(12) UK Patent Application (19) GB (11) 2515785 (13) A

(43) Date of A Publication 07.01.2015

(21) Application No: 1311951.6

(22) Date of Filing: 03.07.2013

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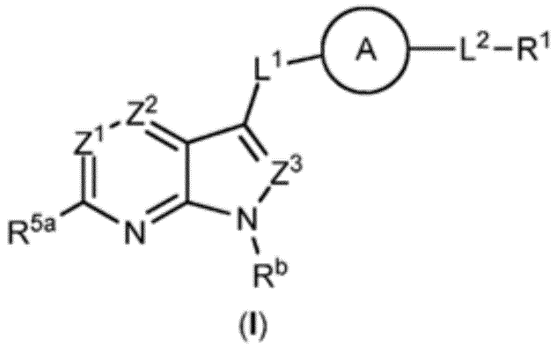
(51) INT CL:
C07D 487/04 (2006.01) ***A61K 31/437*** (2006.01)
A61K 31/519 (2006.01) ***A61P 35/00*** (2006.01)
A61P 35/02 (2006.01) ***C07D 471/04*** (2006.01)

(56) Documents Cited:
WO 2011/008915 A **WO 2010/003133 A**
WO 2008/079346 A **WO 2006/058074 A**
US 20060030583 A1

(58) Field of Search:
INT CL **C07D**
Other: **CAS ONLINE, WPI, EPODOC**

(54) Title of the Invention: **Compounds**
Abstract Title: **Fused-ring heterocyclic compounds and their use as BTK inhibitors**

(57) A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein A is selected from optionally substituted phenyl, pyridinyl and pyrazolyl; L^1 and L^2 are selected from a bond and a linker; R^1 is a substituent; one of Z^1 and Z^2 is selected from a nitrogen atom and an optionally substituted carbon atom and the other of Z^1 and Z^2 is C-N(R^{5b})D-E where R^{5b} is selected from hydrogen and a substituent, D is selected from an optionally substituted alkylene, optionally substituted heteroalkylene and an optionally substituted ring system, E is a substituent; Z^3 is selected from a nitrogen atom and an optionally substituted carbon atom; R^{5a} and R^b is selected from hydrogen and a substituent. These compounds are inhibitors of Bruton's tyrosine kinase (BTK) and are useful for treating conditions treatable by the inhibition of BTK, for example cancer, lymphoma, leukemia and immunological diseases.

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Compounds

[0001] This invention relates to compounds. More specifically, the invention relates to compounds useful as kinase inhibitors, along with processes to prepare the compounds and uses of the compounds. Specifically, the invention relates to inhibitors of Bruton's tyrosine kinase (BTK).

BACKGROUND

[0002] Kinases are a class of enzyme that control the transfer of phosphate groups from phosphate donor groups, for example ATP, to specific substrates. Protein kinases are a subset of kinases and BTK is one such protein kinase.

[0003] BTK is a member of the src-related Tec family of cytoplasmic tyrosine kinases. BTK plays a key role in the signalling pathways of B-cells, affecting B-cell development, activation, signalling and survival. In certain malignancies, B-cells overexpress BTK. These malignant B-cells and the overexpression of BTK by the cells has been associated with the increased proliferation and survival of tumor cells. Inhibition of BTK affects the B-cell signalling pathways, preventing activation of B-cells and inhibiting the growth of malignant B-cells.

[0004] A number of clinical trials have shown that BTK inhibitors are affective against cancer.

[0005] BTK inhibitors that have been reported are Ibrutinib (PCI-32765) and AVL-292. AVL-292 is manufactured by Avila Pharmaceuticals who have filed applications for protein kinases published as WO 2011/090760 and WO 2009/158571. Ibrutinib is disclosed in at least US 2008/0076921. Studies on Ibrutinib have found that it possesses a number of undesirable pharmacological features. For example, Ibrutinib is poorly soluble and is a weak inhibitor of hERG. Furthermore, rat pharmacokinetic data has shown that Ibrutinib has a low estimated fraction absorbed, poor bioavailability and a high clearance rate from the body, with a terminal $T_{1/2}$ of 1.5 hours.

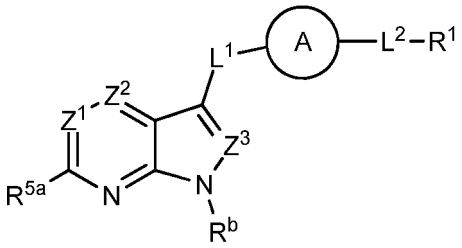
[0006] Since Ibrutinib was first disclosed there have been a number of patent applications concerned with structures closely related to Ibrutinib, for example see WO 2012/158843, WO 2012/158764, WO 2011/153514, WO 2011/046964, US 2010/0254905, US 2010/0144705, US 7718662, WO, 2008/054827 and WO 2008/121742.

[0007] Most recently, WO 2013/010136 disclosed BTK inhibitors with a related structure to Ibrutinib.

SUMMARY OF THE DISCLOSURE

[0008] In accordance with the present invention there is provided compounds as disclosed below. Furthermore, the invention provides compounds capable of inhibiting Bruton's tyrosine kinase (BTK) and the use of these compounds in inhibiting BTK. In accordance with the invention there is provided a method of treating conditions modulated by BTK. The invention provides compounds for use in treating a condition which is modulated by BTK.

[0009] In a first aspect of the invention there is provided a compound according to formula (**I**) and pharmaceutically acceptable salts and solvates thereof:



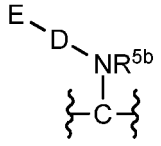
(I)

wherein

A is selected from substituted or unsubstituted phenyl, pyridinyl and pyrazolyl, and wherein the ring may be substituted by 1 to 4 R^a;

R^a is selected from the group comprising: H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OH, SH, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, NR^bR^c, -CN, acyl, $-C(O)R^b$, $-C(O)OR^b$, $-SO_2R^b$, and $-SO_3R^b$;

R^b and R^c are independently selected at each occurrence from: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} acyl, C_{3-7} cycloalkyl, and C_{3-7} halocycloalkyl;

one of Z^1 and Z^2 is  and the other is selected from CR^{5d} or N;

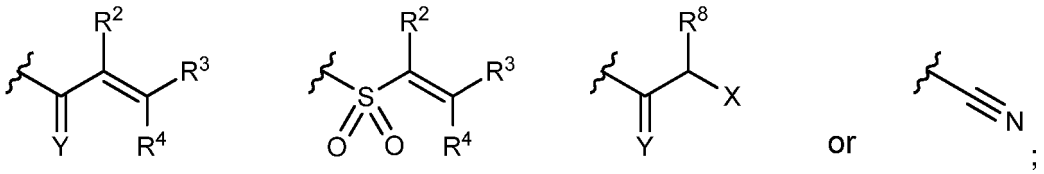
Z^3 is selected from CR^{5c} or N

D is either a substituted or unsubstituted C_{1-6} alkylene chain which is saturated or unsaturated and which may optionally also contain, where chemically possible, 1, 2 or 3 N, O, or S atoms in the chain which are independently chosen at each occurrence;

or D represents a substituted or unsubstituted carbocyclic or heterocyclic moiety which is saturated or unsaturated and which contains from 3 to 8 atoms in the carbocyclic or heterocyclic ring, wherein the ring is optionally substituted with $–NR^b-$, wherein $–NR^b-$ is bonded to the ring and the rest of the molecule;

and wherein, when substituted, the alkylene chain or the carbocyclic or heterocyclic moiety includes 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, $-OR^b$, $-SR^b$, $-NR^bR^c$, NO, =O, -CN, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, $-SO_2R^b$, and SO_3R^b , $-C(O)R^b$ and $C(O)OR^b$;

E is selected from:



;

Y is either O or NR^b and X is halo;

R^1 is $–NR^6R^7$, $-OR^9$, or a substituted or unsubstituted carbocyclic or heterocyclic moiety which is saturated, unsaturated or aromatic and which either contains from 3 to 8 atoms in a single ring or 7 to 14 atoms in a fused polycyclic ring system, when substituted, R^1 contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, $-OR^b$, $-SR^b$, $-NR^bR^c$, NO, =O, -CN, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, $-SO_2R^b$, and SO_3R^b , $-C(O)R^b$ and $C(O)OR^b$;

R^2, R^3, R^4 and R^8 are independently selected from H, halo, $-OR^b$, -CN, $-NR^bR^c$, $-CH_2NR^bR^c$, $-CO_2R^b$, $-C(O)R^b$, $-C(O)NR^bR^c$, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkyl substituted with C_{3-8} cycloalkyl, C_{1-6} alkyl substituted with C_{3-8} heterocycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{3-8} heterocycloalkyl, C_{3-8} cycloalkenyl, C_{3-8} heterocycloalkenyl, aryl, heteroaryl, alkaryl and alkheteroaryl;

or R^2 and R^3 taken together with the carbon atoms to which they are attached form a C_{3-8} cycloalkene and R^4 is independently selected as above;

or R^3 and R^4 taken together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl and R^2 is independently selected as above;

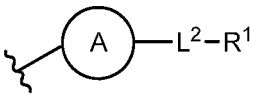
or R^2 and R^4 taken together with the carbon atoms to which they are attached form a C-C triple bond and R^3 is independently selected as above;

R^{5a}, R^{5b}, R^{5c} and R^{5d} are at each occurrence independently selected from H, halo, $-OR^b$, C_{1-6} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{3-8} heterocycloalkyl, C_{3-8} cycloalkenyl, C_{3-8} heterocycloalkenyl, $-NR^bR^c$, $-CO_2R^b$, $-C(O)R^b$ and $-C(O)NR^bR^c$;

R^6 , R^7 and R^9 may be independently be selected from H, substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, $-(CR^dR^e)_n$-aryl and $-SO_2R^b$, wherein n is 0, 1 or 2;

L^1 and L^2 are independently selected from a bond, -O-, $-O(CR^dR^e)_m$-, $-NR^b$-, $-C(O)NR^b$- and $-(CR^dR^e)_m$-, wherein R^d and R^e are independently selected at each occurrence from: H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} acyl, C_{3-7} cycloalkyl, and C_{3-7} halocycloalkyl; and

m is selected from 1, 2, 3 and 4.

