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(54) Titre : INHIBITEURS DE PROTEINES KINASES
(54) Title: PROTEIN KINASE INHIBITORS

(57) Abrégé/Abstract:
The present invention relates to a novel family of protein kinase inhibitors, more specifically the present invention is directed to inhibitors of the members of the Tec and Src protein kinase families. The present invention also relates to processes for the preparation of these compounds, to pharmaceutical compositions comprising them, and to their use in the treatment of proliferative, inflammatory, inflammatory and autoimmune diseases, disorders or conditions in which protein kinase activity is implicated.

ABSTRACT

The present invention relates to a novel family of protein kinase inhibitors, more specifically the present invention is directed to inhibitors of the members of the Tec and Src protein kinase families. The present invention also relates to processes for the preparation of these compounds, to pharmaceutical compositions comprising them, and to their use in the treatment of proliferative, inflammatory, inflammatory and autoimmune diseases, disorders or conditions in which protein kinase activity is implicated.

PROTEIN KINASE INHIBITORS

FIELD OF INVENTION

The present invention relates to a novel family of protein kinase inhibitors, to pharmacological compositions that contain them and to use of the inhibitors to treat diseases disorders and conditions associated with kinase function.

BACKGROUND OF THE INVENTION

Protein kinases are a large group of intracellular and transmembrane signaling proteins in eukaryotic cells (Manning G. et al, (2002) Science, 298: 1912-1934). These enzymes are responsible for transfer of the terminal (gamma) phosphate from ATP to specific amino acid residues of target proteins. Phosphorylation of specific amino acid residues in target proteins can modulate their activity leading to profound changes in cellular signaling and metabolism. Protein kinases can be found in the cell membrane, cytosol and organelles such as the nucleus and are responsible for mediating multiple cellular functions including metabolism, cellular growth and differentiation, cellular signaling, modulation of immune responses, and cell death. Serine kinases specifically phosphorylate serine or threonine residues in target proteins. Similarly, tyrosine kinases, including tyrosine receptor kinases, phosphorylate tyrosine residues in target proteins. Tyrosine kinase families include: Tec, Src, Abl, Jak, Csk, Fak, Syk, Fer, Ack and the receptor tyrosine kinase subfamilies including EGFR, FGFR, VEGFR, RET and Eph.

Kinases exert control on key biological processes related to health and disease. Furthermore, aberrant activation or excessive expression of various protein kinases are implicated in the mechanism of multiple diseases and disorders characterized by benign and malignant proliferation, as well as diseases resulting from inappropriate activation of the immune system (Kyttaris VC, Drug Des Devel Ther, 2012, 6:245-50 and Fabbro D. et al. Methods Mol Biol, 2012, 795:1-34). Thus, inhibitors of select kinases or kinase families are expected to be useful in the treatment of cancer, vascular disease, autoimmune diseases, and inflammatory conditions including, but not limited to: solid tumors, hematological malignancies, thrombus, arthritis, graft versus host disease, lupus

erythematosus, psoriasis, colitis, illeitis, multiple sclerosis, uveitis, coronary artery vasculopathy, systemic sclerosis, atherosclerosis, asthma, transplant rejection, allergy, dermatomyositis, pemphigus, and the like.

Tec kinases are a family of non-receptor tyrosine kinases predominantly, but not exclusively, expressed in cells of hematopoietic origin (Bradshaw JM. Cell Signal. 2010,22:1175-84). The Tec family includes Tec, Bruton's tyrosine kinase (Btk), inducible T-cell kinase (Itk), resting lymphocyte kinase (Rlk/Txk), and bone marrow-expressed kinase (Bmx/Etk). Btk is important in B-cell receptor signaling and regulation of B-cell development and activation (W.N. Khan et al. Immunity, 1995,3:283-299 and Satterthwaite AB et al. Immunol. Rev. 2000,175: 120-127). Mutation of the gene encoding BTK in humans leads to X-linked agammaglobulinemia which is characterized by reduced immune function, including impaired maturation of B cells, decreased levels of immunoglobulin and peripheral B cells, diminished T-cell independent immune response (Rosen FS et al., N Engl. J. Med.,1995, 333:431-440; and Lindvall JM et al. Immunol. Rev. 2005,203:200-215). Btk is activated by Src-family kinases and phosphorylates PLC gamma leading to effects on B-cell function and survival. Additionally, Btk is important in signal transduction in response to immune complex recognition by macrophage, mast cells and neutrophils. Btk inhibition is also important in survival of lymphoma cells (Herman SEM. Blood,2011, 117:6287-6289) suggesting that inhibition of Btk may be useful in the treatment of lymphomas. As such, inhibitors of Btk and related kinases are of great interest as anti-inflammatory as well as anti-cancer agents. Btk is also important for platelet function and thrombus formation suggesting that Btk–selective inhibitors may prove to be useful antithrombotic agents (Liu J. Blood, 2006,108:2596-603).

Bmx, another Tec family member which has roles in inflammation, cardiovascular disease, and cancer (Cenni B. et al. Int Rev Immunol.2012, 31: 166-173) is also important for self-renewal and tumerogenic potential of glioblastoma stem cells (Guryanova OA et al. Cancer Cell Cancer Cell 2011,19:498-511). As such, Bmx inhibitors are expected to be useful in the treatment of various diseases including cancer, cardiovascular disease and inflammation.

The SRC family of tyrosine kinases includes cSRC, Lyn, Fyn, Lck, Hck, Fgr, Blk, Frk, and Yes. cSRC is critically involved in signaling pathways involved in cancer and is often over-expressed in human malignancies (Kim LC et al. (2009) Nat Rev Clin Oncol. 6:587-9). cSRC is involved in signaling downstream of growth factor receptor tyrosine kinases and regulates cell cycle progression suggesting that cSRC inhibition would impact cancer cell proliferation. Furthermore, Src inhibitors or downregulation of Hck sensitize tumor cells to immunotoxins (Lui XF, Mol Cancer Ther. 2013, Oct 21).

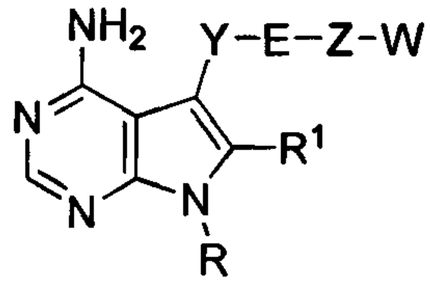
Inhibition of SRC family members may be useful in treatments designed to modulate immune function. SRC family members, including Lck, regulate T-cell receptor signal transduction which leads to gene regulation events resulting in cytokine release, survival and proliferation. Thus, inhibitors of Lck may be useful immunosuppressive agents with potential application in graft rejection and T-cell mediated autoimmune disease (Martin et al. Expert Opin Ther Pat. 2010, 20:1573-93). The Src family member HCK is implicated in regulation of cytokine production suggesting that inhibition of this kinase may be useful in treatment of inflammatory disease (Smolinska MJ et al. J Immunol. 2011;187:6043-51). Additionally, the Src family kinase Fgr is critical for activation of mast cells and IgE-mediated anaphylaxis suggesting that this kinase is a potential therapeutic target for allergic diseases (Lee JH et al. J Immunol. 2011;187:1807-15)

Inhibition of kinases using small molecule inhibitors has successfully led to several approved therapeutic agents used in the treatment of a variety of diseases disorders and conditions. Herein, we disclose a novel family of kinase inhibitors. Further, we demonstrate that modifications in compound substitution can influence kinase selectivity and therefore the biological function of that agent.

SUMMARY OF THE INVENTION

The present invention relates to a novel family of kinase inhibitors. Compounds of this class have been found to have inhibitory activity against members of the Tec and Scr protein kinase families.

One aspect of the present invention is directed to a compound of Formula 1:



Formula 1

or pharmaceutically acceptable salts, solvates, solvates of salts, stereoisomers, tautomers, isotopes, prodrugs, complexes or biologically active metabolites thereof, wherein

R is selected from the group consisting of:

1) hydrogen,

2) alkyl,

3) heteroalkyl,

4) carbocyclyl,

5) heterocyclyl,

6) aryl,

7) heteroaryl,

wherein the alkyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl and heteroaryl may be further substituted;

R^1 is selected from the group consisting of:

1) hydrogen,

2) alkyl,

3) heteroalkyl,

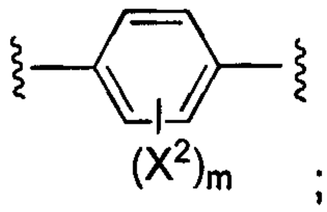
4) carbocyclyl,

5) heterocyclyl,

6) halogen,

wherein the alkyl, heteroalkyl, carbocyclyl and heterocyclyl may be further substituted;

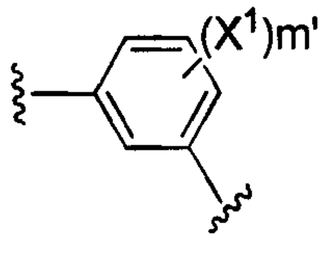
Y is selected from:



;

E is selected from oxygen;

Z is selected from:



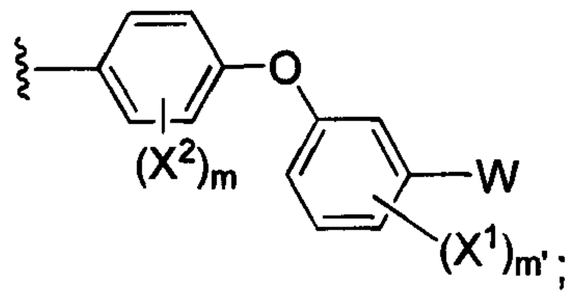
;

W is selected from

1) $-OCH_2R^2$,

2) $-CH_2OR^2$,

Wherein Y-E-Z-W is selected from:



;

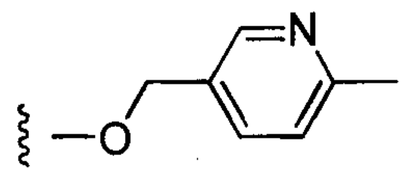
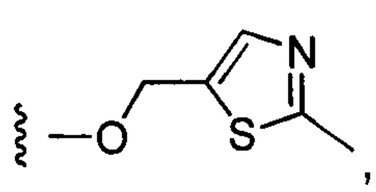
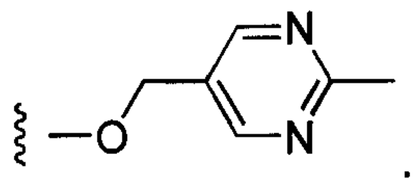
R^2 is selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

X^1 and X^2 are independently selected from hydrogen and halogen;

m is an integer from 0 to 4, and

m' is an integer from 0 to 4.

Preferred embodiments include compounds of Formula 1, where W is selected from the group consisting of:


, 
, or 
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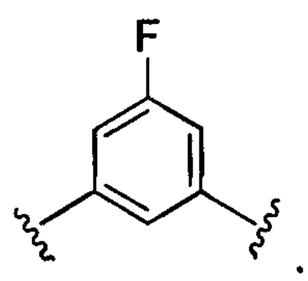
Preferred embodiments include compounds of Formula 1, where Z is selected from the group consisting of: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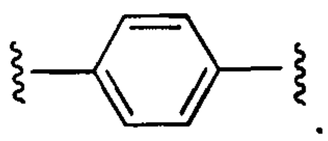
Preferred embodiments include compounds of Formula 1 where Y is selected from the group consisting of: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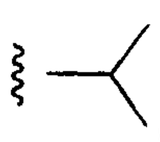
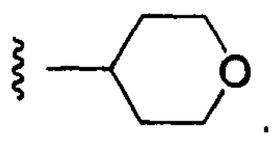
Preferred embodiment includes compounds of Formula 1 where R^1 is selected from hydrogen.

Preferred embodiment includes compounds of Formula 1 where R is selected from the group consisting of:


, or 
.

Another aspect of the present invention provides a pharmaceutical composition comprising a compound of Formula 1 or a pharmaceutically acceptable salts, solvates, solvates of salts, stereoisomers, tautomers, isotopes, prodrugs, complexes or biologically active metabolites thereof and at least one pharmaceutically acceptable carrier, diluent or excipient.

In another aspect, the present invention relates to a compound of the invention as defined herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as defined herein, for use in therapy.

In another aspect, the present invention relates to a compound of the invention as defined herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of subjects suffering from a protein kinase mediated diseases or conditions.

Another aspect of the present invention provides a use of the compound of Formula 1 as an inhibitor of protein kinase, more particularly, as an inhibitor of members of the Src and Tec family of kinases.

A further aspect of the present invention provides a use of the compound of Formula 1 as an inhibitor of protein kinase, more particularly, as an inhibitor of members of the Src or Tec family of kinases.

In another aspect, the present invention relates to the use of a compound of the invention as defined herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for use in the treatment of subjects suffering from a protein kinase mediated diseases or conditions.

In another aspect, the present invention relates to a method of treating a disease or condition associated with protein kinase activity, said method comprising administering to a subject a therapeutically effective amount of a compound of the invention as defined herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as defined herein.

