1H), 7.31-7.36 (m, 1H), 4.46 (s, 1H), 4.25 (m, 4H), 4.18 (d, *J*=8.1 Hz, 1H), 3.97 (d, *J*=2.3 Hz, 2H), 3.93-3.97 (m, 4H), 3.68 (dd, *J*=7.9, 1.7 Hz, 1H), 3.53 (s, 1H), 2.93 (dd, *J*=10.0, 1.5 Hz, 1H), 2.62 (d, *J*=10.2 Hz, 1H), 1.95 (dd, *J*=9.8, 1.9 Hz, 1H), 1.79 (dt, *J*=9.8, 1.1 Hz, 1H).

MS (ES^+) 483.1 (100%, $[M+H]^+$).

4-(1H-Indol-4-yl)-6-(morpholin-4-yl)-12-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-ylmethyl]-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),3,5,9,11-hexaene; methanesulfonic acid

Compound **F** (141mg, 0.29mmol, 1eq) was dissolved in hot EtOAc (100mL) then treated with 0.87 ml of a 0.308M MsOH solution in EtOAc under vigorously swirling. The mixture was set aside overnight. The excess supernatant was decanted (using a small Pasteur pipette) and more EtOAc (50 ml) was added. The suspension was once again shaken vigorously then left to stand at rt overnight. The excess supernatant was once more decanted and the solvent

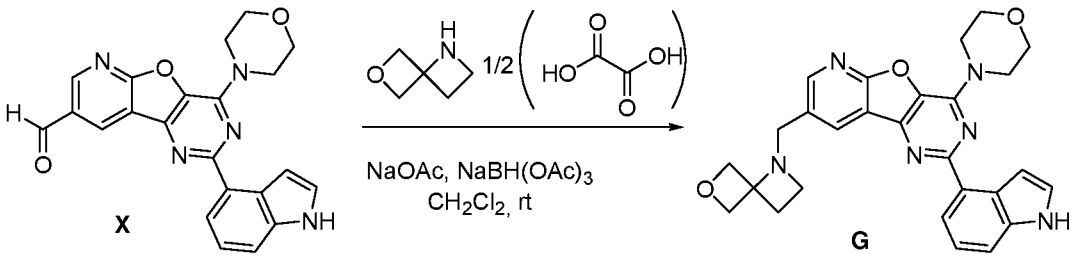
was removed *in vacuo*. The resulting solid was dried in a vacuum oven at 40°C. The salt form of **F** was obtained as a yellow solid (160mg, 95%).

^{1}H NMR (400MHz, DMSO-d_6) δ_H: 11.33 (br. s., 1H), 9.65-10.16 (m, 1H), 9.05 (d, *J*=2.0 Hz, 1H), 8.83-8.90 (m, 1H), 8.20 (d, *J*=7.3 Hz, 1H), 7.58-7.61 (m, 1H), 7.56 (d, *J*=7.8 Hz, 1H), 7.51 (t, *J*=2.8 Hz, 1H), 7.23 (t, *J*=7.7 Hz, 1H), 4.82 (dd, *J*=13.1, 4.5 Hz, 1H), 4.65-4.76 (m, 1H), 4.50-4.59 (m, 2H), 4.11-4.19 (m, 4H), 3.99 (d, *J*=9.6 Hz, 1H), 3.88 (t, *J*=4.5 Hz, 4H), 3.78 (dd, *J*=9.5, 1.4 Hz, 1H), 3.31-3.38 (m, 2H), 2.52-2.57 (m, 1H), 2.30 (s, 3H), 2.02-2.18 (m, 1H).

MS (ES$^+$) 483.2 (100%, [M-MsOH+H]$^+$).