[0010] In embodiments 

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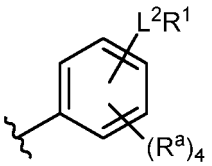
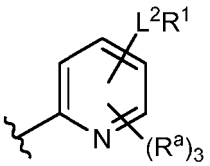
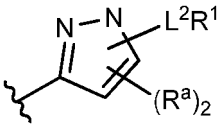
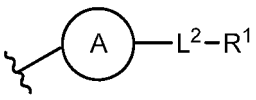






[0011] In embodiments 

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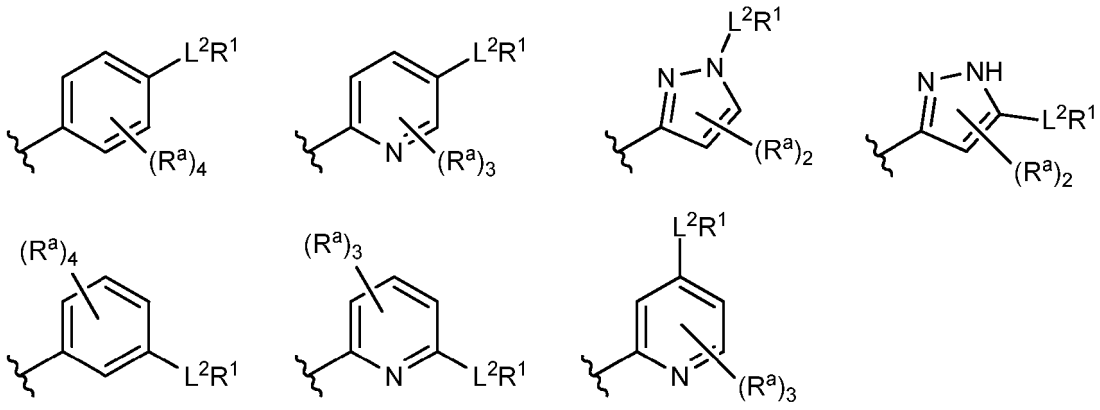


[0012] The group R^1 may be directly substituted on A in certain embodiments, i.e. where L^2 is absent. This R^1 group is an important part of the molecule and may be a carbocyclic or heterocyclic moiety. This group may be saturated or unsaturated and, when unsaturated may also contain an aromatic ring i.e. an aromatic portion as part of a fused or substituted ring system.

[0013] In certain embodiments independent of whether L is present or absent the group R^1 may be $–OR^9$ or a substituted or unsubstituted carbocyclic or heterocyclic moiety which is saturated, unsaturated or aromatic and which either contains from 3 to 8 atoms in a single ring or 7 to 14 atoms in a fused polycyclic ring system, wherein, when substituted, R^1 contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, $-OR^b$, $- SR^b$, $-NR^bR^c$, NO, =O, -CN, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, $-SO_2R^b$, and SO_3R^b , $-C(O)R^b$ and $C(O)OR^b$.

[0014] In certain embodiments R^1 is a substituted or unsubstituted carbocyclic or heterocyclic moiety and which is saturated, unsaturated or aromatic which contains from 3 to 8 atoms in a single ring, wherein, when substituted, R^1 contains 1 to 5 substituents independently selected at each occurrence from the group comprising: $-OR^b$, $- SR^b$, $-NR^bR^c$, NO, =O, -CN, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, $-SO_2R^b$, and SO_3R^b , $-C(O)R^b$ and $C(O)OR^b$.

[0015] In an alternative embodiment R^1 is a substituted or unsubstituted carbocyclic or heterocyclic moiety which is saturated, unsaturated or aromatic and which contains 7 to 14 atoms in a fused polycyclic ring system, wherein, when substituted, R^1 contains 1 to 5 substituents independently selected at each occurrence from the group comprising: $-OR^b$, $- SR^b$, $-NR^bR^c$, NO, =O, -CN, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, $-SO_2R^b$, and SO_3R^b , $-C(O)R^b$ and $C(O)OR^b$.

[0016] In embodiments R^1 is a substituted or unsubstituted carbocyclic moiety which is saturated, unsaturated or aromatic. In alternative embodiments R^1 is a substituted or unsubstituted heterocyclic moiety which is saturated, unsaturated or aromatic.

[0017] In any embodiment the carbocyclic moiety may be cycloalkyl, cycloalkenyl or aryl. Carbocyclic rings generally contain from 3 to 7 carbon atoms in a single ring or 7 to 14 atoms in a fused polycyclic ring system. In any embodiment the heterocyclic moiety may be heterocycloalkyl, heterocycloalkenyl or heteroaryl. Heterocyclic rings generally contain from 3 to 7 carbon atoms in a single ring or 7 to 14 atoms in a fused polycyclic ring system

[0018] In an embodiment R^1 is a substituted or unsubstituted heterocyclic moiety which is saturated, unsaturated or aromatic and the heteroatom is N. In an embodiment R^1 is a substituted or unsubstituted heterocycloalkyl, heterocycloalkenyl or heteroaryl, wherein the heteroatom is N. The heterocycloalkyl, heterocycloalkenyl or heteroaryl may have 1, 2 or 3 nitrogen atoms, optionally 1 or 2.

[0019] In any embodiment the carbocyclic moiety may be selected from substituted or unsubstituted: cycloheptanyl, cyclohexanyl, cyclohexenyl, cyclopentanyl, cyclopentenyl, cyclobutanyl, cyclopropanyl, indenyl, phenyl, tetralin and naphthyl.

[0020] In any embodiment the heterocyclic moiety may be selected from substituted or unsubstituted: piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, pyrolidinyl, imidazolidinyl, succinimidyl, pyrazolidinyl, tetrahydrofuranyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, oxetanyl, azetidinyl, oxiranyl, aziridinyl, oxepanyl, azepane, oxazepane, diazepane furanyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, dihydroindazolyl, dihydrobenzimidazolyl, qiunolinyl, isoquinolinyl, tetrahydroqiunolinyl, tetrahydroisoquinolinyl,phtalazinyl, tetrahydrophthalazinyl, quinazolinyl, tetrahydroquinazolinyl, chromanyl and isochromanyl.

[0021] In a further embodiment R^1 may be a substituted or unsubstituted ring selected from: piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, pyrolidinyl, imidazolidinyl, succinimidyl, pyrazolidinyl, tetrahydrofuranyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, oxetanyl, azetidinyl, oxiranyl, aziridinyl, oxepanyl, azepane, oxazepane and diazepane, wherein the ring may be bound to L^2 through either a N atom or a C atom. R^1 may be a substituted or unsubstituted ring selected from: furanyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl, wherein the ring may be bound to L^2 through either a N atom or a C atom. R^1 may be a substituted or unsubstituted ring selected from: indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, dihydroindazolyl, dihydrobenzimidazolyl, qiunolinyl, isoquinolinyl,

tetrahydroqiunolinyl, tetrahydroisoquinolinyl,phtalazinyl, tetrahydrophthalazinyl, quinazolinyl, tetrahydroquinazolinyl, chromanyl and isochromanyl.

[0022] In an embodiment, R^1 may be a substituted or unsubstituted ring selected from: cycloheptanyl, cyclohexanyl, cyclohexenyl, cyclopentanyl, cyclopentenyl, cyclobutanyl, cyclopropanyl, indenyl. R^1 may be a substituted or unsubstituted ring selected from phenyl, tetralin or naphthyl.

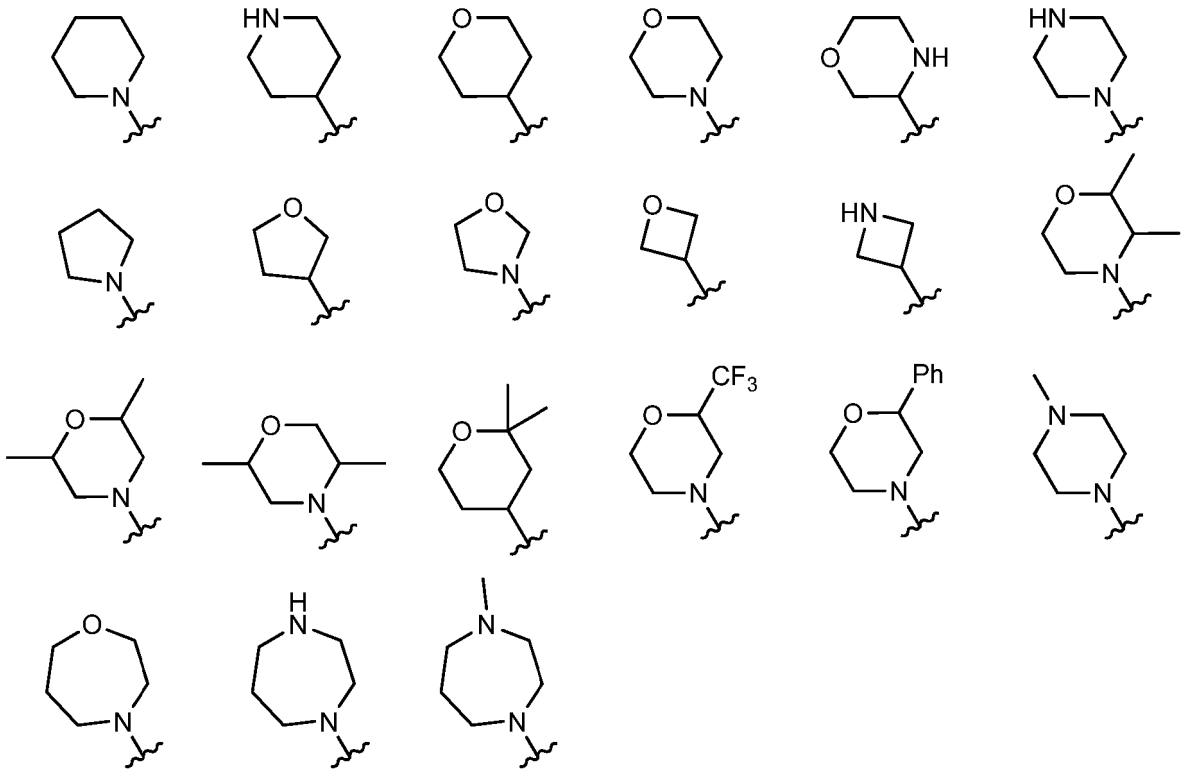
[0023] In a further embodiment R^1 may be a substituted or unsubstituted ring selected from: phenyl, pyridiyl piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, pyrolidinyl, imidazolidinyl, succinimidyl, pyrazolidinyl, tetrahydrofuranyl, oxazolidinyl, isoxazolidinyl, azetidinyl, oxetanyl, aziridinyl, azepane, oxazepane and diazepane, wherein the ring may be bound to L^2 through either a N atom or a C atom.