Another aspect of the present invention provides a compound, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a proliferative disorder. In a particular embodiment, the proliferative disorder is a cancer.

A further aspect of the present invention provides the use of a compound, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for use in the treatment of a proliferative disorder, such as cancer.

In another aspect, the present invention provides a method of treating a proliferative disorder, said method comprising administering to a subject a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as defined herein. In a particular embodiment, the proliferative disorder is a cancer.

Another aspect of the present invention provides a method of modulating kinase function, the method comprising contacting a cell with a compound of the present invention in an amount sufficient to modulate the enzymatic activity of a given kinase or kinases, from Src and Tec family kinases, thereby modulating the kinase function.

A further aspect of the present invention provides a method of modulating kinase function, the method comprising contacting a cell with a compound of the present invention in an amount sufficient to modulate the enzymatic activity of a given kinase or kinases, from Src or Tec family kinases, thereby modulating the kinase function.

Another aspect of the present invention provides a method of inhibiting cell proliferation or survival *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound as defined herein, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment the present invention provides a method of producing a protein kinase inhibitory effect in a cell or tissue, said method comprising contacting the cell or tissue with an effective amount of a compound, or a pharmaceutically acceptable salt or solvate thereof.

In other embodiment, the present invention provides a method of producing a protein kinase inhibitory effect *in vivo*, said method comprising administering to a subject an effective amount of a compound, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the present invention provides a method of modulating the target kinase function. The method comprising:

a) contacting a cell with a compound of the present invention in an amount sufficient to modulate the target kinase function, thereby

b) modulating the target kinase activity and signaling.

The present invention further provides a method of synthesis a compound, or a pharmaceutically acceptable salt or solvate thereof, as defined herein.

Another aspect of the present invention provides a probe, the probe comprising a compound of Formula 1 labeled with a detectable label or an affinity tag. In other words, the probe comprises a residue of a compound of Formula 1 covalently conjugated to a detectable label. Such detectable labels include, but are not limited to, a fluorescent moiety, a chemiluminescent moiety, a paramagnetic contrast agent, a metal chelate, a radioactive isotope-containing moiety and biotin.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention relates to novel kinase inhibitors. These compounds are found to have activity as inhibitors of protein kinases, including members of the SRC and Tec kinase families.

Compounds of the present invention may be formulated into a pharmaceutical composition which comprises an effective amount of a compound of the instant invention with a pharmaceutically acceptable diluent or carrier.

The term "pharmaceutically effective amount" refers to any amount of the composition for the prevention and treatment of subjects that is effective in treating a disease or condition associated with protein kinase activity.

Pharmaceutical Compositions

According to the present invention there is provided a pharmaceutical composition which comprises a compound of Formula 1, or a pharmaceutically acceptable salt or solvate

thereof, in association with at least one pharmaceutically acceptable excipient, diluent or carrier.

The pharmaceutical compositions may be in a conventional pharmaceutical form suitable for oral administration (e.g., tablets, capsules, granules, powders and syrups), parenteral administration (e.g., injections (intravenous, intramuscular, or subcutaneous)), drop infusion preparations, inhalation, eye lotion, topical administration (e.g., ointment), or suppositories. Regardless of the route of administration selected, the compounds may be formulated into pharmaceutically acceptable dosage forms by conventional methods known to those skilled in the art.

The phrase "pharmaceutically acceptable" is employed herein to refer to those ligands, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be acceptable in the sense of being compatible with the other ingredients of the formulation, including the active ingredient, and not injurious or harmful to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch, potato starch, and substituted or unsubstituted β-cyclodextrin; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20)

phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

The term "pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic acid addition salts of the compound(s). These salts can be prepared *in situ* during the final isolation and purification of the compound(s), or by separately reacting a purified compound(s) in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, laurylsulphonate salts, and amino acid salts, and the like (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66: 1-19).

The pharmaceutical compositions of the present invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art.

In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound(s). These salts can likewise be prepared *in situ* during the final isolation and purification of the compound(s), or by separately reacting the purified compound(s) in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., *supra*).

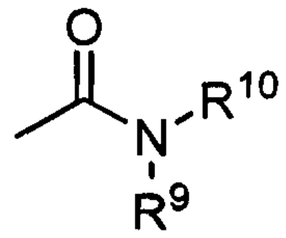
As used herein, the term "affinity tag" means a ligand or group, linked either to a compound of the present invention or to a protein kinase domain, that allows the conjugate to be extracted from a solution.

The term "alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. Representative alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, cyclopropylmethyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. The terms "alkenyl" and "alkynyl" refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively. Representative alkenyl groups include vinyl, propen-2-yl, crotyl, isopenten-2-yl, 1,3-butadien-2-yl), 2,4-pentadienyl, and 1,4-pentadien-3-yl. Representative alkynyl groups include ethynyl, 1- and 3-propynyl, and 3-butynyl. In certain preferred embodiments, alkyl substituents are lower alkyl groups, e.g., having from 1 to 6 carbon atoms. Similarly, alkenyl and alkynyl preferably refer to lower alkenyl and alkynyl groups, e.g., having from 2 to 6 carbon atoms. As used herein, "alkylene" refers to an alkyl group with two open valencies (rather than a single valency), such as $-(CH_2)_{1-10}-$ and substituted variants thereof.

The term "alkoxy" refers to an alkyl group having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxy.

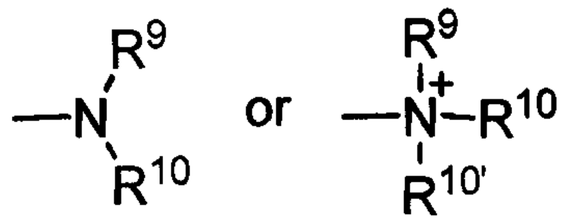
The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group, thereby forming an ether.

The terms "amide" and "amido" are art-recognized as an amino-substituted carbonyl and includes a moiety that can be represented by the general formula:



wherein R^9, R^{10} are as defined above. Preferred embodiments of the amide will not include imides, which may be unstable.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by the general formulae:



wherein R^9, R^{10} and $R^{10'}$ each independently represent a hydrogen, an alkyl, an alkenyl, $-(CH_2)_p-R^8$, or R^9 and R^{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R^8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocyclyl or a polycyclyl; and p is zero or an integer from 1 to 8. In preferred embodiments, only one of R^9 or R^{10} can be a carbonyl, e.g., R^9, R^{10}, and the nitrogen together do not form an imide. In even more preferred embodiments, R^9 and R^{10} (and optionally $R^{10'}$) each independently represent a hydrogen, an alkyl, an alkenyl, or $-(CH_2)_p-R^8$. In certain embodiments, the amino group is basic, meaning the protonated form has a $pK_a \geq 7.00$.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group, for example $-(CH_2)_p$-Ar.

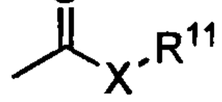
The term "heteroaralkyl", as used herein, refers to an alkyl group substituted with a heteroaryl group, for example $-(CH_2)_p$-Het.

The term "aryl" as used herein includes 5-, 6-, and 7-membered substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, anthracene, and phenanthrene.

The terms "carbocycle" and "carbocyclyl", as used herein, refer to a non-aromatic substituted or unsubstituted ring in which each atom of the ring is carbon. The terms "carbocycle" and "carbocyclyl" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is carbocyclic, e.g., the other cyclic rings can be cycloalkyls,

cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Representative carbocyclic groups include cyclopentyl, cyclohexyl, 1-cyclohexenyl, and 3- cyclohexen-1-yl, cycloheptyl.

The term "carbonyl" is art-recognized and includes such moieties as can be represented by the general formula:



wherein X is a bond or represents an oxygen or a sulfur, and R^{11} represents a hydrogen, an alkyl, an alkenyl, $-(CH_2)_p-R^8$ or a pharmaceutically acceptable salt. Where X is oxygen and R^{11} is not hydrogen, the formula represents an "ester". Where X is oxygen, and R^{11} is hydrogen, the formula represents a "carboxylic acid".

The terms "heteroaryl" includes substituted or unsubstituted aromatic 5- to 7-membered ring structures, more preferably 5- to 6-membered rings, whose ring structures include one to four heteroatoms. The term "heteroaryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, isoxazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like.
The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

The terms "heterocyclyl" or "heterocyclic group" refer to substituted or unsubstituted non-aromatic 3- to 10-membered ring structures, more preferably 3- to 7-membered rings, whose ring structures include one to four heteroatoms. The term terms "heterocyclyl" or "heterocyclic group" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heterocyclyl groups include, for example, tetrahydrofuran, tetrahydropyran, piperidine, piperazine, pyrrolidine, morpholine, lactones, and lactams.

The term "hydrocarbon", as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocycle, alkyl, alkenyl, alkynyl, and combinations thereof.

The terms "polycyclyl" or "polycyclic" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Each of the rings of the polycycle can be substituted or unsubstituted.

As used herein, the term "probe" means a compound of the invention which is labeled with either a detectable label or an affinity tag, and which is capable of binding, either covalently or non-covalently, to a protein kinase domain. When, for example, the probe is non-covalently bound, it may be displaced by a test compound. When, for example, the probe is bound covalently, it may be used to form cross-linked adducts, which may be quantified and inhibited by a test compound.

The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more atoms of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any

permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate.

Compounds of the invention also include all isotopes of atoms present in the intermediates and/or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

Therapeutic Uses and Applications

The compounds of the present invention are inhibitors of protein kinase activity.

An aspect of the present invention provides a method of inhibiting protein kinase activity in a cell, the method comprising administering to said cell compound of Formula I as defined herein, or a pharmaceutically acceptable salt or solvate thereof.

In a further aspect, the present invention provides a method of inhibiting protein kinase *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound, or a pharmaceutically acceptable salt or solvate thereof, as defined herein.

A further aspect of the present invention provides a method of inhibiting protein kinase activity in a human or animal subject, the method comprising administering to said subject an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, the protein kinase is selected from the following group: Tec, Src, Abl, Jak, Csk, Fak, Syk, FerAck kinases, and receptor protein kinases. Preferably the protein kinases are from Tec and Src kinase family. In a particular embodiment the protein kinase is Bruton's tyrosine kinase (Btk).

The compounds of the present invention are suitable for the treatment of diseases or conditions in which one or more of the protein kinase targets outlined above are implicated.

In one embodiment, the compounds are suitable for inhibition of a proliferative disorder mediated by one of the aforementioned protein kinase targets.

The term "proliferative disorder" is used herein in a broad sense to include any disorder that requires control of deleterious cell proliferation , for example cancers and other disorders associated with uncontrolled cellular proliferation such as dermatological disorders such as psoriasis, certain viral disorders, certain cardiovascular diseases such as restenosis and cardiomyopathy, certain CNS disorders, auto-immune disorders such as glomerulonephritis and rheumatoid arthritis, hormone-related diseases, metabolic disorders, stroke, alopecia, emphysema, inflammatory diseases, or infectious diseases such fungal diseases or parasitic disorders such as malaria. In these disorders, the compounds of the present invention may induce apoptosis or maintain stasis within the desired cells as required.

The term "protein kinase mediated disease" is used herein associated with abnormal cellular responses triggered by protein kinase-mediated events. Furthermore, aberrant activation or excessive expression of various protein kinases are implicated in the mechanism of multiple diseases and disorders characterized by benign and malignant proliferation. These diseases include, but are not limited to allergies and asthma, Alzheimer's disease, autoimmune diseases, bone diseases, cancer, cardiovascular diseases, inflammatory diseases, hormone-related diseases, metabolic diseases, neurological and neurodegenerative diseases. Thus, inhibitors of kinase families are expected to be suitable in the treatment of cancer, vascular disease, autoimmune diseases, and inflammatory conditions including, but not limited to: solid tumors, hematological malignancies, thrombus, arthritis, graft versus host disease, lupus

erythematosus, psoriasis, colitis, illeitis, multiple sclerosis, uveitis, coronary artery vasculopathy, systemic sclerosis, atherosclerosis, asthma, transplant rejection, allergy and dermatomyositis.

In one embodiment, the compound of Formula I or pharmaceutically acceptable salts, solvates, solvates of salts, stereoisomers, tautomers, isotopes, prodrugs, complexes, or biologically active metabolites thereof, is acting by inhibiting one or more of the host cell kinases involved in cell proliferation, cell survival, viral replication, cardiovascular disorders, neurodegeneration, autoimmunity, a metabolic disorder, stroke, alopecia, an inflammatory disease or an infectious disease.

In one embodiment, the proliferative disorder is cancer. The cancer may be selected from the group consisting of chronic lymphocytic leukaemia (CLL), lymphoma, leukaemia, breast cancer, lung cancer, prostate cancer, colon cancer, melanoma, pancreatic cancer, ovarian cancer, squamous carcinoma, carcinoma of head and neck, endometrial cancer, and oesophageal carcinoma.