Example G

4-(1H-indol-4-yl)-6-(morpholin-4-yl)-12-{6-oxa-1-azaspiro[3.3]heptan-1-ylmethyl}-8-oxa-3,5,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),3,5,9,11-hexaene



Intermediate **X** (125mg, 0.31mmol), 6-oxa-1-azaspiro[3.3]heptane hemioxalate (134mg, 0.93mmol, 3eq) and NaOAc (76mg, 0.93mmol, 3eq) were suspended in CH_2Cl_2 (16 mL) at rt. The mixture was stirred for 15mins then $NaBH(OAc)_3$ (131mg, 0.62mmol, 2eq) was added. The resulting suspension was stirred at rt overnight. The reaction mixture was then partitioned with 0.5 N NaOH (8 mL) and extracted with CH_2Cl_2 (2 x 10mL). The combined organics were washed with 50% brine (5mL) then dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was dissolved in DMSO (2 mL) and purified by basic preparative LCMS to yield **G** as a white solid (48mg, 32%).

^{1}H NMR (DMSO-d_6) δ_H: 11.30 (br s, 1H), 8.62 (s, 2H), 8.18 (d, J=7.6 Hz, 1H), 7.51-7.58 (m, 2H), 7.46-7.51 (m, 1H), 7.22 (t, J=7.7 Hz, 1H), 4.89 (d, J=7.6 Hz, 2H), 4.55 (d, J=7.3 Hz, 2H), 4.08-4.17 (m, 4H), 4.03 (s, 2H), 3.81-3.91 (m, 4H), 3.03 (t, J=6.7 Hz, 2H), 2.32 (t, J=6.7 Hz, 2H).

MS (ES^+) 483.3 (100%, $[M+H]^+$).

Biological Data

Fold form selectivity inhibition data against PI3K isoforms, as determined using a HTRF biochemical assay, is listed below.

Example	Fold IC_{50}			
	p110β/p110α	p110β/p110γ	p110δ/p110α	p110δ/p110γ
A	*	*	**	**
B	**	**	**	**
D	**	**	**	**
E	**	**	**	**

Key : * = ≥ 10x ≥ 50x; ** = ≥ 50x

Example	IC_{50} (nM) PI3K			
	p110α	p110β	p110δ	p110γ
G	*	*	*	**

Key: **** ≥ 10uM; *** ≤ 10uM ≥ 1uM; ** ≤ 1uM ≥ 500nM; * ≤ 500nM

Rodent Pharmacokinetic Comparative Data

Disclosed compounds have increased bioavailability and reduced clearance (data below for mice).

Example A

The following protocol was used to determine oral bioavailability and clearance, and the results are shown below:

- Species = male mouse;
- Strain = CD1;
- n = 3 male mice per time point per route;
- Terminal blood sampling at 8 time points (5min, 10min, 0.5hr, 1hr, 3hr, 6hr, 8hr and, 24hr);

- Collection of plasma, bio-analysis and report of AUC, AUMC, Vss, CL, half-life, MRT and bioavailability.

Formulation: 10% DMSO, 90% Saline

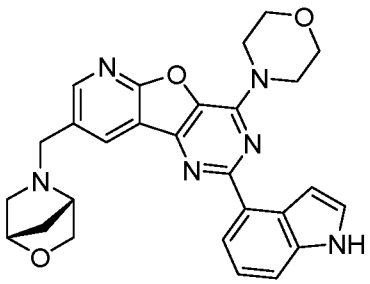
Dosing: 10mg/kg P.O. and 5mg/kg I.V.

Plasma PK Summary:

Parameters – IV, 5mg/kg	**Value – Mesylate Salt**
$t_{1/2}$ (hr)	1.3
T_{max} (hr)	0.08
C_{max} (ng/mL)	2640
AUC_{last} (hr*ng.mL)	3905
AUC_{all} (hr*ng/mL)	3905
AUC_{inf} (hr*ng/mL)	3946
Clearance (mL/hr/Kg)	1267
Vd (mL/Kg)	2441

Parameters – PO, 10mg/kg	**Value – Mesylate Salt**
$t_{1/2}$ (hr)	1.3
T_{max} (hr)	1.00
C_{max} (ng/mL)	1973
AUC_{last} (hr*ng/mL)	5625
AUC_{all} (hr*ng/mL)	5625
AUC_{inf} (hr* ng/mL)	5822
F	73.77%

Example A



Oral bioavailability (F) = 74%

Clearance = 21mL/min/kg

Example B

The following protocol was used to determine oral bioavailability and clearance, and the results are shown below:

- Species = male mouse;
- Strain = Balb/c;
- 18 male mice were divided into two groups Group 1 (3 mg/kg; I.V.), Group 2 (10 mg/kg; P.O.) with each group comprising of nine mice;
- Blood samples (approximately 60 µL) were collected from retro orbital plexus under light isoflurane anesthesia such that the samples were obtained at pre-dose, 0.08, 0.25, 0.5, 1, 2, 4, 8 and 24 hr (I.V.) and pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hr (P.O.);
- The blood samples were collected from a set of three mice at each time point in labeled micro centrifuge tube containing K2EDTA as anticoagulant;
- Plasma samples were separated by centrifugation of whole blood and stored below -70^{o}C until bioanalysis;
- All samples were processed for analysis by protein precipitation using acetonitrile (ACN) and analyzed with fit for purpose LC/MS/MS method (LLOQ: 2.02 ng/mL);
- Pharmacokinetic parameters were calculated using the non-compartmental analysis tool of Phoenix WinNonlin (Version 6.3).

Formulation:

Animals in Group 1 were administered intravenously with Example B solution formulation in 20% Propylene Glycol, 50% of PEG 400 and 30% of (20% HPβCD in water) via tail vein at a dose of 3 mg/kg.

Animals in Group 2 were administered with oral solution formulation of Example B in 20% Propylene Glycol, 50% of PEG 400 and 30% of (20% HPβCD in water) at a dose of 10 mg/kg;

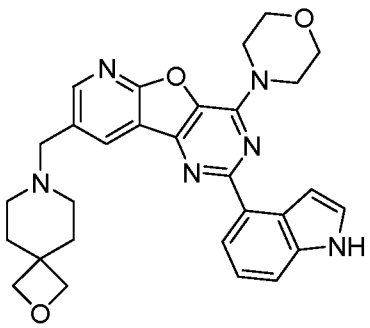
Dosing: 10mg/kg P.O. and 3mg/kg I.V.

Plasma PK Summary:

Parameters – IV, 3mg/kg	**Value – Mesylate Salt**
$t_{1/2}$ (hr)	1.23
C_{max} (ng/mL)	621.42
AUC_{last} (hr*ng.mL)	1512.20
AUC_{inf} (hr*ng/mL)	1512.20
Clearance (mL/hr/Kg)	1983.6
Vss (L/Kg)	5.51

Parameters – PO, 10mg/kg	**Value – Mesylate Salt**
T_{max} (hr)	1.00
C_{max} (ng/mL)	779.58
AUC_{last} (hr*ng/mL)	3725.56
AUC_{inf} (hr* ng/mL)	4103.86
F	74%

Example B



Oral bioavailability (F) = 74%

Clearance = 33mL/min/kg

Example G

The following protocol was used to determine oral bioavailability and clearance, and the results are shown below:

- Species = male mouse;
- Strain = Balb/c;
- 18 male mice were divided into two groups Group 1 (3 mg/kg; I.V.), Group 2 (10 mg/kg; P.O.) with each group comprising of nine mice;
- Blood samples (approximately 60 µL) were collected from retro orbital plexus under light isoflurane anesthesia such that the samples were obtained at pre-dose, 0.08, 0.25, 0.5, 1, 2, 4, 8 and 24 hr (I.V.) and pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hr (P.O.);
- The blood samples were collected from set of three mice at each time point in labeled micro centrifuge tube containing K2EDTA as anticoagulant;
- Plasma samples were separated by centrifugation of whole blood and stored below -70^{o}C until bioanalysis;
- All samples were processed for analysis by protein precipitation using acetonitrile (ACN) and analyzed with fit for purpose LC/MS/MS method (LLOQ: 2.47 ng/mL);
- Pharmacokinetic parameters were calculated using the non-compartmental analysis tool of Phoenix WinNonlin (Version 6.3).

Formulation:

Animals in Group 1 were administered intravenously with Example G solution formulation in 5% NMP, 5% solutol HS-15 in 90% HPβCD solution (20% HPβCD in RO water) at 3 mg/kg dose.