[0024] In an embodiment R^1 is selected from substituted or unsubstituted: $-OC_{1-4}$ alkyl, phenyl, morpholinyl, pyridiyl, benzosuccinimidyl, quinolinyl and isoquinolinyl.

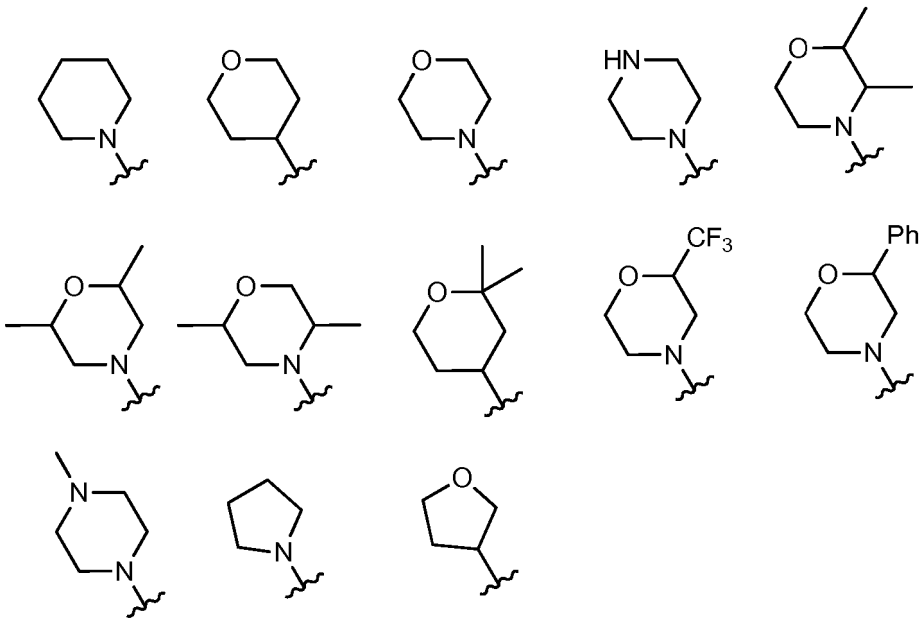
[0025] In an embodiment R^1 is selected from substituted or unsubstituted: $-OC_{1-4}$ alkyl, phenyl, morpholinyl and pyridiyl.

[0026] In a preferred embodiment R^1 morpholinyl, phenyl, or methoxy.

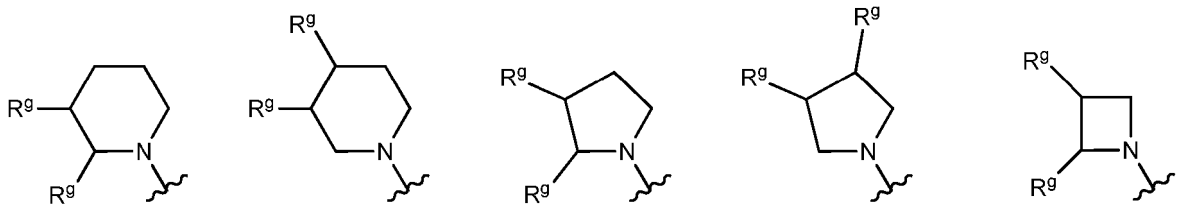
[0027] In a further embodiment, the group defined by R^1 in any of the compounds of the invention may be selected from substituted or unsubstituted:



[0028] In a preferred embodiment, the group defined by R^1 in any of the compounds of the invention may be selected from substituted or unsubstituted:

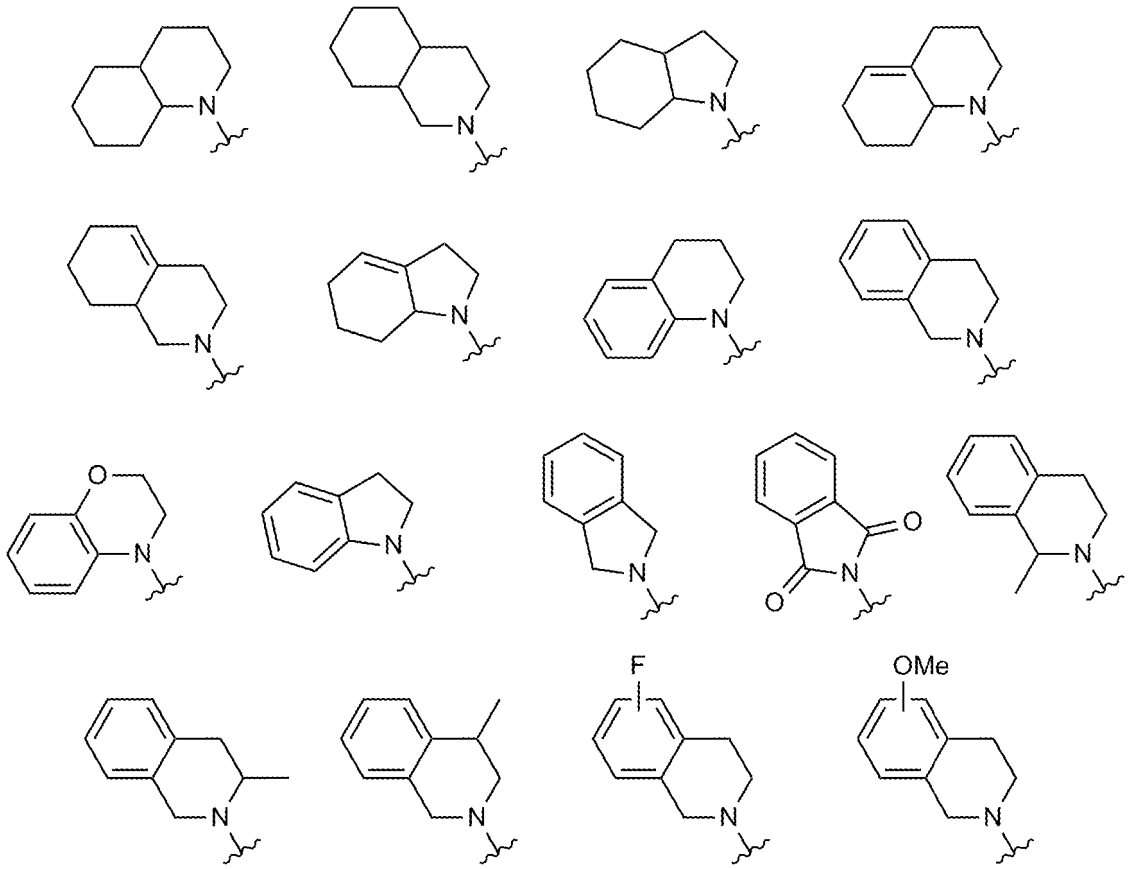


[0029] In an embodiment R^1 may be selected from substituted or unsubstituted:

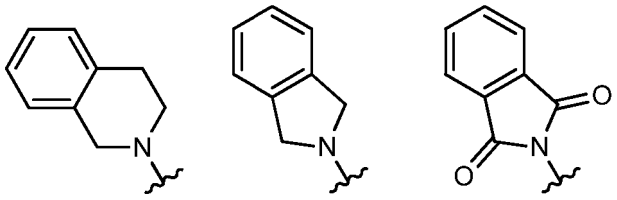


wherein two R^g groups form a C_{4-8} ring with the carbon atoms to which they are attached, wherein the C_{4-8} ring is a saturated or unsaturated hydrocarbon ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated hydrocarbon ring with 4, 5, 6, 7, or 8 carbon atoms and 1, 2 or 3 heteroatoms.

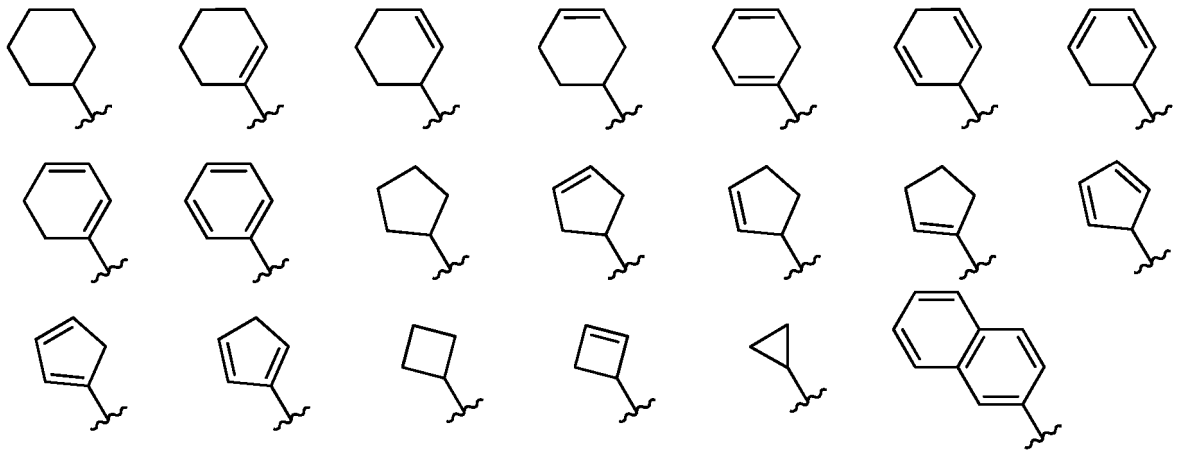
[0030] In an embodiment, R^1 is selected from substituted or unsubstituted:



[0031] In an embodiment R^1 is selected from substituted or unsubstituted:



[0032] In an embodiment, the group defined by R^1 in any of the compounds of the invention may be selected from substituted or unsubstituted:



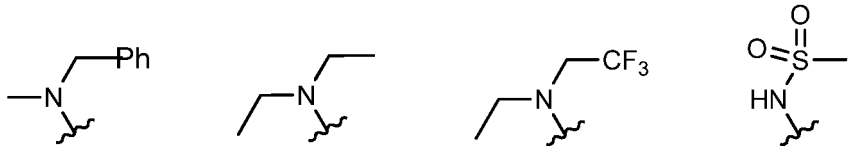
[0033] In an embodiment R^1 is $-NR^6R^7$.