Tec kinases is a family of non-receptor tyrosine kinases predominantly, but not exclusively, expressed in cells of hematopoietic origin. The Tec family comprises: Tec, Bruton's tyrosine kinase (Btk), inducible T-cell kinase (Itk), resting lymphocyte kinase (Rlk/Txk), and bone marrow-expressed kinase (Bmx/Etk).

Btk is activated by Src-family kinases and phosphorylates PLC gamma leading to effects on B-cell function and survival. Additionally, Btk is important in signal transduction in response to immune complex recognition by macrophage, mast cells and neutrophils. Btk inhibition is also important in survival of lymphoma cells (Herman SEM. Blood,2011, 117:6287-6289) suggesting that inhibition of Btk may be useful in the treatment of lymphomas. Bmx, another Tec family member are expected to be suitable in the treatment of various diseases including cancer, cardiovascular disease and inflammation.

In further aspect of the present invention, the compound of Formula I or pharmaceutically acceptable salts, solvates, solvates of salts, stereoisomers, tautomers,

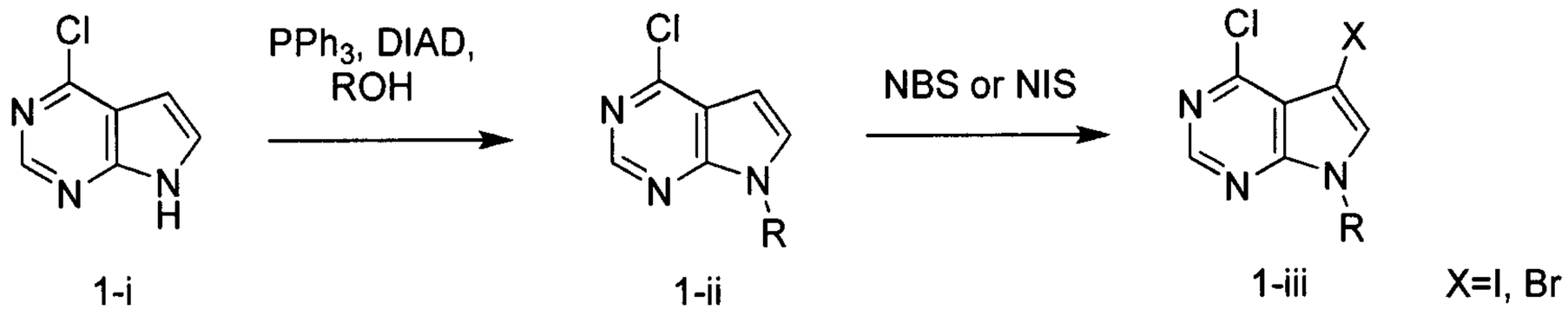
isotopes, prodrugs, complexes, or biologically active metabolites thereof, is acting as inhibitor of cell kinases as anti-inflammatory, anti-cancer and as antithrombotic agents.

As defined herein an effect against a proliferative disorder mediated by a kinase within the scope of the present invention may be demonstrated by the ability to inhibit a purified kinase *in vitro* or to inhibit cell proliferation or survival in an *in vitro* cell assay, for example in Btk Kinase Inhibition Assay and Splenic Cell Proliferation Assay. These assays are described in more details in the accompany examples.

General Synthetic Methods

In the description of the synthetic methods described below and in the referenced synthetic methods that are used to prepare the starting materials, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be selected by a person skilled in the art.

The following section describes general synthetic method(s) which may be useful in the preparation of compounds of the instant invention.

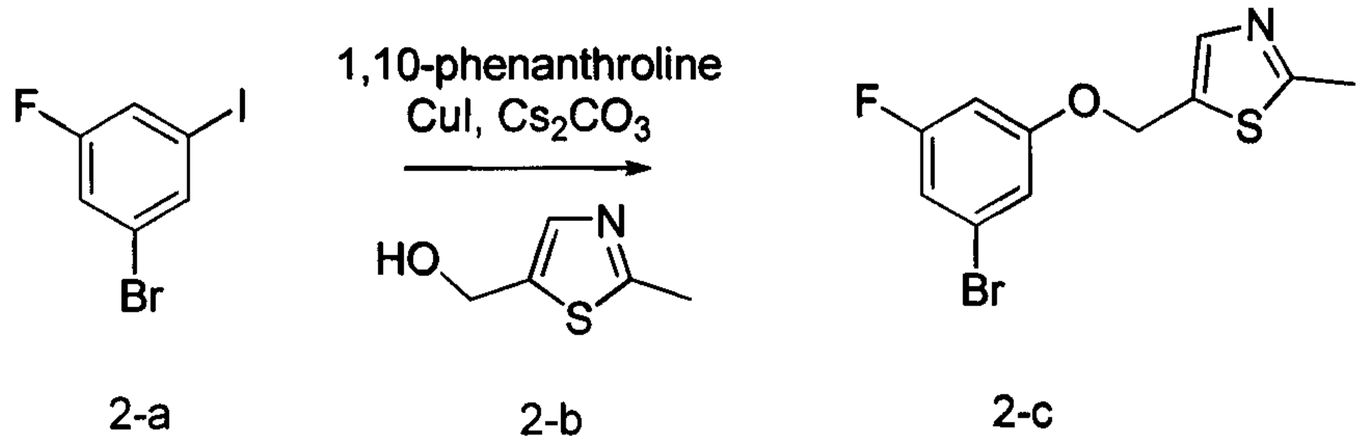

Cl
N
N
N
H
1-i
PPh3, DIAD,
ROH
Cl
N
N
N
R
1-ii
NBS or NIS
Cl
X
N
N
N
R
1-iii
X=I, Br
1-iii
NH4OH
NH2
X
N
N
N
R
1-iv
base, ligand,
catalyst
OH
(X2)m
B
O
O
1-v
NH2
OH
(X2)m
N
N
N
R
1-vi
1-vi
base, ligand,
catalyst
m'(X1)
W
O
NH2
(X2)m
N
N
N
R
1-viii
m'(X1)
W
Br
1-vii

Scheme 1

Examples

The following synthetic methods are intended to be representative of the chemistry used to prepare compounds of the instant invention and are not intended to be limiting.

Synthesis of intermediate 2-c:

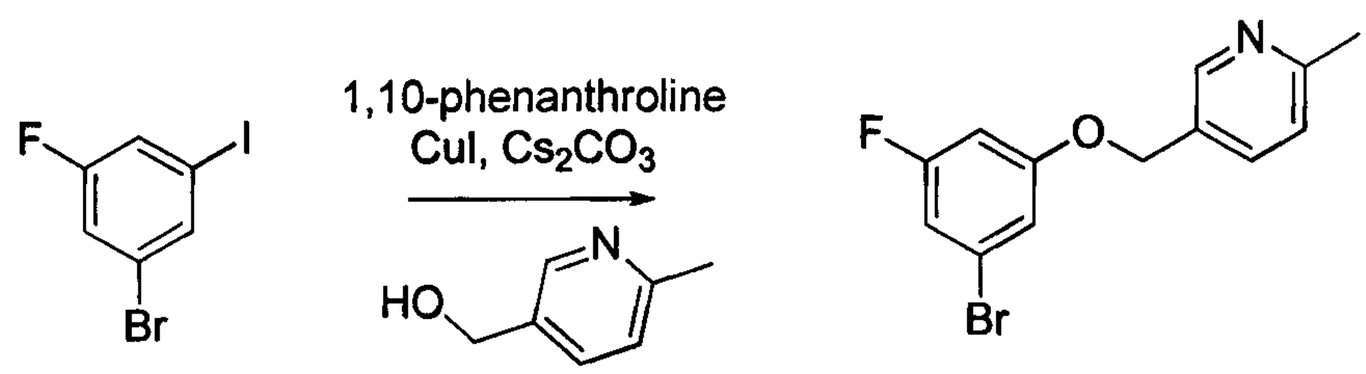


2-a 2-b 2-c

Scheme 2

To a solution of 1-bromo-3-fluoro-5-iodobenzene 2-a (7.5 g, 25.0 mmol) in 1,4-dioxane (12.5 ml) was added (2-methylthiazol-5-yl)methanol 2-b (3.5 g, 27.5 mmol), 1,10-phenanthroline (901 mg, 5.0 mmol), copper (I) iodide (476 mg, 2.50 mmol) and cesium carbonate (11.40 g, 35.0 mmol). The reaction was stirred at 110°C for 2 days and then cooled to room temperature, diluted with ethyl acetate and filtered over celite. A saturated aqueous solution of ammonium chloride was added to the filtrate, the organic layer was separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 2-c as a beige oil which solidify upon standing.

Synthesis of intermediate 3-b:



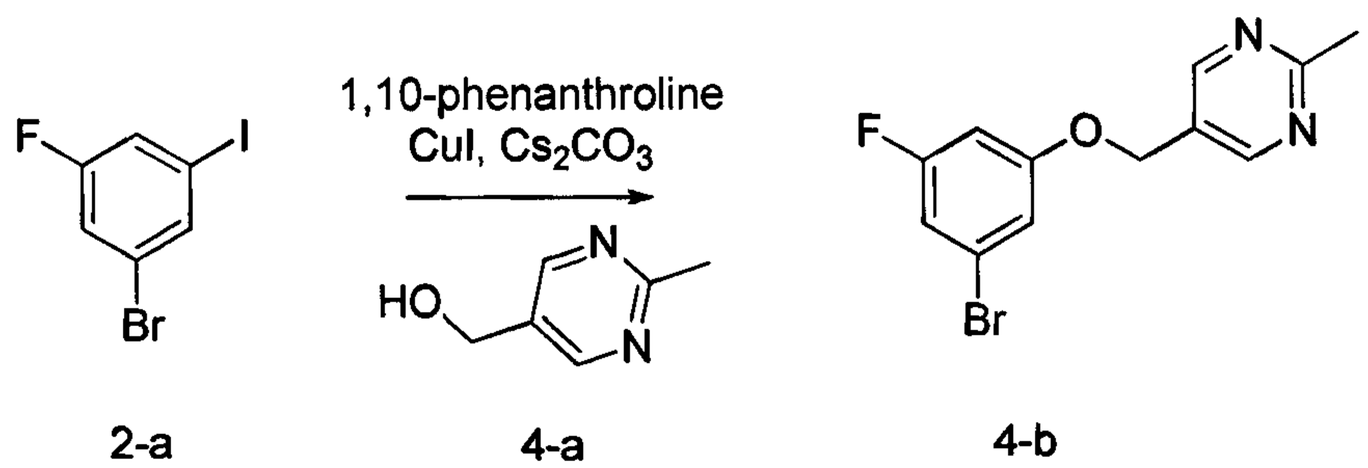
2-a 3-a 3-b

Scheme 3

To a solution of 1-bromo-3-fluoro-5-iodobenzene 2-a (5.0 g, 16.62 mmol) in toluene (8.3 ml) was added (6-methylpyridin-3-yl) methanol 3-a (2.25 g, 18.28 mmol), 1,10-

phenanthroline (599 mg, 3.32 mmol), copper (I) iodide (316 mg, 1.66 mmol) and cesium carbonate (7.58 g, 23.26 mmol). The reaction was stirred at 110°C for 2 days and then cooled to room temperature, diluted with ethyl acetate and filtered over celite. A saturated aqueous solution of ammonium chloride was added to the filtrate, the organic layer was separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 3-b as a beige solid.

Synthesis of intermediate 4-b:

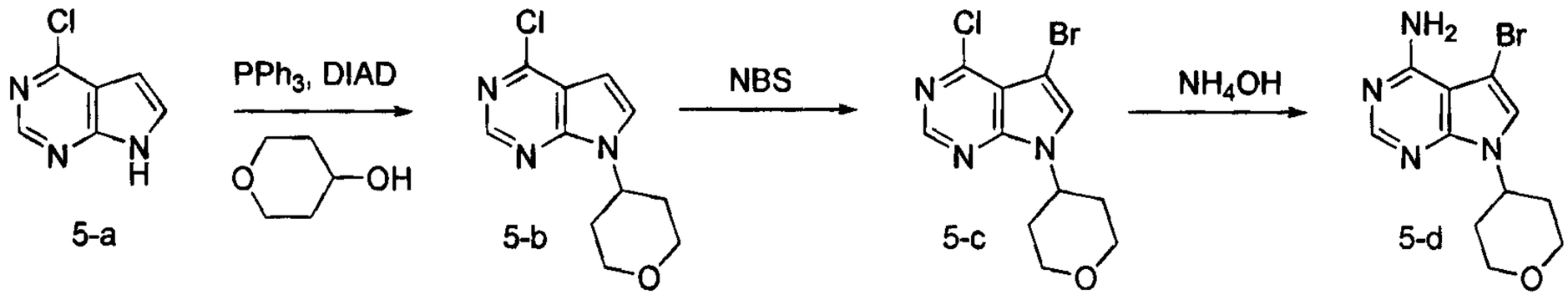


2-a 4-a 4-b

Scheme 4

To a solution of 1-bromo-3-fluoro-5-iodobenzene 2-a (5.0 g, 16.62 mmol) in toluene (8.3 ml) was added (2-methylpyrimidin-5-yl)methanol 4-a (2.26 g, 18.28 mmol), 1,10-phenanthroline (599 mg, 3.32 mmol), copper (I) iodide (316 mg, 1.66 mmol) and cesium carbonate (7.58 g, 23.26 mmol). The reaction was stirred at 110°C for 2 days and then cooled to room temperature, diluted with ethyl acetate and filtered over celite. A saturated aqueous solution of ammonium chloride was added to the filtrate, the organic layer was separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 4-b as a beige solid.