Animals in Group 2 were administered orally with 10 mg/kg solution formulation of Example G in 5% NMP, 5% solutol HS-15 in 90% HPβCD solution (20% HPβCD in RO water)

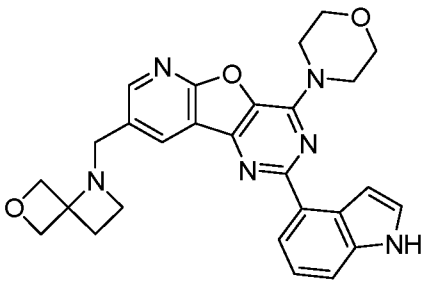
Dosing: 10mg/kg P.O. and 3mg/kg I.V.

Plasma PK Summary:

Parameters – IV, 3mg/kg	Value – Mesylate Salt
$t_{1/2}$ (hr)	0.59
C_{max} (ng/mL)	2205.80
AUC_{last} (hr*ng.mL)	1918.37
AUC_{inf} (hr*ng/mL)	1935.24
Clearance (mL/hr/Kg)	1550.4
Vss (L/Kg)	1.25

Parameters – PO, 10mg/kg	Value – Mesylate Salt
T_{max} (hr)	0.25
C_{max} (ng/mL)	833.35
AUC_{last} (hr*ng/mL)	1892.53
AUC_{inf} (hr* ng/mL)	2144.97
F	30%

Example G



Oral bioavailability (F) = 30%

Clearance = 26 mL/min/kg

Comparative Example (Example I in WO2011/021038)

The following protocol was used to determine oral bioavailability and clearance, and the results are shown below:

- Species = male mouse;
- Strain = CD1;
- n=3 male mice per time point per route;
- Terminal blood sampling at 8 time points (5min, 10min, 0.5hr, 1hr, 3hr, 6hr, 8hr and, 24hr);

- Collection of plasma, bio-analysis and report of AUC, AUMC, Vss, CL, half-life, MRT and bioavailability.

Formulation: 10% DMSO, 90% Saline

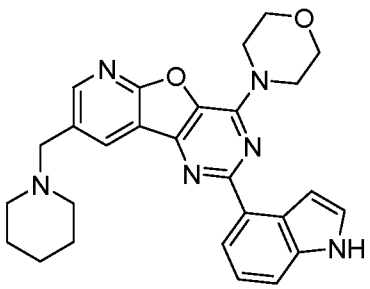
Dosing: 10mg/kg P.O. and 5mg/kg I.V.

Plasma PK Summary:

Parameters – IV, 5mg/kg	Value – Mesylate Salt	Value – HCl Salt
$t_{1/2}$ (hr)	1.6	7.6
T_{max} (hr)	0.08	0.08
C_{max} (ng/mL)	1618	1712
AUC_{last} (hr*ng.mL)	1245	1479
AUC_{all} (hr*ng/mL)	1245	1479
AUC_{inf} (hr*ng/mL)	1261	1515
Clearance (mL/hr/Kg)	3966	3300
Vd (mL/Kg)	4601	10063

Parameters – PO, 10mg/kg	Value – Mesylate Salt	Value – HCl Salt
$t_{1/2}$ (hr)	1.9	1.8
T_{max} (hr)	1.0	1.0
C_{max} (ng/mL)	212	322
AUC_{last} (hr*ng/mL)	657	849
AUC_{all} (hr*ng/mL)	657	849
AUC_{inf} (hr* ng/mL)	700	896
F	27.8%	29.6%

Example I in WO2011/021038 (Comparative)



Oral bioavailability (F) = 28%

Clearance = 66mL/min/kg

Summary

Compound	Oral Bioavailability (F)	Clearance (mL/min/kg)
Example A	74	21
Example B	74	33
Example G	30	26
Example I from WO2011/021038 (comparative)	28	66