[0034] In embodiments R^6 and R^7 are independently selected from: H, C_{1-6} alkyl, C_{1-6} haloalkyl, -$(CR^dR^e)_n$ -aryl and $–SO_2R^b$, wherein n is 0, 1 or 2.

[0035] In embodiments R^6 is C_{1-6} alkyl and R^7 is C_{1-6} alkyl, C_{1-6} haloalkyl, -$(CR^dR^e)_n$ -aryl, wherein n is 0, 1 or 2.

[0036] In embodiments R^6 is methyl, ethyl or propyl and R^7 is methyl, ethyl or propyl. In embodiments R^6 is methyl or ethyl and R^7 is C_{1-6} haloalkyl, optionally C_{1-6} fluoroalkyl. In embodiments R^6 is methyl, ethyl or propyl and R^7 is $–(CH_2)_n$ -phenyl wherein n is 0 or 1. In embodiments R^6 is H and R^7 is $–SO_2R^b$, wherein R^b is methyl, ethyl or fluoromethyl.

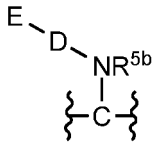
[0037] In an embodiment, the group defined by R^1 in any of the compounds of the invention may be selected from substituted or unsubstituted:



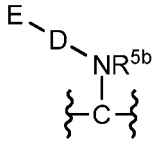
[0038] In an embodiment R^1 is $–OR^9$.

[0039] In embodiments R^9 is independently selected from: H, C_{1-6} alkyl, C_{1-6} haloalkyl, -$(CR^dR^e)_n$ -aryl and $–SO_2R^b$, wherein n is 0, 1 or 2.

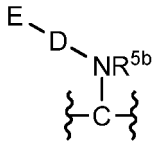
[0040] In embodiments R^9 is C_{1-6} alkyl, optionally methyl.

[0041] In an embodiment Z^1 is 

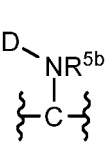
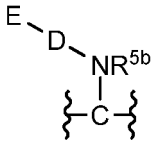
and Z^2 is selected from CR^{5d} or N. In an embodiment Z^2 is CR^{5d}. In an alternative embodiment Z^2 is N.

[0042] In an embodiment Z^2 is 

and Z^1 is selected from CR^{5d} or N. In an embodiment Z^1 is CR^{5d}. In an alternative embodiment Z^1 is N.

[0043] In an embodiment Z^1 is 

, Z^2 is N and Z^3 is CR^{5c}.

[0044] In an embodiment Z^1 is N, Z^2 is  and Z^3 is CR^{5c}. In an embodiment Z^1 is N, Z^2 is  and Z^3 is N.

[0045] In an embodiment D is either a substituted or unsubstituted C_{1-6} alkylene chain which is saturated or unsaturated and which may optionally also contain, where chemically possible, 1, 2 or 3 N, O, or S atoms in the chain which are independently chosen at each occurrence;

or wherein D represents a substituted or unsubstituted carbocyclic or heterocyclic moiety which is saturated or unsaturated and which contains from 3 to 8 atoms in the carbocyclic or heterocyclic ring;

and wherein, when substituted, the alkylene chain or the carbocyclic or heterocyclic moiety includes 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, $-OR^b$, $-SR^b$, $-NR^bR^c$, NO, =O, -CN, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, $-SO_2R^b$, and SO_3R^b , $-C(O)R^b$ and $C(O)OR^b$.

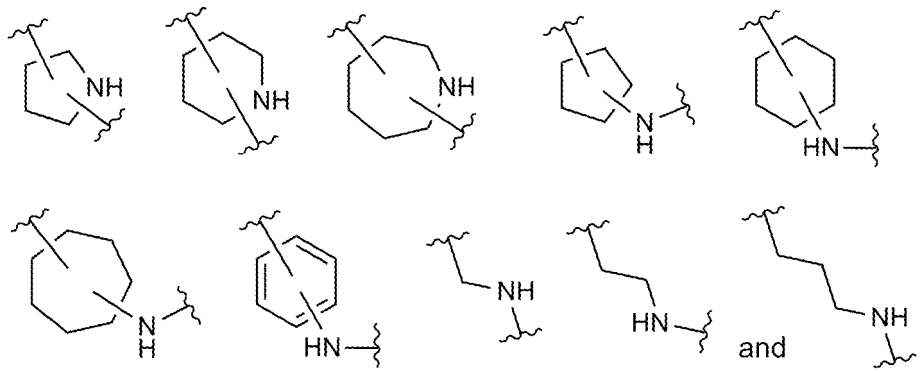
[0046] In an embodiment, D is selected from a substituted or unsubstituted saturated C_{1-6} alkylene chain containing, where chemically possible, 1, 2 or 3, optionally 1 or 2, N, O or S atoms in the chain which are independently chosen at each occurrence;

or D represents a substituted or unsubstituted saturated heterocyclic moiety which contains from 3 to 8 atoms in the heterocyclic ring and contains, where chemically possible, 1, 2 or 3, optionally 1 or 2, N, O or S atoms in the ring which are independently chosen at each occurrence. In embodiments the alkylene chain and the heterocyclic ring contain 1 heteroatom selected from N, O or S, optionally N. In embodiments the alkylene chain and the heterocyclic ring contain 1 nitrogen atom and the nitrogen atom is the point of connection with group E.

[0047] In an embodiment, D is selected from substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-8} heterocycloalkyl and substituted or unsubstituted C_{3-8} heterocycloalkenyl. In embodiments D may be selected from substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-8} heterocycloalkyl and substituted or unsubstituted C_{3-8} heterocycloalkenyl where N is the heteroatom and D comprises 1 or 2 nitrogen atoms.

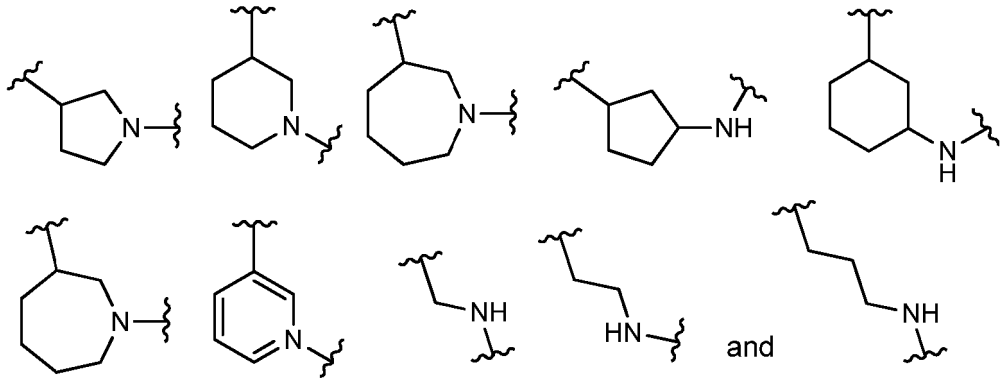
[0048] In an embodiment D is unsubstituted. In an alternative embodiment D is substituted. In an embodiment D is substituted with halo, optionally fluoro.

[0049] In an embodiment, D may be selected from:

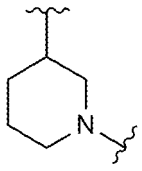


and D may be substituted or unsubstituted. In particular, D may be unsubstituted.

[0050] In an embodiment, D may be selected from:

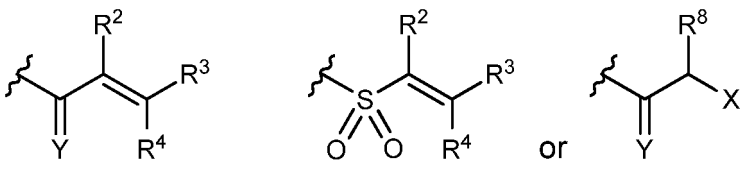


[0051] In an embodiment, D may be:

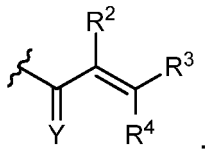


[0052] Optionally, D is substituted by a halo group, for example, fluoro.

[0053] In an embodiment E is:



[0054] In one embodiment E is:



[0055] In embodiments Y is O. In alternative embodiments Y is NR^a wherein R^a is H or methyl.

[0056] In embodiments X is chloro, bromo or fluoro, optionally chloro.

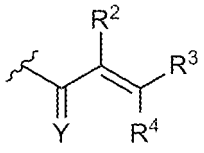
[0057] In an embodiment, R^2, R^3, R^4 and R^8 may be independently selected from hydrogen, fluorine, chlorine, bromine, iodine, -CN, $-CH_2NR^bR^c$, C_{1-6} alkyl, C_{1-6} alkyl substituted with C_{3-8} cycloalkyl, C_{1-6} alkyl substituted with C_{3-8} heterocycloalkyl, C_{1-6} haloalkyl, aryl, heteroaryl, alkaryl and alkheteroaryl.

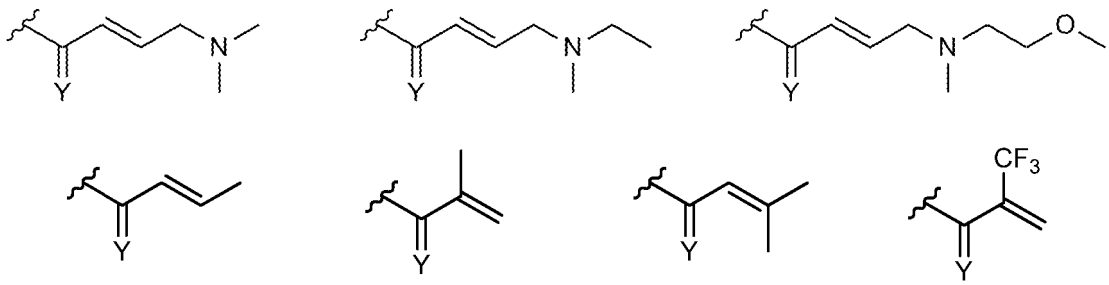
[0058] In another embodiment, R^2, R^3, R^4 and R^8 may be independently selected from hydrogen, fluorine, chlorine, bromine, iodine, -CN, $-CH_2NR^bR^c$ and C_{1-6} alkyl, where R^b and R^c are independently selected from hydrogen and C_{1-6} alkyl.