Synthesis of intermediate 5-c:



Scheme 5

Step 1: Intermediate 5-b

To a solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine 5-a (3.0 g, 19.54 mmol) and tetrahydro-2H-pyran-4-ol (2.99 g, 29.3 mmol) in THF (150 mL) were sequentially added triphenylphosphine (6.7 g, 25.4 mmol) and DIAD (4.9 ml, 25.4 mmol). The solution was stirred at room temperature overnight. Volatiles were removed under reduced pressure. Purification by silica gel chromatography provided intermediate 5-b as a beige gum.

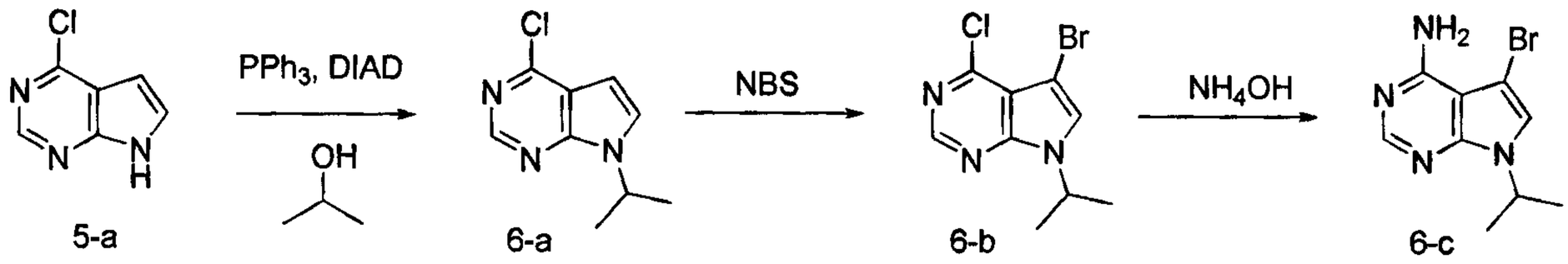
Step 2: Intermediate 5-c

To a solution of intermediate 5-b (2.5 g, 10.5 mmol) in DMF (26.3 ml) cooled to 0°C, was slowly added a 0.7N solution of N-bromosuccinimide in DMF (16.5 ml, 11.5 mmol). The reaction mixture was stirred for15 minutes at 0°C. Water (70 mL) was added; a precipitate formed and was collected by filtration to provide intermediate 5-c as a beige solid.

Step 3: Intermediate 5-d

To a solution of intermediate 5-c (2.6 g, 8.2 mmol) in iPrOH (41.4 ml) was added ammonium hydroxide (56.0 ml). The reaction mixture was stirred for 36 hours at 90 °C then cooled to room temperature. Volatiles were removed under reduced pressure. The residue was triturated in water; a precipitated formed and was collected by filtration to provide intermediate 5-d as a beige solid.

Synthesis of intermediate 6-c:



Scheme 6

Step 1: Intermediate 6-a

To a solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine 5-a (3.0 g, 19.54 mmol) and 2-propanol (1.5 g, 26.0 mmol) in THF (100 mL) were sequentially added triphenylphosphine (4.4 g, 16.9 mmol) and DIAD (3.3 ml, 16.9 mmol). The solution was stirred at 50°C for 5 days then cooled to room temperature. Volatiles were removed under reduced pressure. Purification by silica gel chromatography provided intermediate 6-a as a beige gum.

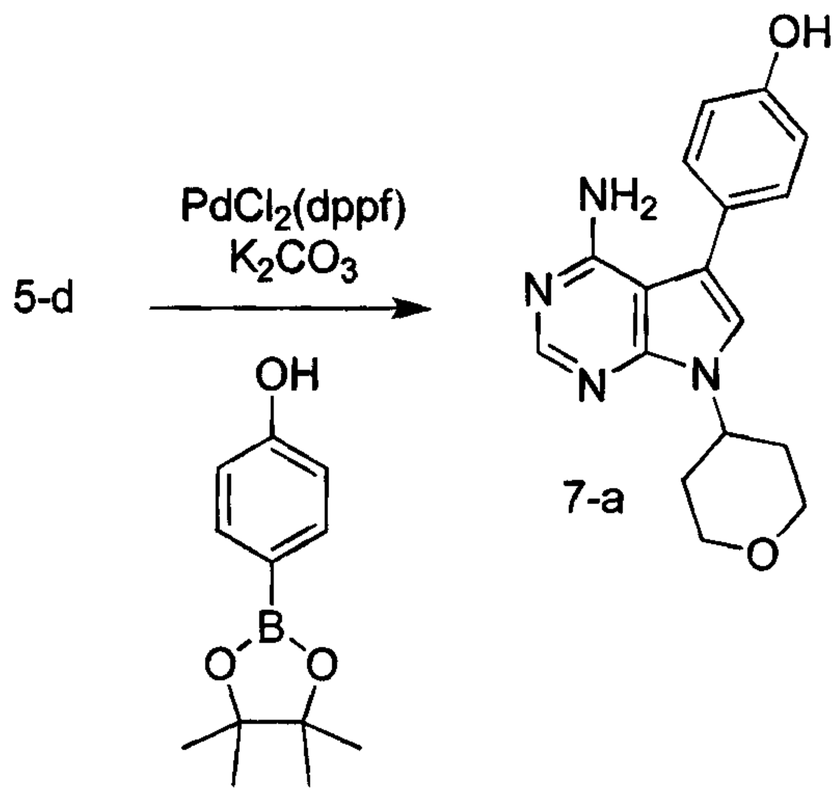
Step 2: Intermediate 6-b

To a solution of intermediate 6-a (2.1 g, 10.7 mmol) in DMF (26.8 ml) cooled to 0°C, was slowly added a 0.7N solution of N-bromosuccinimide in DMF (16.8 ml, 11.8 mmol). The reaction mixture was stirred 15min at 0°C. Water (70 mL) was added; a precipitate formed and was collected by filtration to provide intermediate 6-b as a beige solid.

Step 3: Intermediate 6-c

To a solution of intermediate 6-b (2.6 g, 9.2 mmol) in iPrOH (12.9 ml) was added ammonium hydroxide (18.0 ml). The reaction mixture was stirred overnight at 90 °C then cooled to room temperature. Volatiles were removed under reduced pressure. The residue was triturated in water; a precipitated formed and was collected by filtration to provide intermediate 6-c as a beige solid.

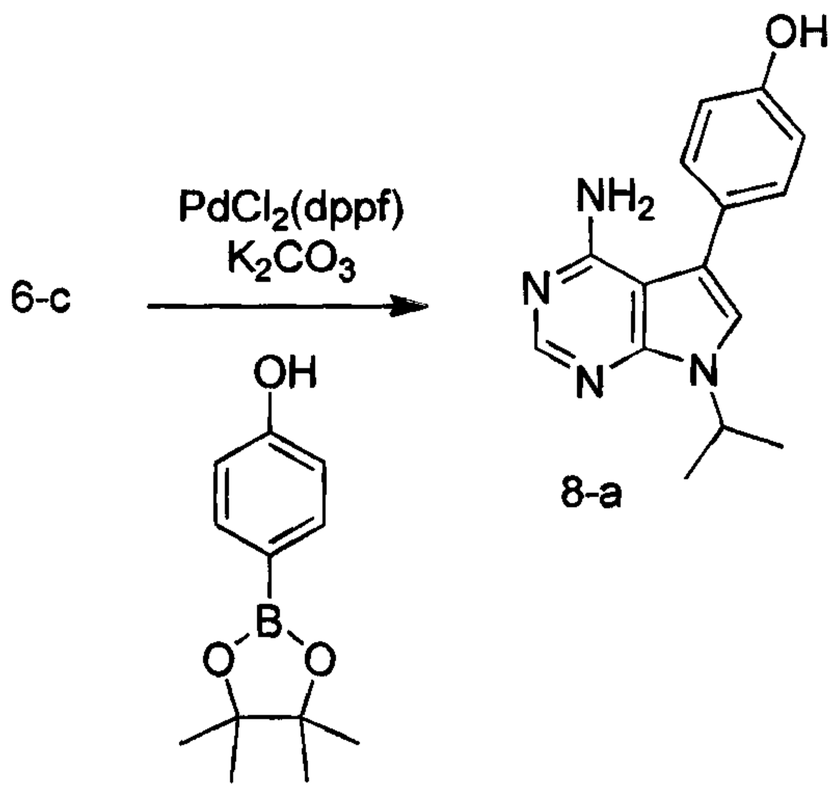
Synthesis of intermediate 7-a:



Scheme 7

To a solution of intermediate 5-d (2.3 g, 7.7 mmol) in DME (48 ml) were added potassium carbonate (3.3 g, 23.9 mmol), water (11.9 ml) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.9 g, 8.9 mmol). The mixture was degassed and $PdCl_2$(dppf) (428 mg, 0.6 mmol) was added under nitrogen . The reaction mixture was stirred for 2 days at 90 °C then cooled to room temperature. Volatiles were removed under reduced pressure. Purification by silica gel chromatography provided intermediate 7-a as a brown solid.

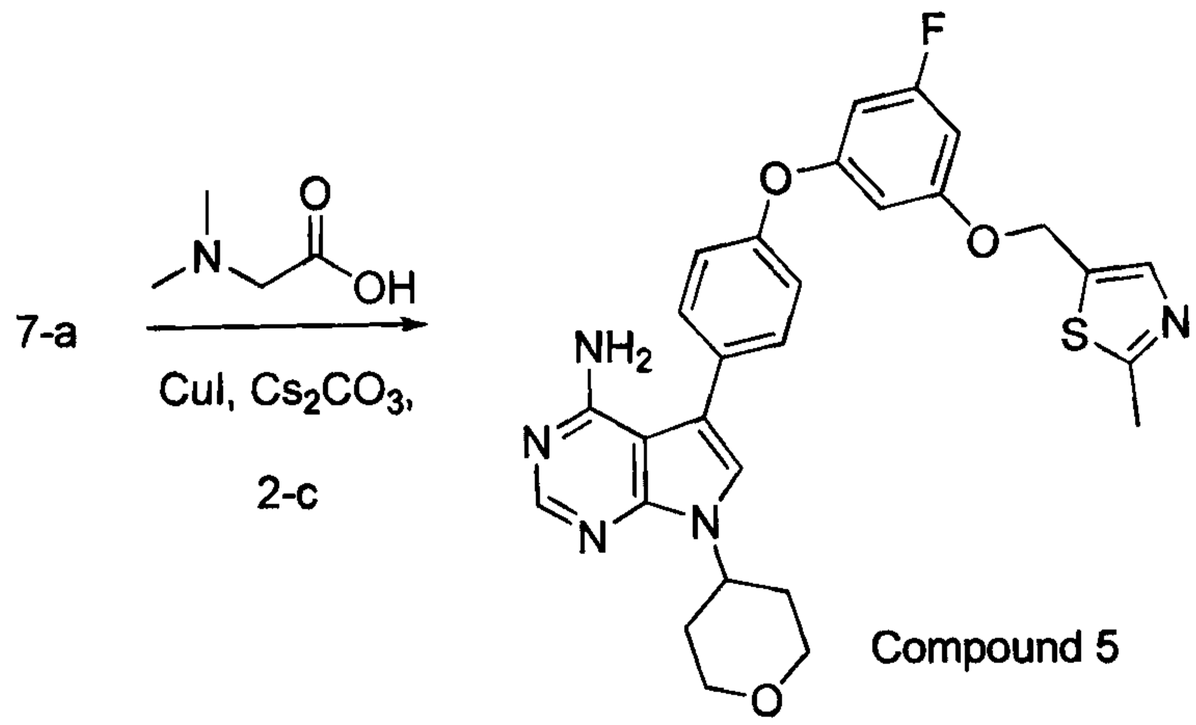
Synthesis of intermediate 8-a:



Scheme 8

To a solution of intermediate 6-c (2.4 g, 9.4 mmol) in DME (58 ml) were added potassium carbonate (4.0 g, 29.2 mmol), water (14.5 ml) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (2.4 g, 10.8 mmol). The mixture was degassed and $PdCl_2$(dppf) (347 mg, 0.5 mmol) was added under nitrogen . The reaction mixture was stirred overnight at 90 °C then cooled to room temperature. Volatiles were removed under reduced pressure. Purification by silica gel chromatography provided intermediate 8-a as a brown solid.