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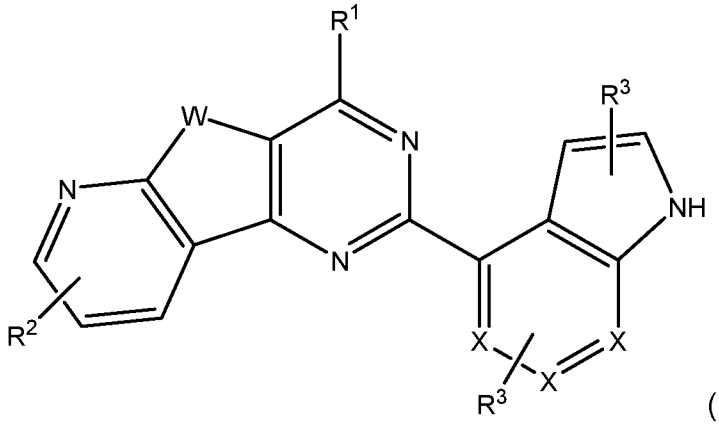
CLAIMS

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;

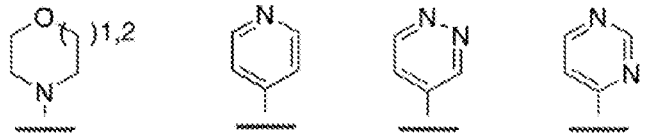
R^2 is LY;

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

Y is an optionally substituted fused, bridged or spirocyclic non-aromatic 5-12 membered heterocycle containing up to 4 heteroatoms selected from N or O; and

each R^3 is independently H, C_1-C_{10} alkyl, halogen, fluoro C_1-C_{10} alkyl, O-C_1-C_{10} alkyl, NH-C_1-C_{10} alkyl, S-C_1-C_{10} alkyl, O-fluoro C_1-C_{10} alkyl, NH-acyl, NH-C(O)-NH-C_1-C_{10} alkyl, C(O)-NH-C_1-C_{10} alkyl, aryl or heteroaryl.

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



3. The compound according to claim 1 or 2, wherein R^1 is morpholine.

4. The compound according to any one of the preceding claims, wherein W is O or S.

5. The compound according to any one of the preceding claims, wherein W is O.

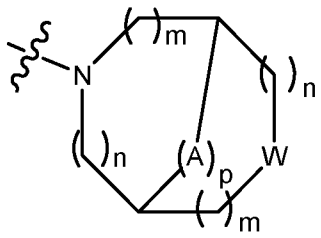
6. The compound according any one of the preceding claims, wherein X is CH.

7. The compound according to any one of the preceding claims, wherein R^3 is H.

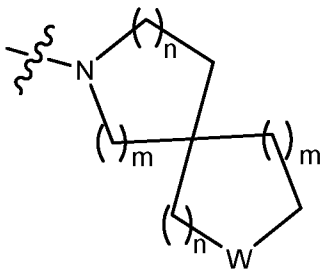
8. The compound according to any one of the preceding claims, wherein L is C_1-C_{10} alkylene, preferably methylene.

9. The compound according to any one of the preceding claims, wherein Y contains one or two heteroatoms, preferably two heteroatoms.

10. The compound according to any one of the preceding claims, wherein Y is selected from:



or



wherein:

A is selected from O, S, NR^4 or optionally substituted C_1-C_3 alkylene, C_2-C_3 alkenylene or C_2-C_3 alkynylene;

W is NR^4, O or CH_2;

wherein R^4 is H or optionally substituted C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_2-C_{10} alkynyl;

p is selected from 0 or 1;