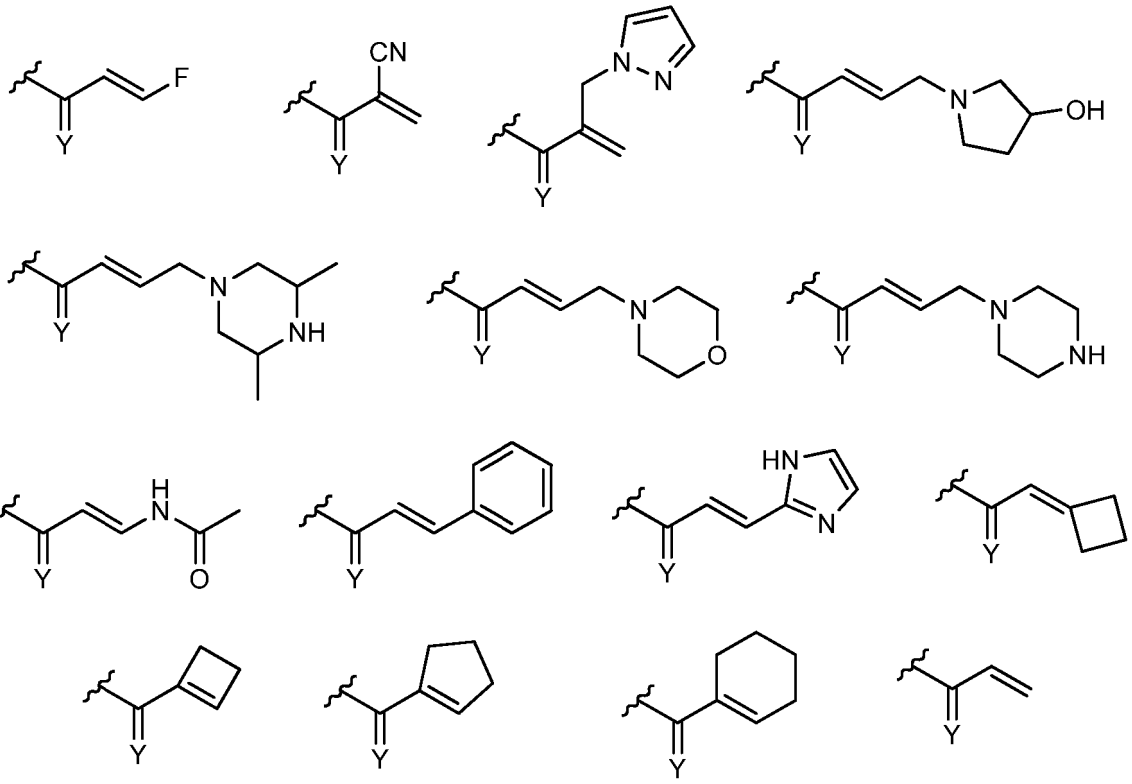
[0059] In an embodiment, two of R^2, R^3 and R^4 may be hydrogen and the other may be fluorine, chlorine, bromine, iodine, -CN, $-CH_2NR^bR^c$ and C_{1-6} alkyl, where R^b and R^c are independently selected from hydrogen and C_{1-6} alkyl, e.g. R^2 and R^3 may be hydrogen; or R^3 and R^4 may be hydrogen; or R^2 and R^4 may be hydrogen.

[0060] In a preferred embodiment, R^2, R^3, and R^4 are all hydrogen.

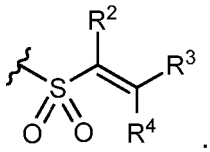
[0061] In an embodiment R^8 is selected from H, C_{1-6} alkyl (eg methyl, ethyl) and aryl.

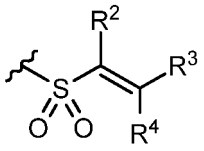
[0062] In all embodiments  , wherein Y is O or NR^b, may be selected from:

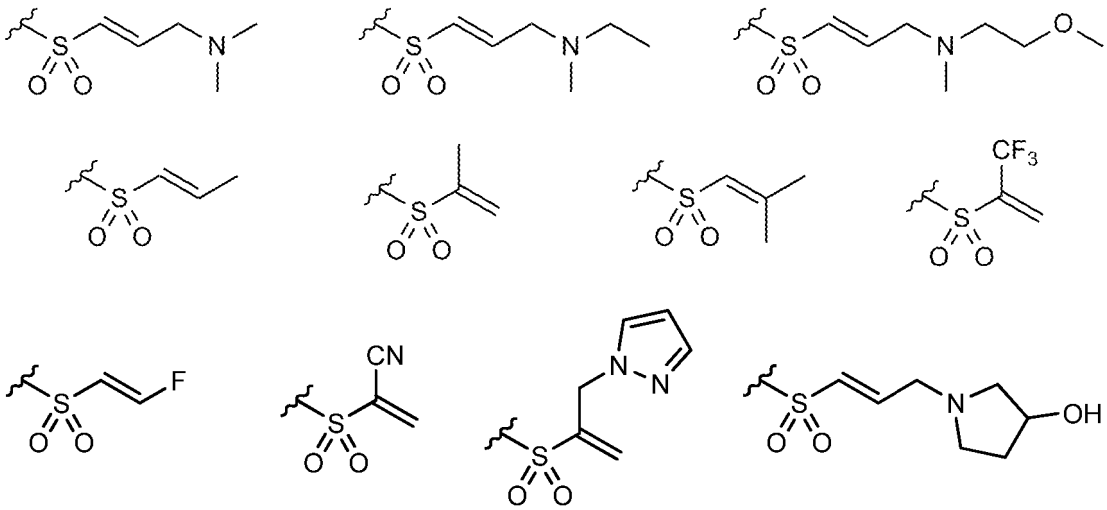


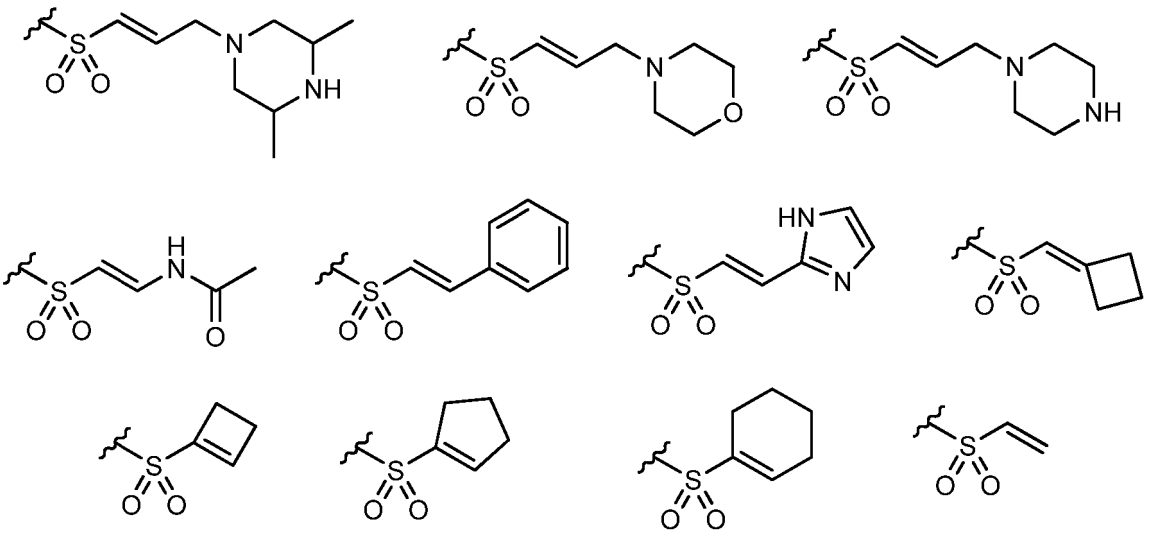


[0063] In another embodiment E is:

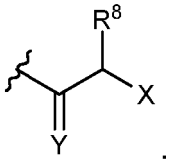


[0064] In all embodiments  may be selected from:

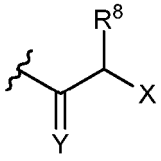


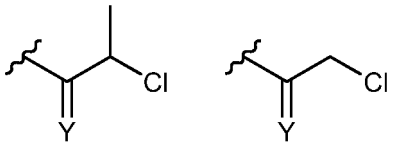


[0065] In an embodiment E is:

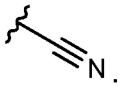


.

[0066] In all embodiments  , wherein Y is O or NR^a, may be selected from:



[0067] In an alternative embodiment E is:



.

[0068] In an embodiment, R^{5a}, R^{5b}, R^{5c} and R^{5d} are hydrogen or methyl.

[0069] In an embodiment, R^a is hydrogen.

[0070] In an embodiment, R^b and R^c are independently selected from hydrogen or methyl. Optionally, R^b and R^c may be hydrogen. In an embodiment R^b is H or methyl and R^c is H.

[0071] In an embodiment, R^d and R^e are independently selected from hydrogen, methyl or fluoro. Optionally, R^d and R^e may be hydrogen.

[0072] In embodiments L^2 is selected from a bond, $–O(CR^dR^e)_m$- $-(CR^dR^e)_m$-, -O-, $–NR^b$- and $–C(O)NR^b$-. In embodiments m is 1 or 2, optionally m is 1. In embodiments R^d and R^e are independently selected from hydrogen, fluorine, chlorine, bromine, iodine, C_{1-6} alkyl and C_{1-6} haloalkyl and R^b is selected from hydrogen, C_{1-6} alkyl and C_{1-6} haloalkyl. In embodiments R^b, R^d and R^e are independently hydrogen or C_{1-6} alkyl.

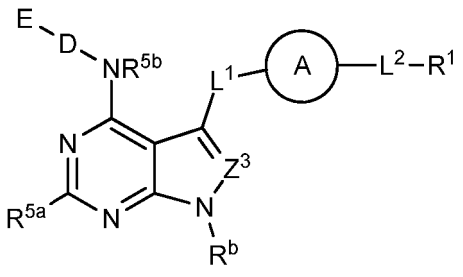
[0073] In embodiments L^2 is selected from a bond, $–OCH_2$-, $-CH_2$-, -O-, –NH-and C(O)NH-, optionally $-CH_2$-, -O- or $-NH_2$-.

[0074] In embodiments L^1 is selected from a bond, $-(CR^dR^e)_m$-, -O- and $–NR^b$-. In embodiments m is 1 or 2, optionally m is 1. In embodiments R^d and R^e are independently selected from hydrogen, fluorine, chlorine, bromine, iodine, C_{1-6} alkyl and C_{1-6} haloalkyl and R^b is selected from hydrogen, C_{1-6} alkyl and C_{1-6} haloalkyl. In embodiments R^b, R^d and R^e are independently hydrogen or C_{1-6} alkyl.