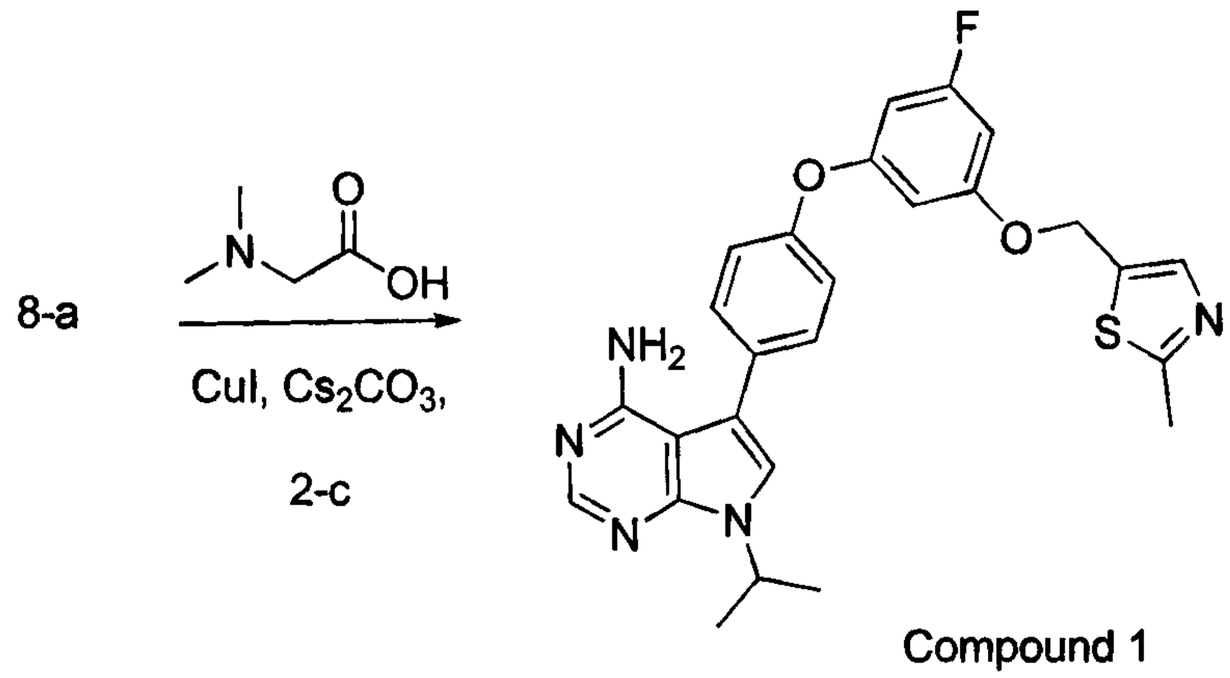
Synthesis of Compound 5:



Scheme 9

A solution of intermediate 7-a (210 mg, 0.7 mmol), intermediate 2-c (245 mg, 0.8 mmol), N,N-Dimethylglycine (209 mg, 2.0 mmol), cesium carbonate (882 mg, 2.7 mmol) and copper(I) iodide (129 mg, 0.7 mmol) in 1,4-dioxane (1.0 ml) was heated in a pressure vessel at 110 °C for 36 hours then cooled to room temperature. Ethyl acetate was added, the reaction was adsorbed on silica gel. Purification by silica gel chromatography provided compound 5 as a beige solid. MS (m/z) M+H= 532.3

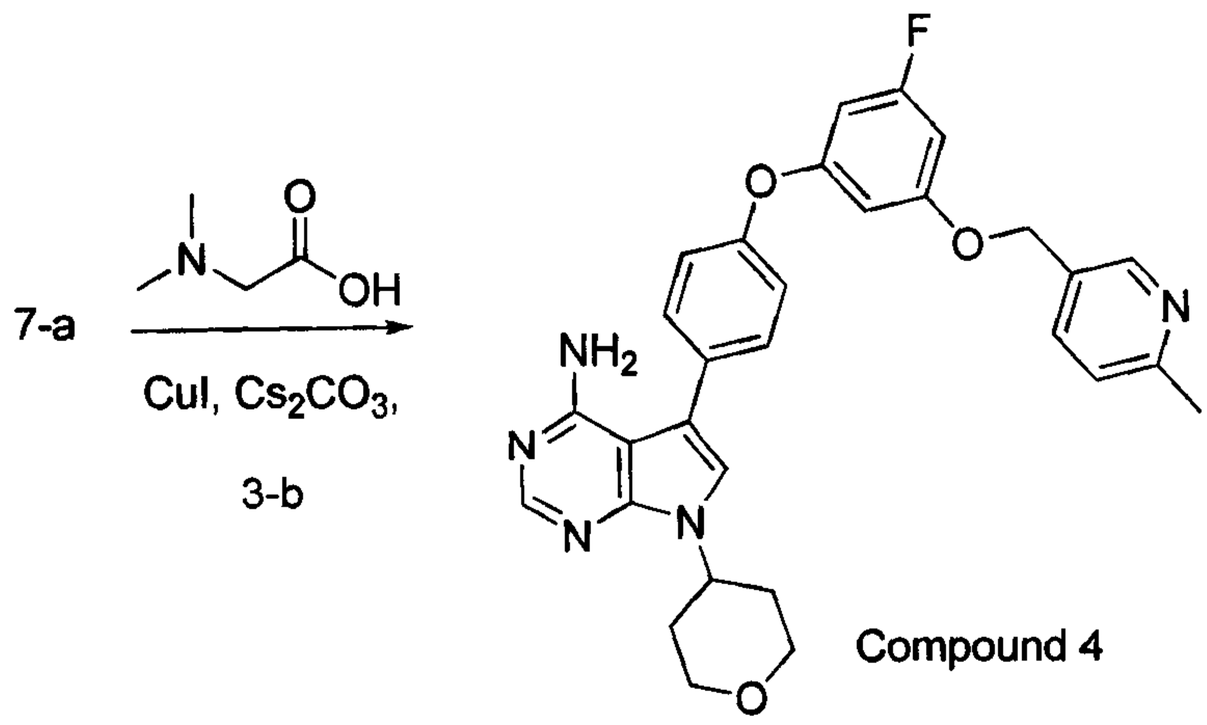
Synthesis of Compound 1:



Scheme 10

A solution of intermediate 8-a (200 mg, 0.7 mmol), intermediate 2-c (270 mg, 0.9 mmol), N,N-Dimethylglycine (115 mg, 1.2 mmol), cesium carbonate (729 mg, 2.2 mmol) and copper(I) iodide (71 mg, 0.4 mmol) in 1,4-dioxane (1.0 ml) was heated in a pressure vessel at 110 °C for 36 hours then cooled to room temperature. Ethyl acetate was added, the reaction was adsorbed on silica gel. Purification by silica gel chromatography provided compound 1 as a beige solid. MS (m/z) M+H= 490.2

Synthesis of Compound 4:

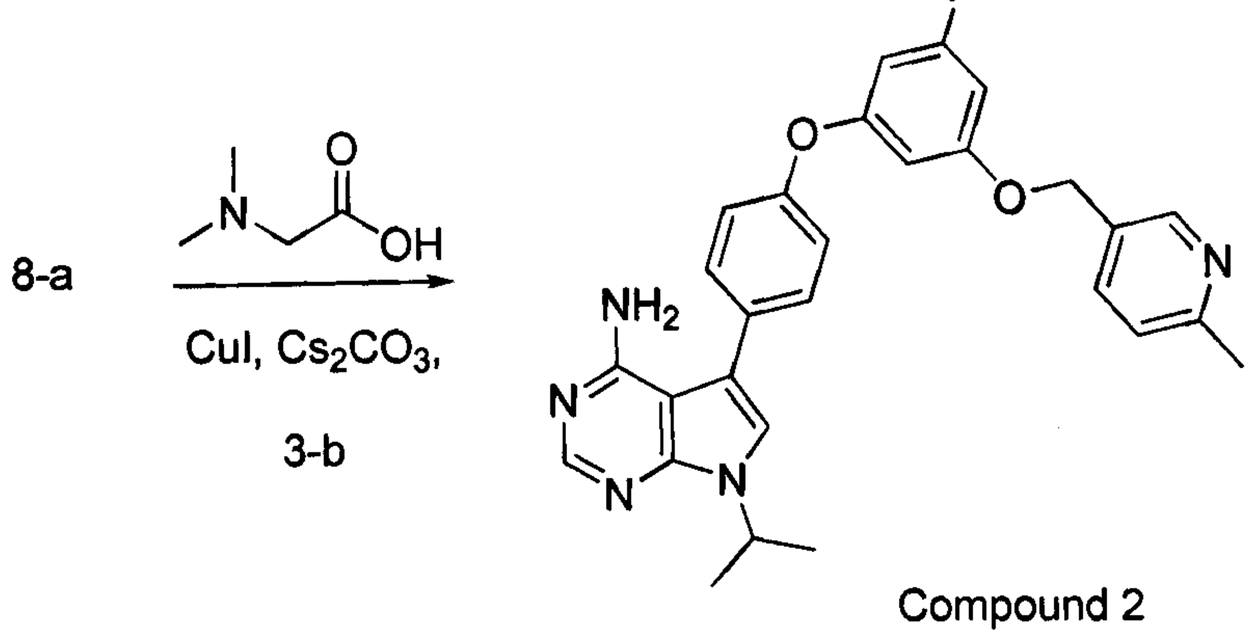


Scheme 11

A solution of intermediate 7-a (210 mg, 0.7 mmol), intermediate 3-b (240 mg, 0.8 mmol), N,N-Dimethylglycine (209 mg, 2.0 mmol), cesium carbonate (882 mg, 2.7 mmol) and copper(I) iodide (129 mg, 0.7 mmol) in 1,4-dioxane (1.0 ml) was heated in a pressure vessel at 110 °C for 36 hours then cooled to room temperature. Ethyl acetate was

added, the reaction was adsorbed on silica gel. Purification by silica gel chromatography provided compound 4 as a beige solid. MS (m/z) M+H= 526.3

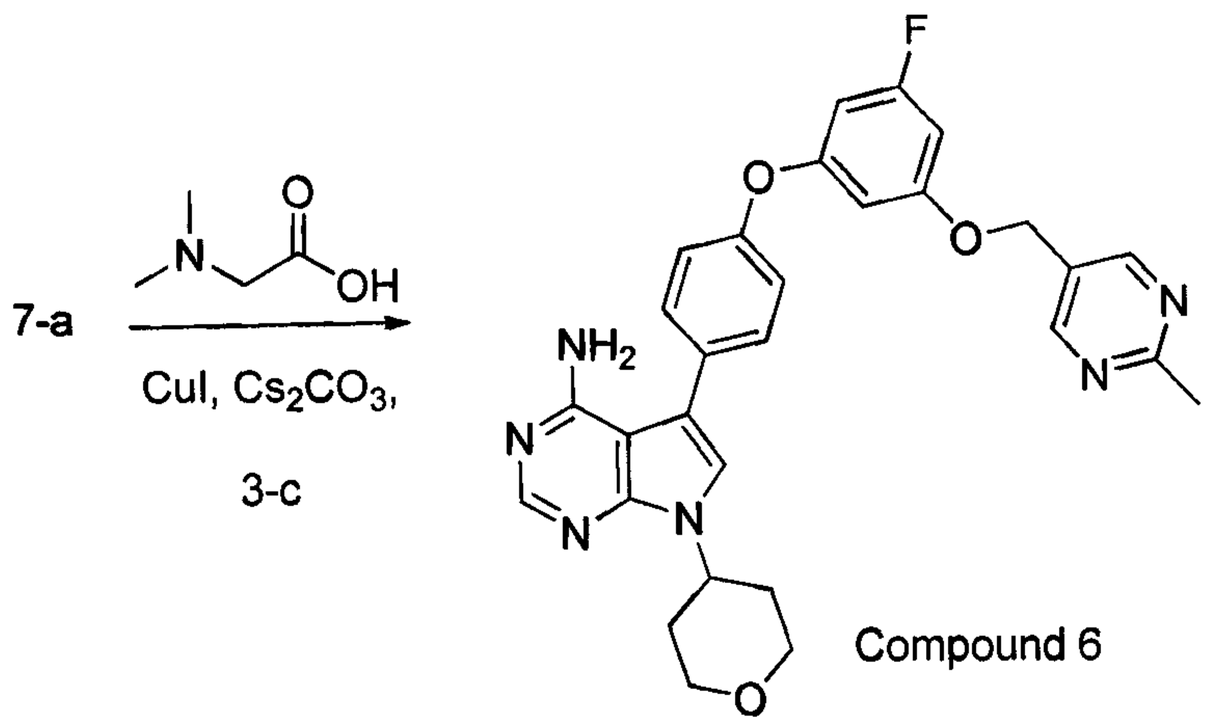
Synthesis of Compound 2:



Scheme 12

A solution of intermediate 8-a (200 mg, 0.7 mmol), intermediate 3-b (265 mg, 0.9 mmol), N,N-Dimethylglycine (115 mg, 1.2 mmol), cesium carbonate (729 mg, 2.2 mmol) and copper(I) iodide (71 mg, 0.4 mmol) in 1,4-dioxane (1.0 ml) was heated in a pressure vessel at 110 °C for 36 hours then cooled to room temperature. Ethyl acetate was added, the reaction was adsorbed on silica gel. Purification by silica gel chromatography provided compound 2 as a beige solid. MS (m/z) M+H= 484.2