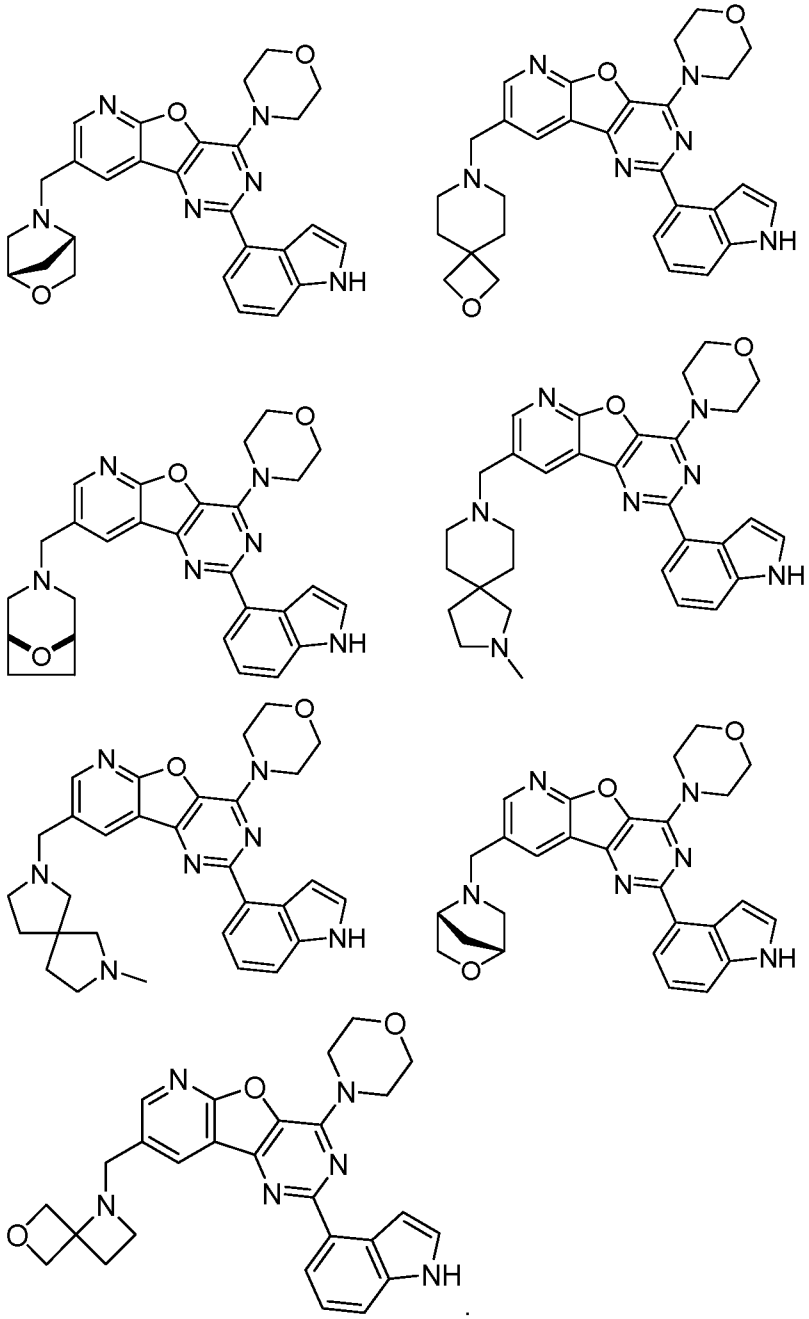
each m is independently selected from 0, 1 or 2; and

each n is independently selected from 1, 2 or 3.

11. The compound according to claim 10, wherein A is O or C_1-C_3 alkylene, preferably methylene.

12. The compound according to claim 10 or 11, wherein W is O or CH_2, preferably O.

13. A compound according to any preceding claim, which is illustrated by any one of the following structures:



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

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

16. A compound or composition according to claim 15, wherein the therapy is of cancer, an immune disorder or an inflammatory disorder.

17. A compound or composition according to claim 16, wherein the cancer is a leukaemia or a PTEN-negative solid tumour.

18. A compound according to claim 15 or claim 16, wherein the therapy is of rheumatoid arthritis.

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

20. Use of a compound or composition as defined in any of claims 1 to 14, for the manufacture of a medicament for use in therapy.

21. Use according to claim 20, wherein the therapy is as defined in any of claims 16 to 19.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/050396

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/14 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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/021038 A1 (KARUS THERAPEUTICS LTD [GB]; SHUTTLEWORTH STEPHEN JOSEPH [GB]; CECIL A) 24 February 2011 (2011-02-24) cited in the application page 1, line 7 - line 29 page 40; example K claim 1 -----	1-21
X	WO 2010/052569 A2 (UNIV BASEL [CH]; CMILJANOVIC VLADIMIR [CH]; CMILJANOVIC NATASA [CH]; G) 14 May 2010 (2010-05-14) page 1, paragraph 1 - page 7, paragraph 1 page 194; examples 483-485 claims 1, 8 -----	1-21

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 2015	25/03/2015

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

Information on patent family members

International application No
PCT/GB2015/050396

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