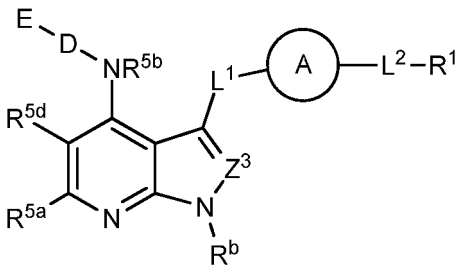
[0075] In embodiments L^1 is selected from a bond, $-CH_2$-, -O- and –NH-, optionally a bond or $-CH_2$-.

[0076] The embodiments and definitions of the various substituents, R^1 etc, described above may be applied individually, or in any combination of one another, and independently, to the compounds of the invention.

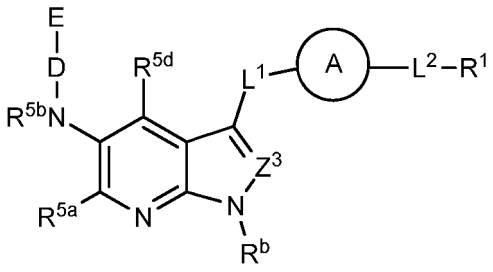
[0077] In embodiments the compound of formula (**I**) is a compound according to formula (**II**), a compound according to formula (**III**) or a compound according to formula (**IV**) and pharmaceutically acceptable salts and solvates thereof:



(**II**)

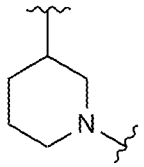


(**III**)

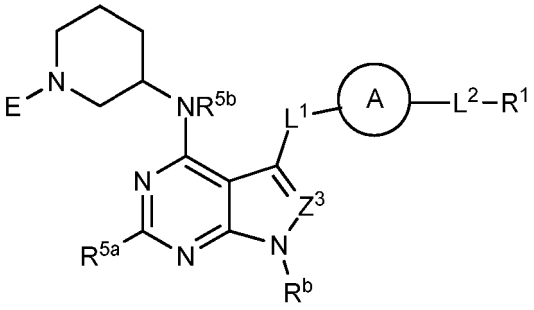


(**IV**)

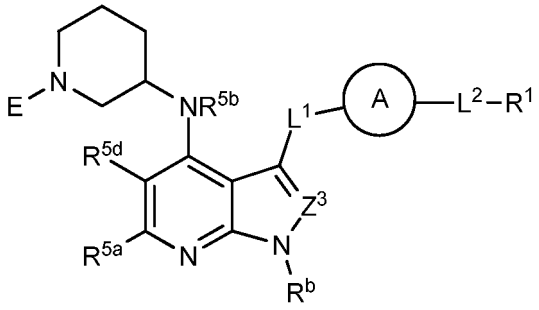
[0078] In the case when D is:



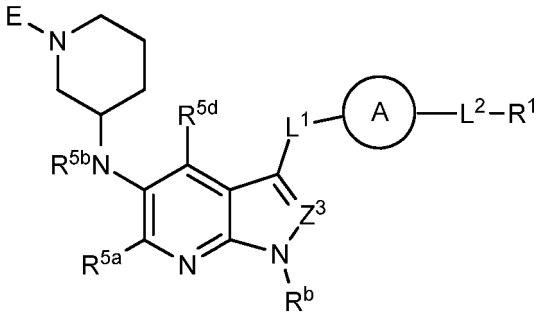
the compound of formula **(I)** may be a compound according to formula (**V**), a compound according to formula (**VI**) or a compound according to formula (**VII**) and pharmaceutically acceptable salts and solvates thereof:



(**V**)

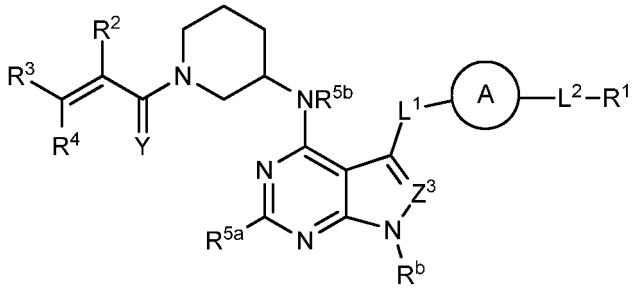


(**VI**)

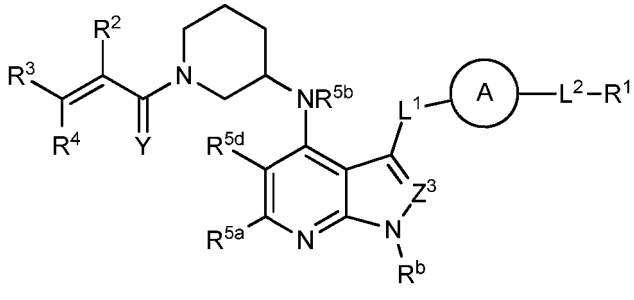


(**VII**)

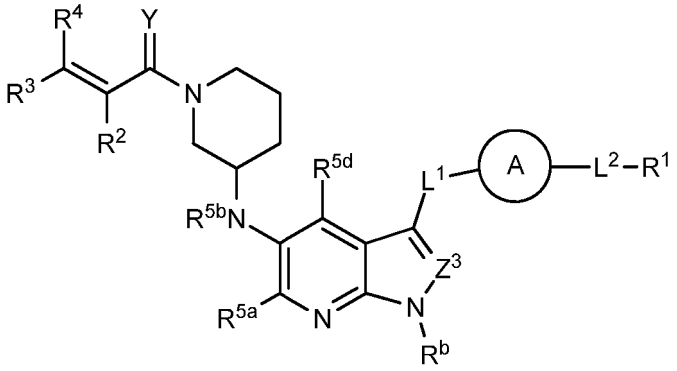
[0079] In embodiments the compound of formula **(I)** is a compound according to formula (**Va**), a compound according to formula (**VIa**) or a compound according to formula (**VIIa**) and pharmaceutically acceptable salts and solvates thereof:



(**Va**)

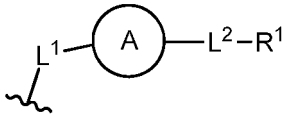


(**VIa**)

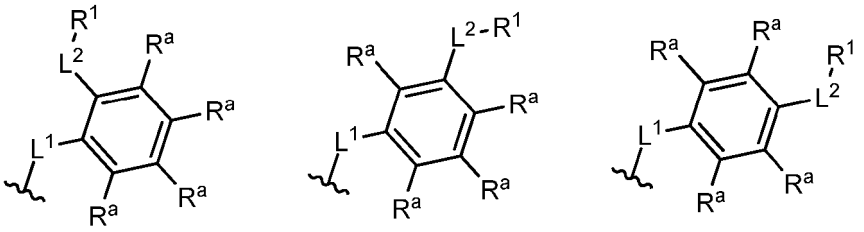


(**VIIa**)

[0080] In all embodiments, the group represented by:

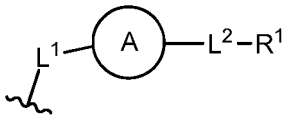


may be selected from:

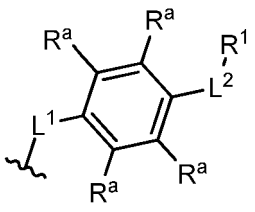


[0081] In all embodiments R^a may be selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OH and C_{1-6} alkoxy. In particular, R^a may be H.

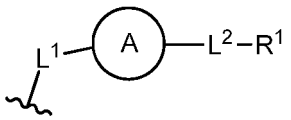
[0082] The group represented by:



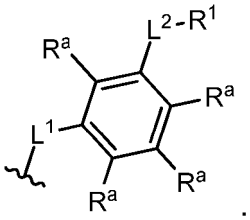
may be



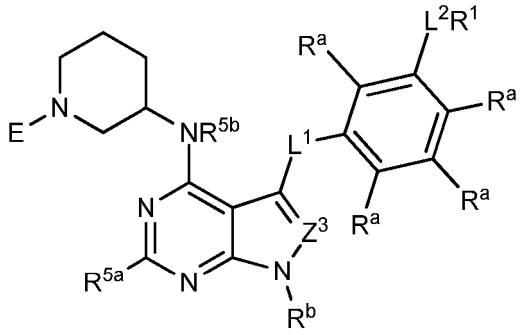
[0083] In particular, the group represented by:



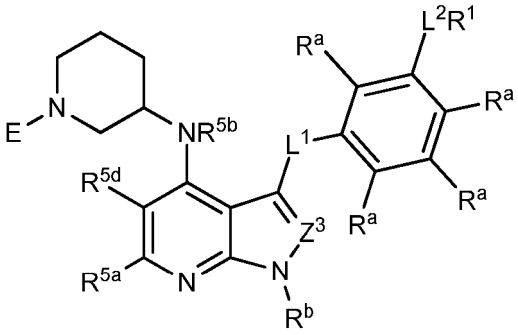
may be



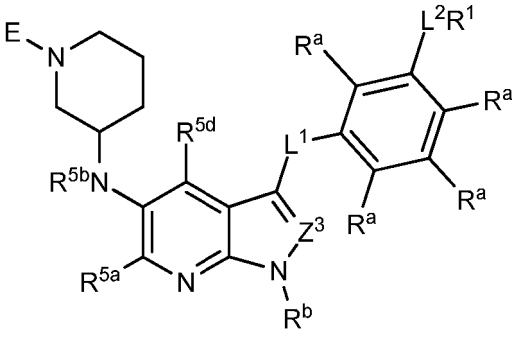
[0084] In embodiments, the compound of formula (**I**) is a compound according to formula (**VIII**), a compound according to formula (**IX**) or a compound according to formula (**X**) and pharmaceutically acceptable salts and solvates thereof:



(**VIII**)



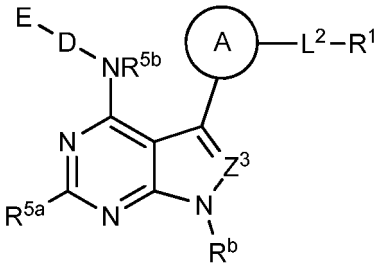
(**IX**)



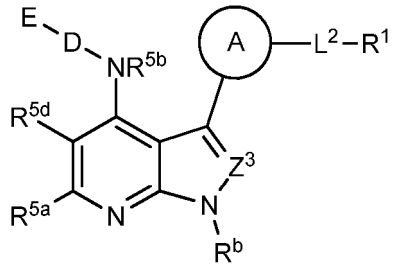
(**X**)

[0085] In all embodiments L^1 may be selected from a bond, -O-, $-NH_2-$ and $-CH_2-$. In all embodiments L^2 may be selected from a bond, -O-, $-NH_2-$ and $-CH_2-$. L^1 may be a bond. L^2 may be -O- or $-CH_2-$. In embodiments L^1 is a bond and L^2 is -O-. In embodiments L^1 is a bond and L^2 is $-CH_2-$.