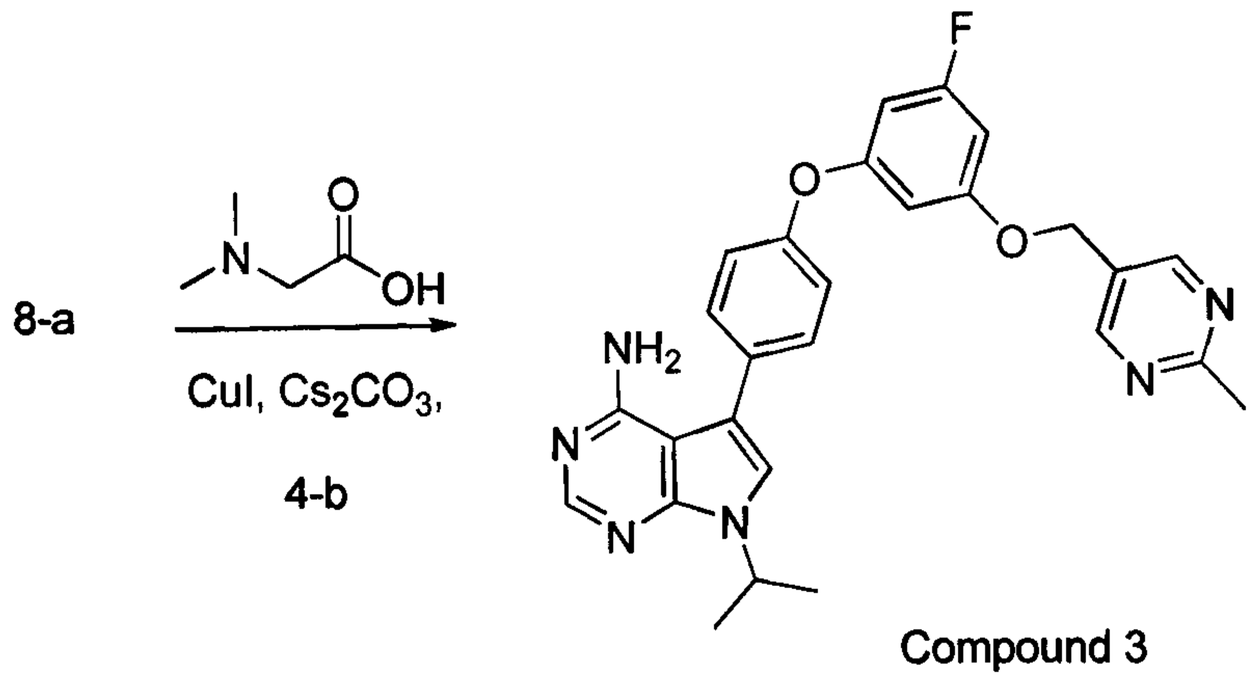
Synthesis of Compound 6:



Scheme 13

A solution of intermediate 7-a (210 mg, 0.7 mmol), intermediate 3-c (241 mg, 0.8 mmol), N,N-Dimethylglycine (209 mg, 2.0 mmol), cesium carbonate (882 mg, 2.7 mmol) and copper(I) iodide (129 mg, 0.7 mmol) in 1,4-dioxane (1.0 ml) was heated in a pressure vessel at 110 °C for 36 hours then cooled to room temperature. Ethyl acetate was added, the reaction was adsorbed on silica gel. Purification by silica gel chromatography provided compound 6 as a beige solid. MS (m/z) M+H= 527.2

Synthesis of Compound 3:

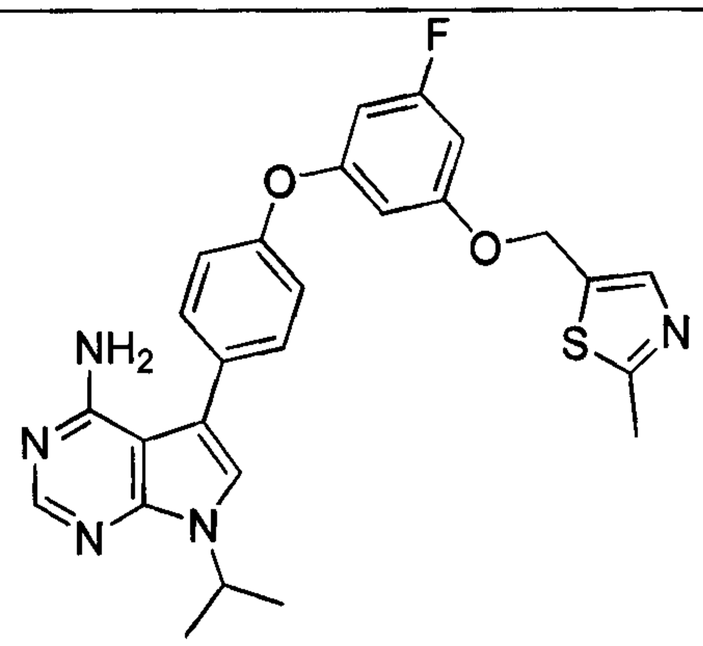
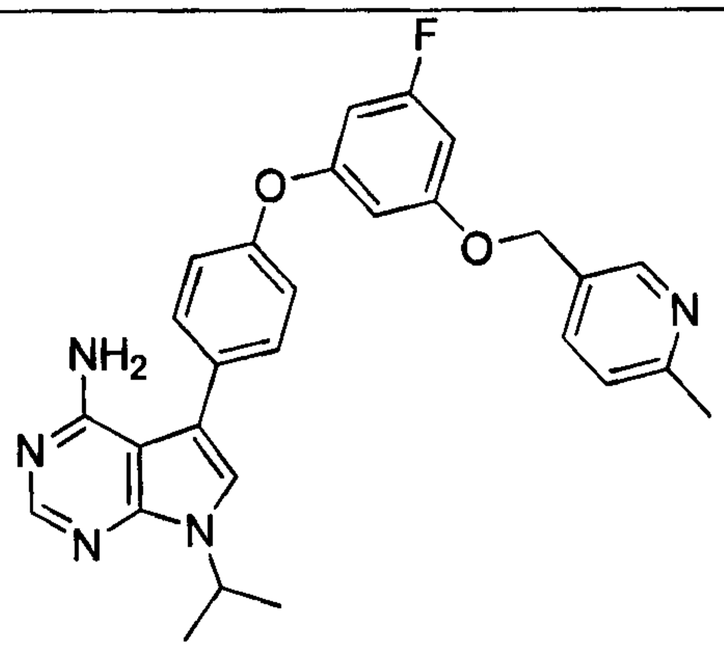
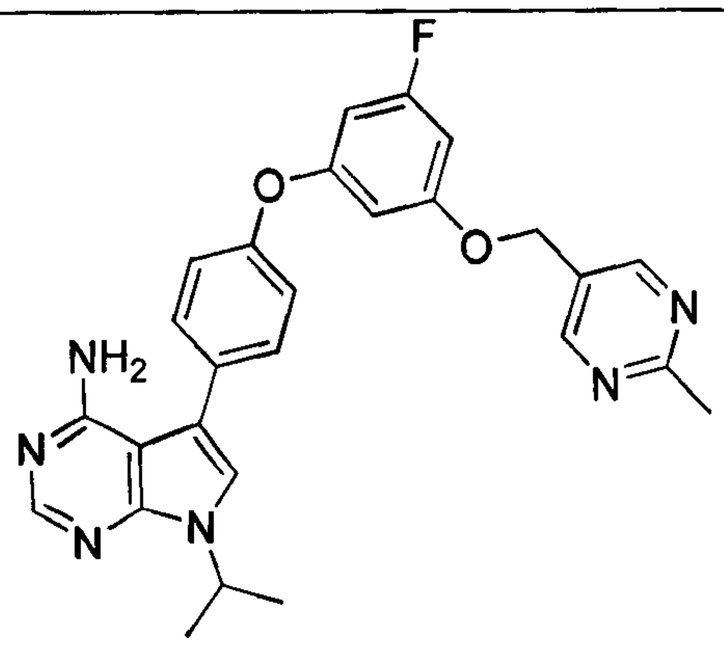


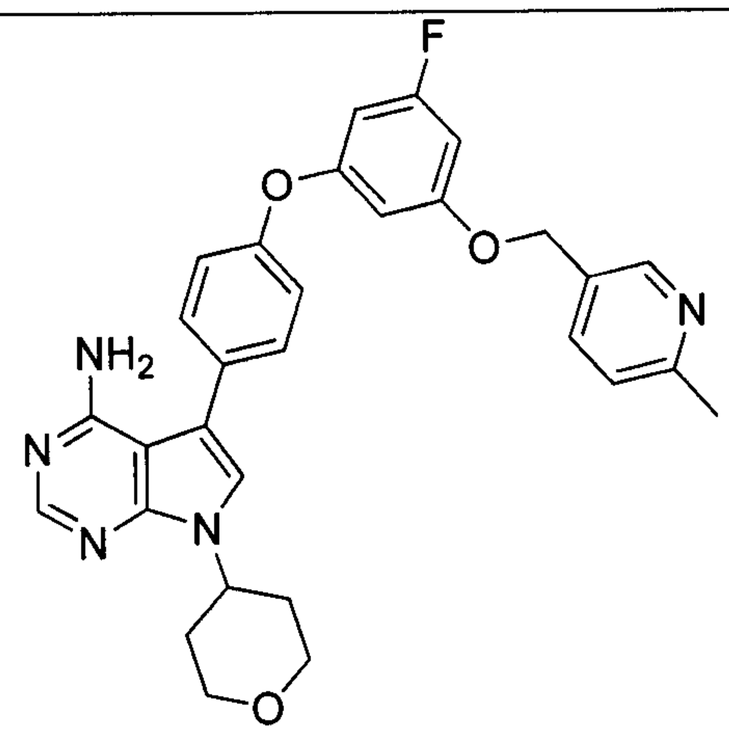
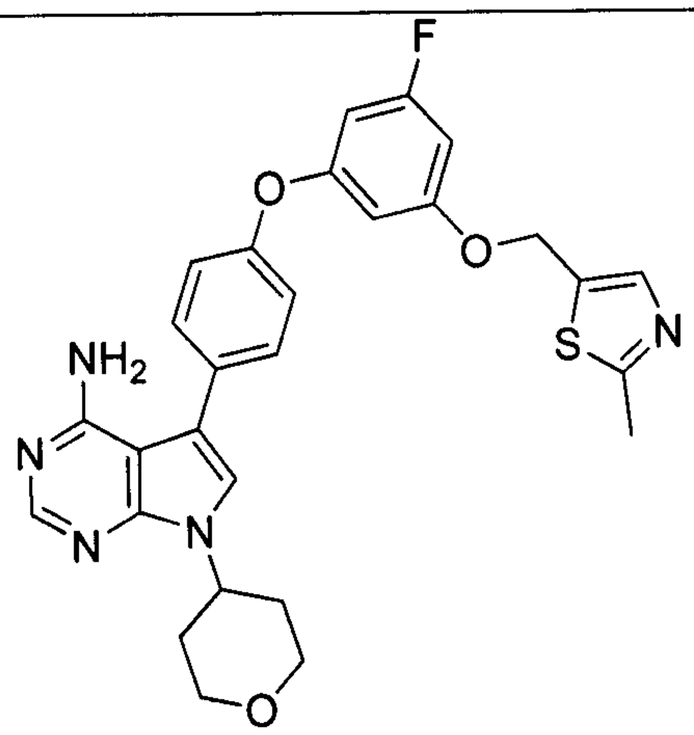
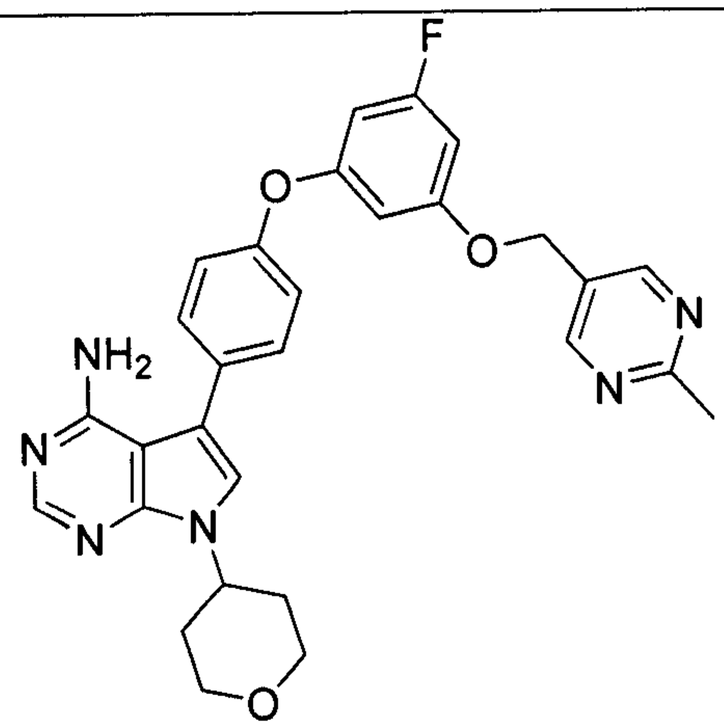
Compound 3

Scheme 14

A solution of intermediate 8-a (200 mg, 0.7 mmol), intermediate 4-b (266 mg, 0.9 mmol), N,N-Dimethylglycine (115 mg, 1.2 mmol), cesium carbonate (729 mg, 2.2 mmol) and copper(I) iodide (71 mg, 0.4 mmol) in 1,4-dioxane (1.0 ml) was heated in a pressure vessel at 110 °C for 36 hours then cooled to room temperature. Ethyl acetate was added, the reaction was adsorbed on silica gel. Purification by silica gel chromatography provided compound 3 as a beige solid. MS (m/z) M+H= 485.2

Table 1: Example Compounds of Formula 1

Compound	Structure	MS (m/z)
1		$[M+H]^+$= 490.2
2		$[M+H]^+$= 484.2
3		$[M+H]^+$= 485.2

4		$[M+H]^+$= 526.3
5		$[M+H]^+$= 532.3
6		$[M+H]^+$= 527.2

Biological assays

Assays for determining kinase activity are described in more detail in the accompanying examples.

Kinase Inhibition

Btk Kinase Inhibition Assay

Fluorescence polarization-based kinase assays were performed in 384 well-plate format using histidine tagged recombinant human full-length Bruton Agammaglobulinemia Tyrosine Kinase (Btk) and a modified protocol of the KinEASE ™ FP Fluorescein Green Assay supplied from Millipore. Kinase reaction were performed at room temperature for 60 minutes in presence of 250 µM substrate, 10 µM ATP and variable test article concentrations. The reaction was stopped with EDTA/kinease detection reagents. Phosphorylation of the substrate peptide was detected by fluorescence polarization measured with a Tecan 500 instrument. From the dose-response curve obtained, the IC_{50} was calculated using Graph Pad Prisms® using a non linear fit curve. The Km for ATP on each enzyme was experimentally determined and the Ki values calculated using the Cheng-Prusoff equation (see: Cheng Y, Prusoff WH. (1973) Relationship between the inhibition constant (K1) and the concentration of inhibitor which causes 50 per cent inhibition (I_{50}) of an enzymatic reaction". *Biochem Pharmacol* **22** (23): 3099–108).

k_i values are reported in Tables 2:

Table 2: Inhibition of Btk

Compound	k_i (nM)
1	a
2	a
3	a
4	a
5	a
6	a

a - Ki< 100 nM; b – 100 nM<Ki<1000 nM, c – ki>1000 nM

Cellular Assays

Splenic Cell Proliferation Assay

Proliferation of splenocytes in response to anti-IgM can be blocked by inhibition of Btk. Splenocytes were obtained from 6 week old male CD1 mice (Charles River Laboratories Inc.). Mouse spleens were manually disrupted in PBS and filtered using a 70um cell strainer followed by ammonium chloride red blood cell lysis. Cells were washed,

resuspended in Splenocyte Medium (HyClone RPMI supplemented with 10% heat-inactivated FBS, 0.5X non-essential amino acids, 10 mM HEPES, 50 uM beta mercaptoethanol) and incubated at 37 °C, 5% CO_2 for 2h to remove adherent cells. Suspension cells were seeded in 96 well plates at 50,000 cells per well and incubated at 37°C, 5% CO_2 for 1h. Splenocytes were pre-treated in triplicate with 10,000 nM curves of Formula 1 compounds for 1h, followed by stimulation of cell proliferation with 2.5ug/ml anti-IgM $F(ab')_2$ (Jackson ImmunoResearch) for 72h. Cell proliferation was measured by Cell Titer-Glo Luminescent Assay (Promega). EC_{50} values (50% proliferation in the presence of compound as compared to vehicle treated controls) were calculated from dose response compound curves using GraphPad Prism SoftwareEC_{50} values are reported in Table 3:

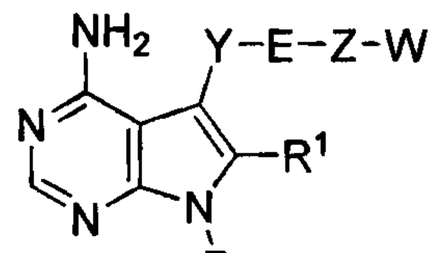
Table 3: Inhibition of splenic cell proliferation

Compound	EC_{50} (nM)
1	a
2	a
3	a
4	a
5	a
6	a

a – EC_{50}<100 nM; b – 100 nM<EC_{50}<1000 nM, c – EC_{50}>1000 nM

CLAIMS

1. A compound of Formula 1:



R

Formula 1

or pharmaceutically acceptable salts, solvates, solvates of salts, stereoisomers, tautomers, isotopes, prodrugs, complexes or biologically active metabolites thereof, wherein

R is selected from the group consisting of:

1) hydrogen,

2) alkyl,

3) heteroalkyl,

4) carbocyclyl,

5) heterocyclyl

6) aryl,

7) heteroaryl;

wherein the alkyl, heteroalkyl, carbocyclyl, heterocycyl, aryl and heteroaryl are optionally substituted;

R^1 is selected from the group consisting of:

1) hydrogen,

2) alkyl,

3) heteroalkyl,

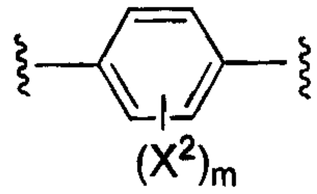
4) carbocyclyl,

5) heterocyclyl,

6) halogen,

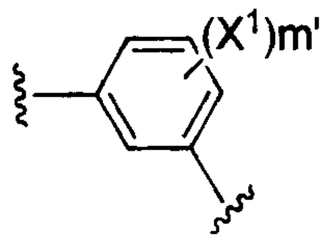
wherein the alkyl, heteroalkyl, carbocyclyl and heterocyclyl are optionally substituted;

Y is selected from:



E is selected from oxygen;

Z is selected from:

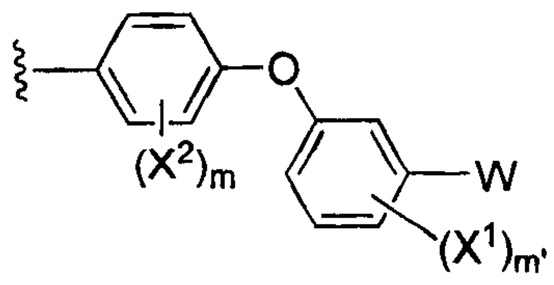


W is selected from:

1) $-OCH_2R^2$,

2) $-CH_2OR^2$;

Wherein Y-E-Z-W is selected from:



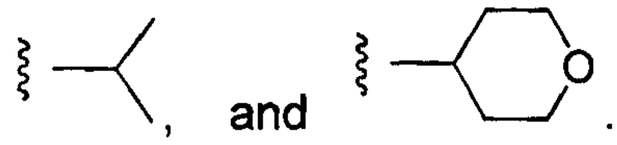
R^2 is selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

X^1 and X^2 are independently selected from hydrogen and halogen;

m is an integer from 0 to 4, and

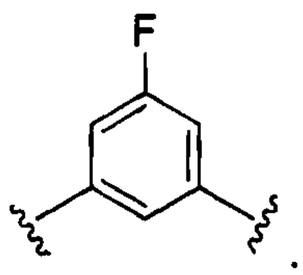
m' is an integer from 0 to 4.

2. The compound according to claim 1, wherein R is selected from the group consisting of:

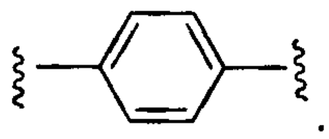


3. The compound according to claim 1, wherein R^1 is selected from hydrogen.

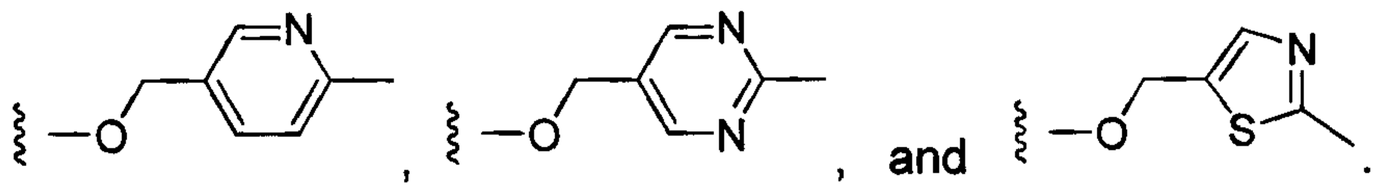
4. The compound according to claim 1, wherein Z is selected from



5. The compound according to claim 1, wherein Y is selected from

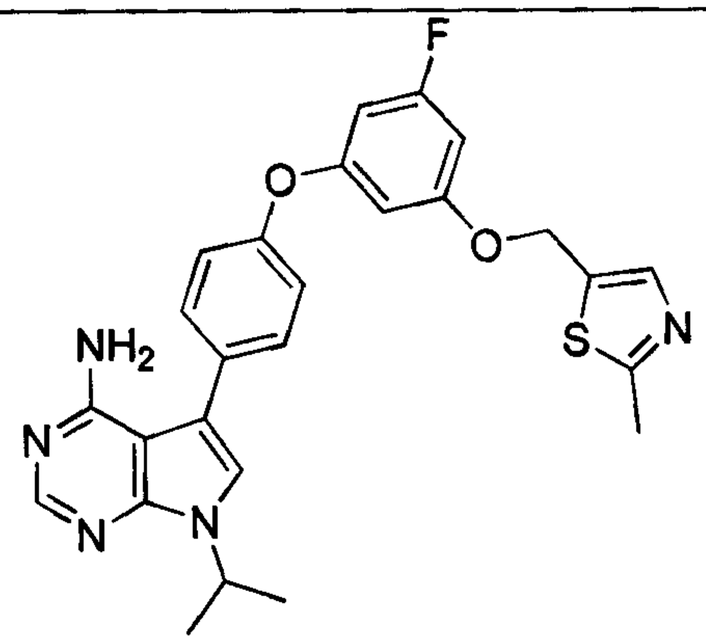
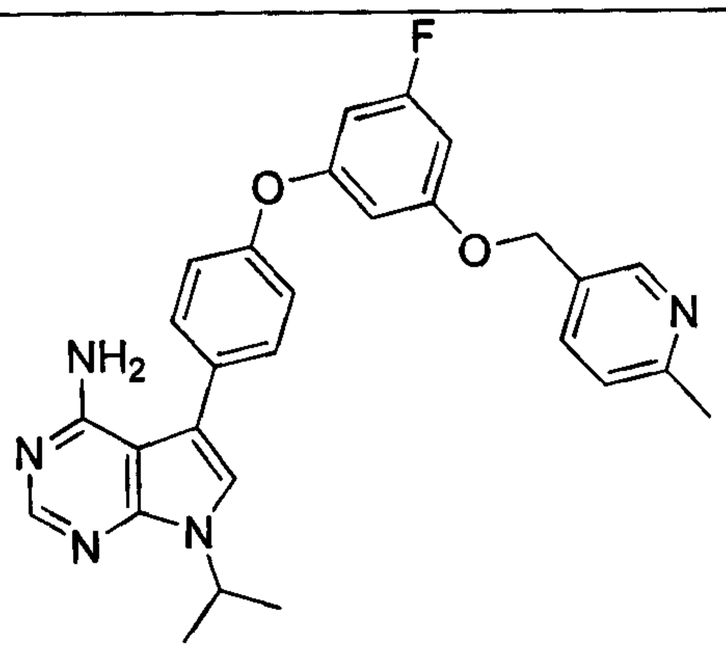
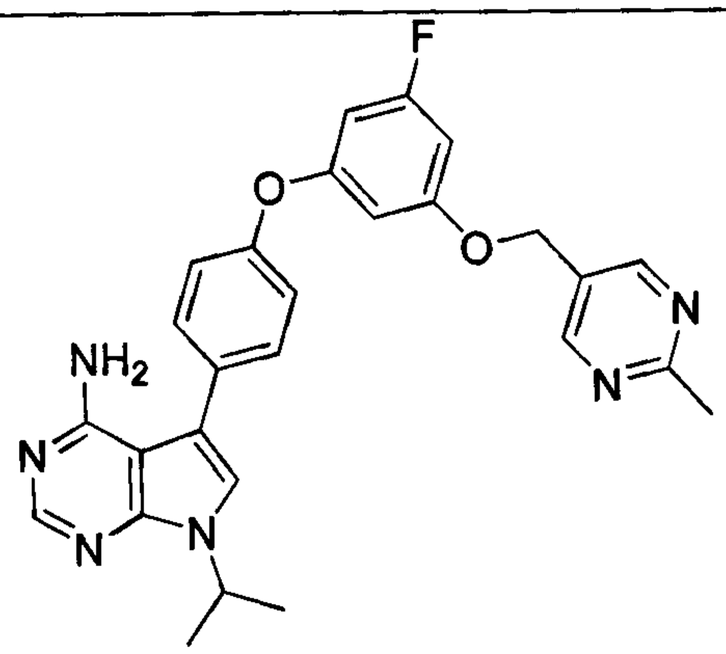
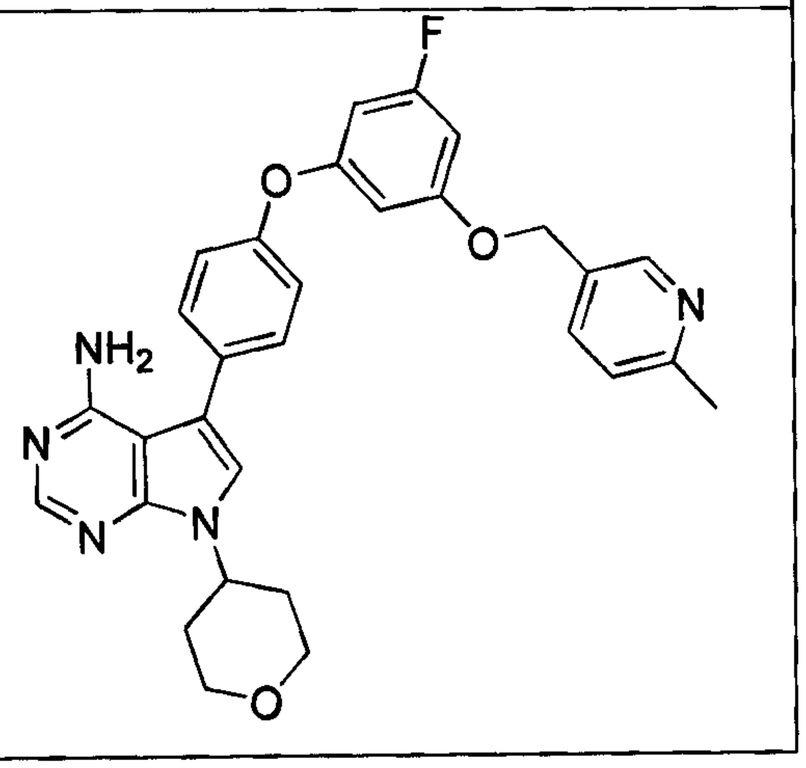


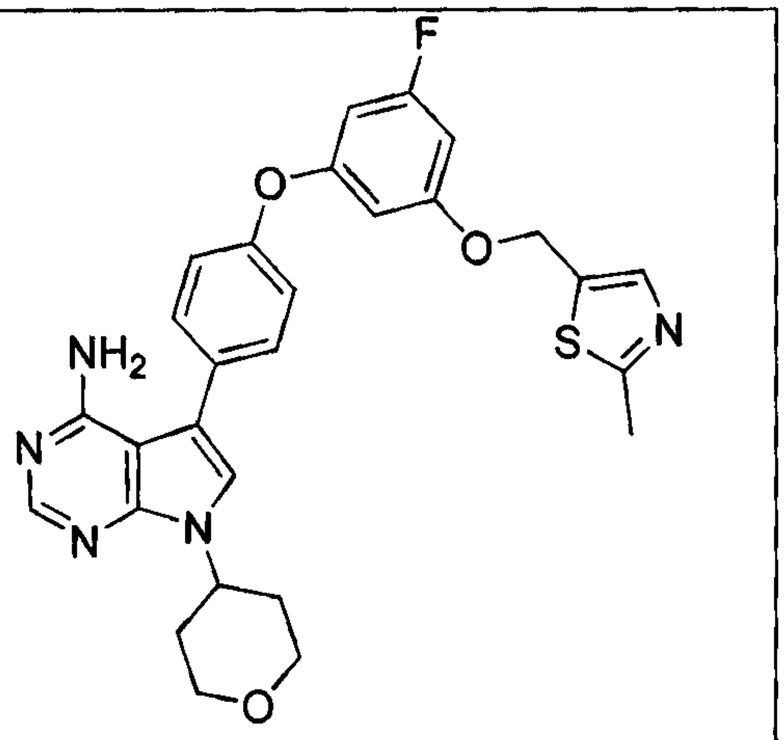
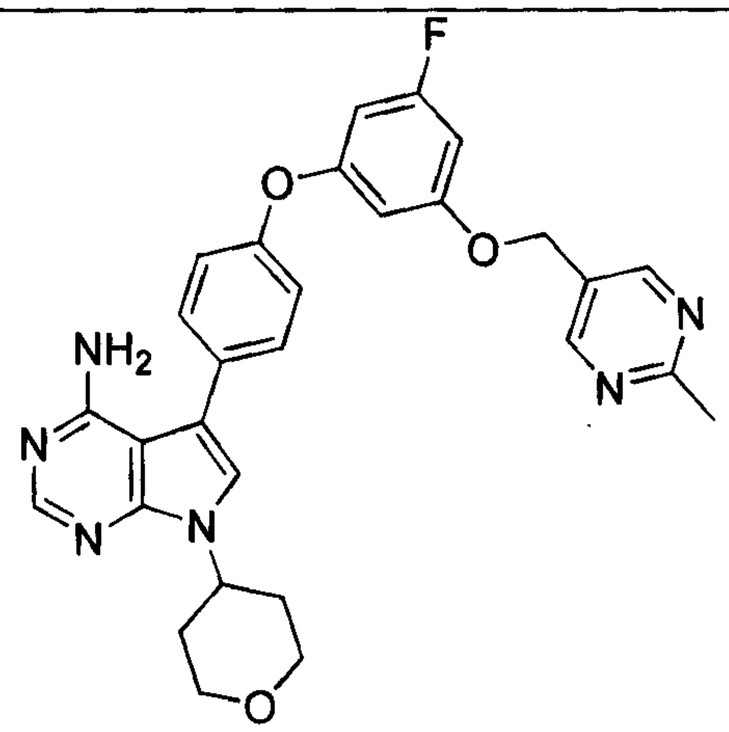
6. The compound according to claim 1, wherein W is selected from the group consisting of:



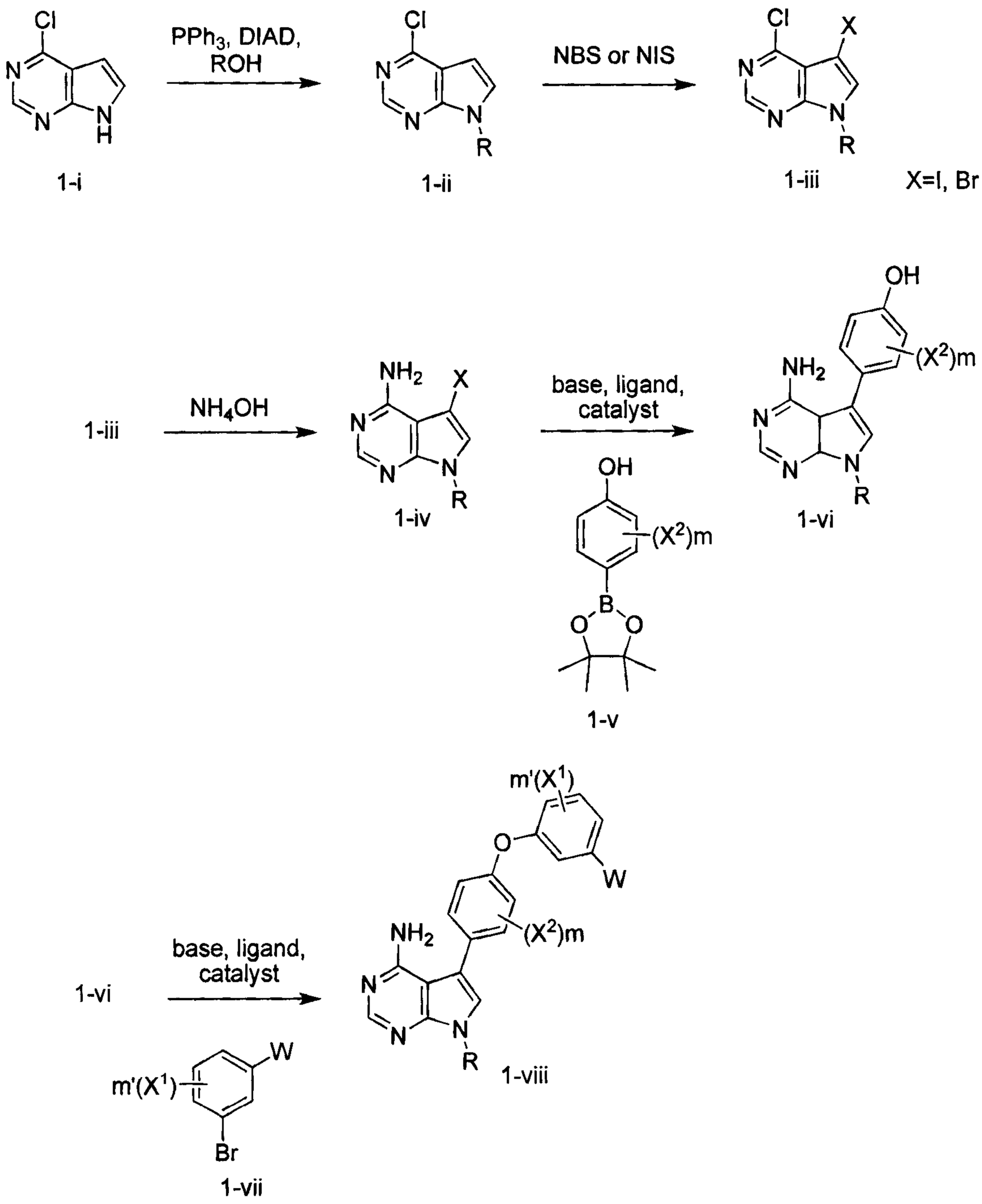
7. A compound selected from the group consisting of:

Compound	Structure

1	
2	
3	
4	

5	
6	

8. A method of manufacturing a compound of Formula 1, wherein said method comprises the following steps:



9. A compound of Formula 1 useful for the treating of proliferative, inflammatory and autoimmune diseases.

10. A compound of Formula 1 for use as a medicament.

11. A pharmaceutical composition comprising a compound of Formula 1 for use in a method for the treatment of a subject suffering from a protein kinase mediated disease, disorder or condition in which kinase family member activity is implicated.

12. A pharmaceutical composition comprising a compound of any one of claims 1 to 7 and at least one pharmaceutically acceptable carrier, excipient or diluent.

13. The pharmaceutical composition according to claim 11, wherein a protein kinase mediated disease, disorder or condition is in which Tec kinase family member activity is implicated.

14. The pharmaceutical composition according to claim 11, wherein a protein kinase mediated disease, disorder or condition is in which Src kinase family member activity is implicated.

15. Use of a compound of Formula 1 for the treatment of proliferative, inflammatory and autoimmune diseases.

16. Use of the pharmaceutical composition of claim 11 for the treatment of proliferative, inflammatory and autoimmune diseases.

17. The use of a compound according to any one of claims 1 to 16, wherein the pharmaceutical composition is suitable for the treatment of a subject suffering from a protein kinase mediated disease, disorder or condition associated with Tec and Src kinase family members.

18. Use of a compound of Formula 1 for the manufacture of a pharmaceutical composition suitable for the treatment of proliferative, inflammatory and autoimmune diseases.

19. The use of a compound according to any one of claims 15 to 18, wherein the disease, disorder or condition is in which Btk kinase activity is implicated.

20. A method for treating a subject suffering from a protein kinase mediated disease or condition, comprising administering to the subject a therapeutically effective amount of a compound of Formula 1, or a pharmaceutically acceptable salt, or solvate thereof.

21. The method of claim 20, wherein the disease, disorder or condition is associated with Tec and Src kinase family members.

22. The method of claim 20, wherein the disease, disorder or condition is associated with Btk kinase activity.

23. A method of modulating kinase activity function in a subject comprising administering a therapeutically effective amount of a compound of any one of claims 1 to 7, to said subject to modulate the enzymatic activity of a protein kinase.

24. A method of inhibiting protein kinase in a cell or tissue comprising contacting the cell or tissue with an effective amount of a compound, or a pharmaceutically acceptable salt or solvate thereof, according to any one of claims 1 to 7.

25. A method of inhibiting protein kinase activity, comprising administering to a human or animal subject an effective amount of a compound, or a pharmaceutically acceptable salt or solvate thereof, according to any one of claims 1 to 7.

26. The method according to any one of claims 23 to 25, wherein said target kinase function is associated with Tec kinase family members activity.

27. The method according to any one of claims 23 to 25, wherein said target kinase function is associated with Src kinase family members activity.

28. A probe comprising a compound of any one of claims 1 to 7 and a detectable label or affinity tag for said compound.

29. The probe according to claim 28, wherein the detectable label is selected

from the group consisting of: a fluorescent moiety, a chemiluminescent moiety, a paramagnetic contrast agent, a metal chelate, a radioactive isotope-containing moiety and biotin.