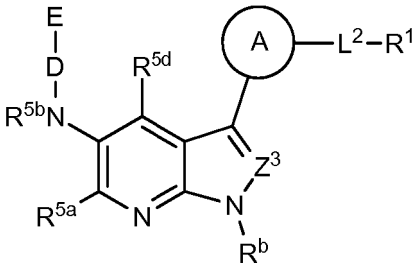
[0086] In embodiments the compound of formula (**I**) may be a compound according to formula (**XI**), a compound according to formula (**XII**) or a compound according to formula (**XIII**) and pharmaceutically acceptable salts and solvates thereof:



(**XI**)

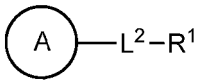


(**XII**)

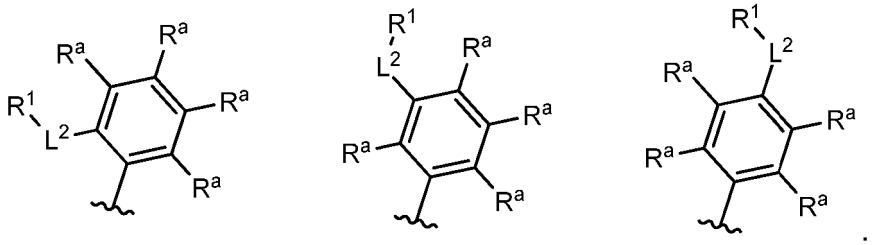


(**XIII**)

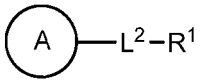
[0087] In all embodiments where L^1 is a bond, the group represented by:



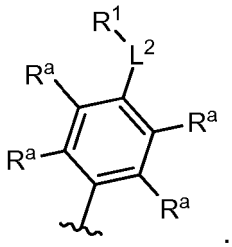
may be selected from:



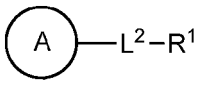
[0088] The group represented by:



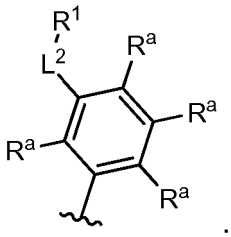
may be



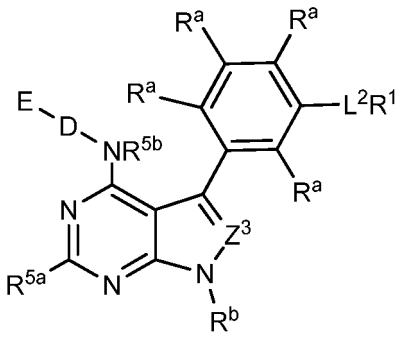
[0089] In particular, the group represented by:



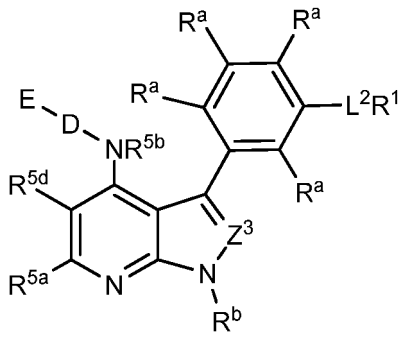
may be



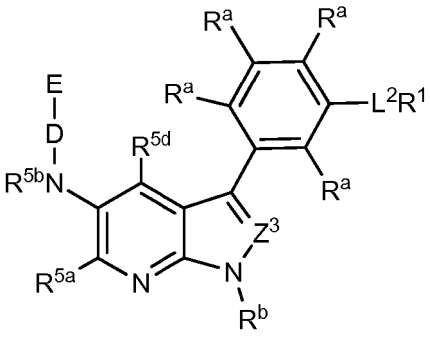
[0090] Therefore, the compound of formula (**I**) may be a compound according to formula (**XIV**), a compound according to formula (**XV**) or a compound according to formula (**XVI**) and pharmaceutically acceptable salts and solvates thereof:



(**XIV**)

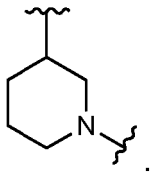


(**XV**)

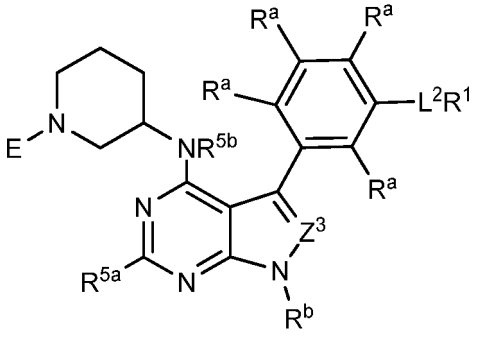


(**XVI**)

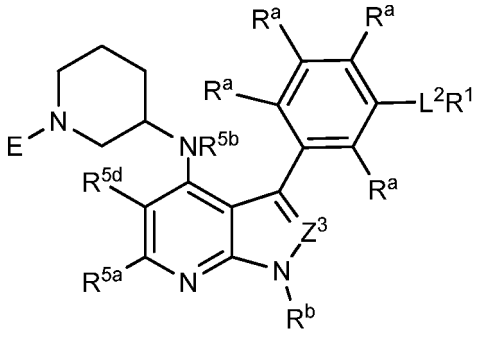
[0091] In embodiments, L^1 may be a bond and D may be:



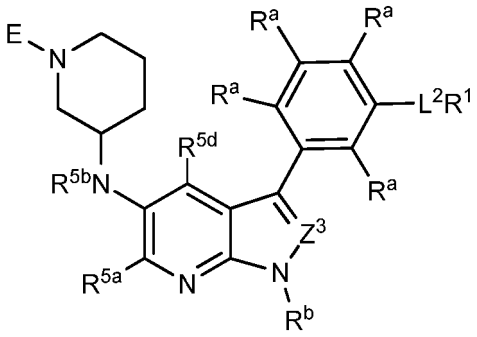
[0092] The compounds of formula (**I**) may be a compound according to formula (**XVII**), a compound according to formula (**XVIII**) or a compound according to formula (**XIX**) and pharmaceutically acceptable salts and solvates thereof:



(**XVII**)

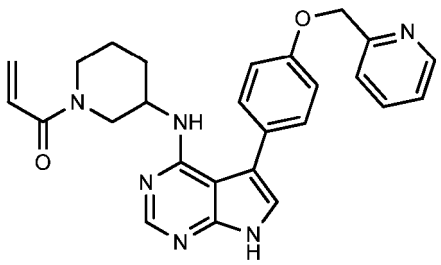


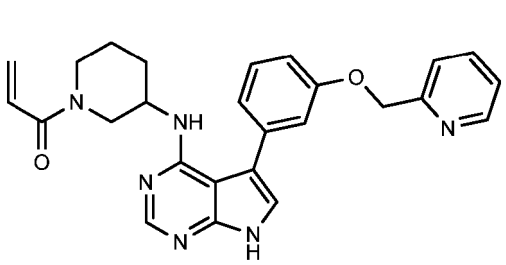
(**XVIII**)

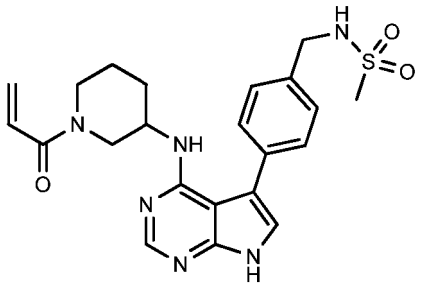


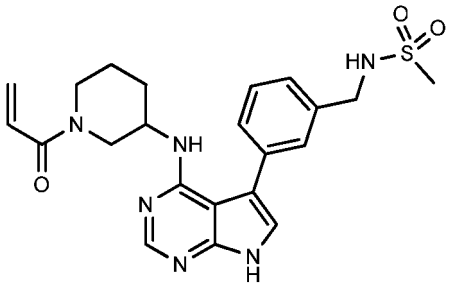
(**XIX**)

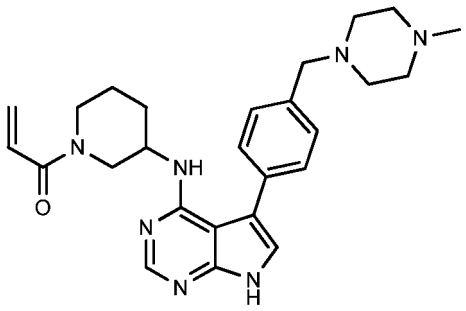
[0093] Compounds of the invention include:

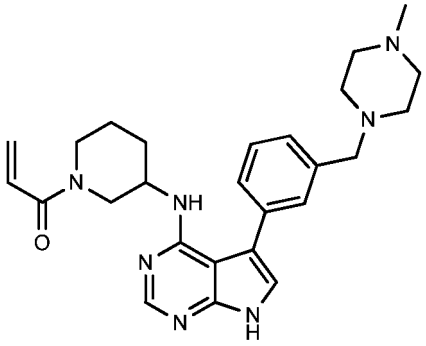


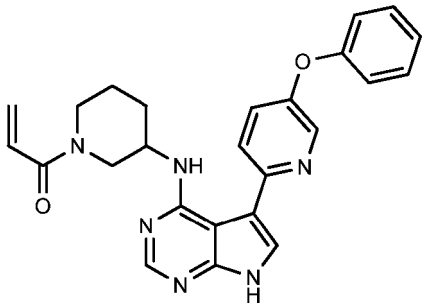


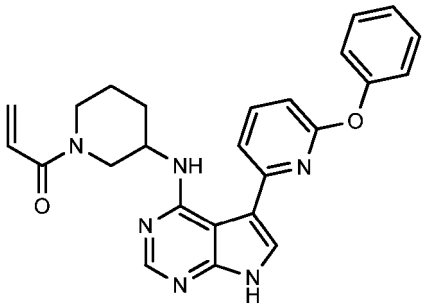


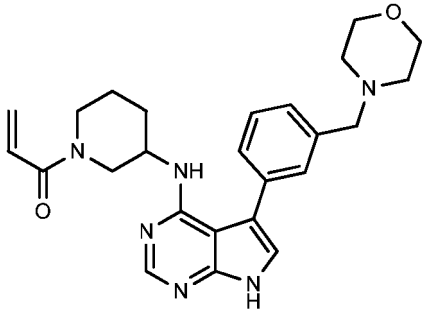


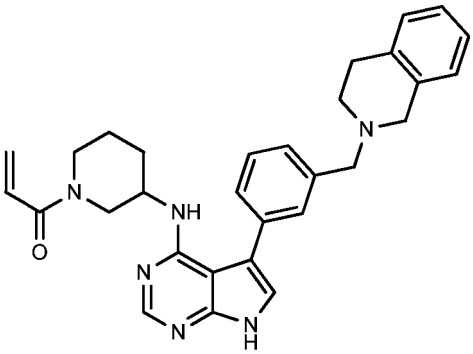


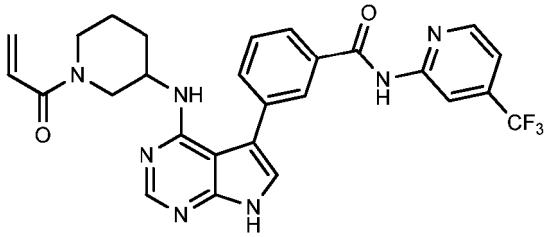


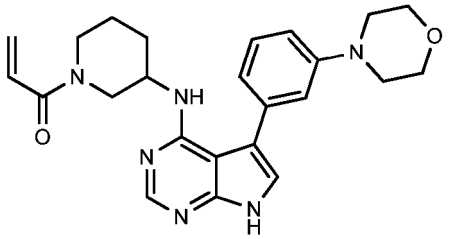


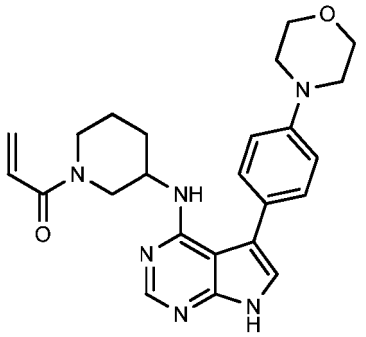


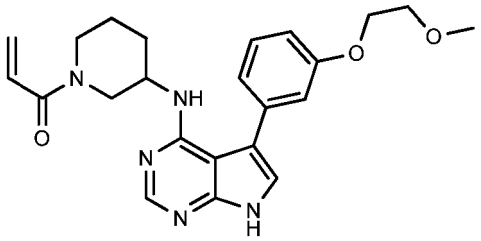


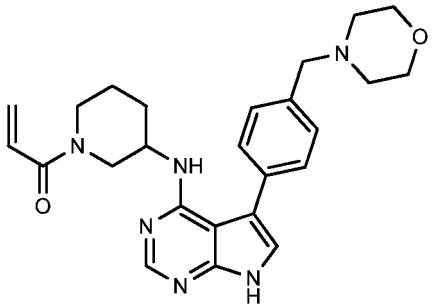


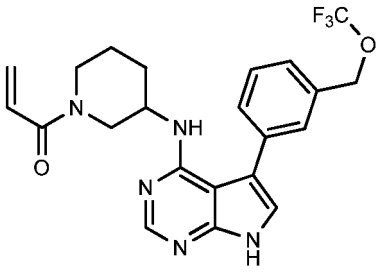


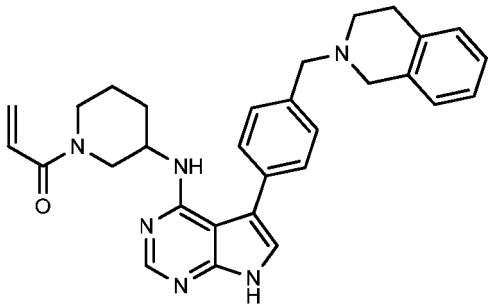


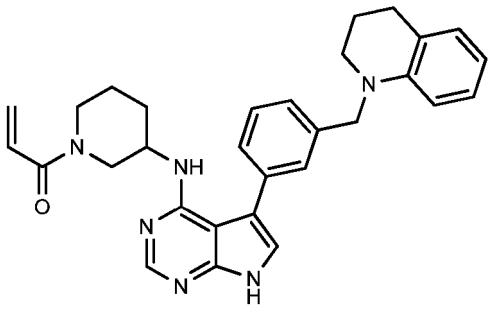


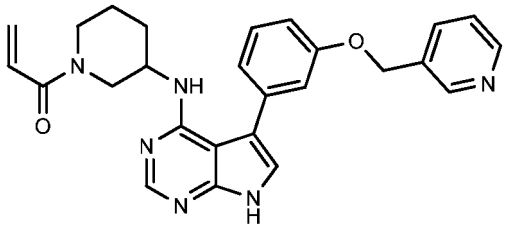


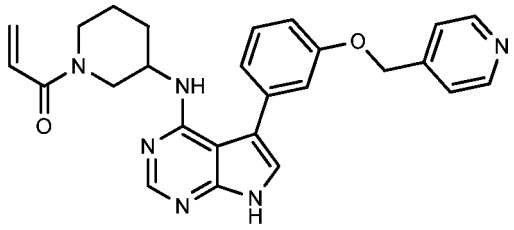


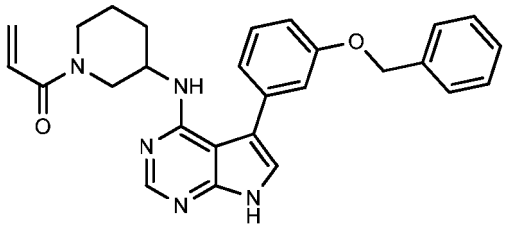


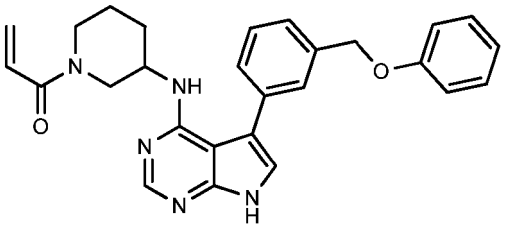


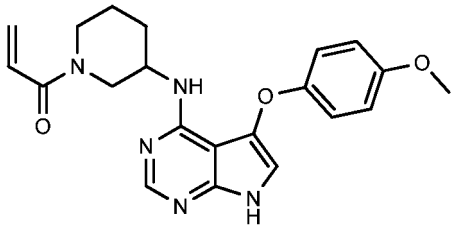




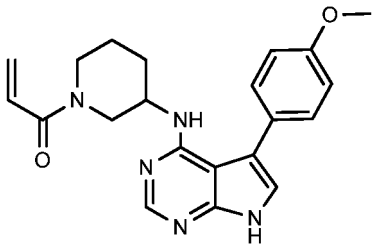


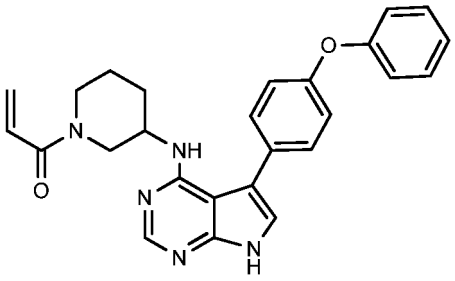


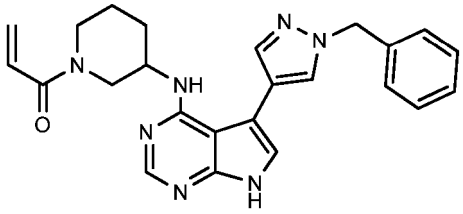


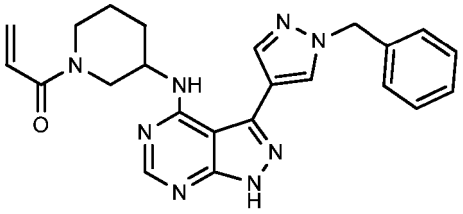


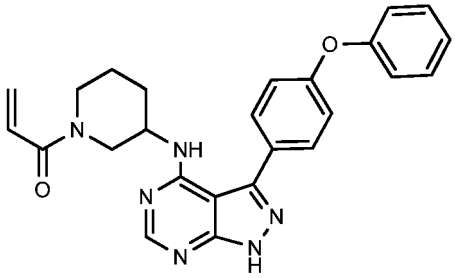
[0094] Preferred compounds of the invention include:

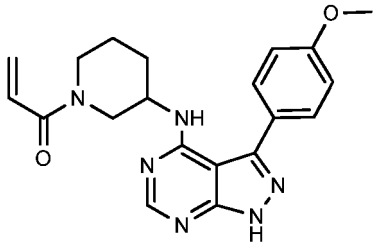


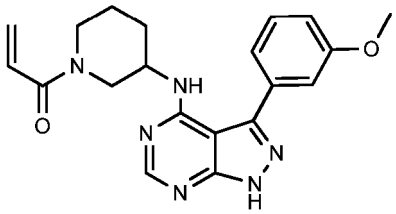


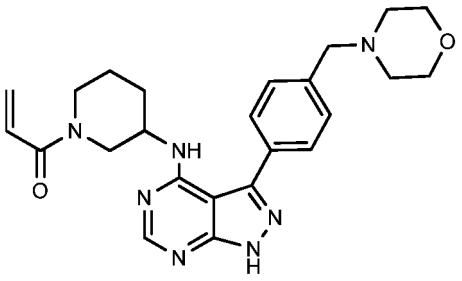


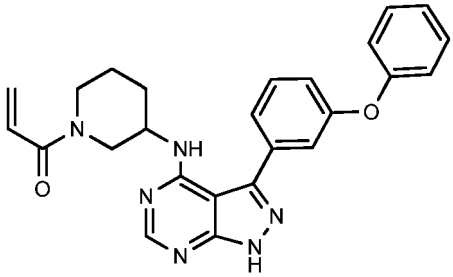


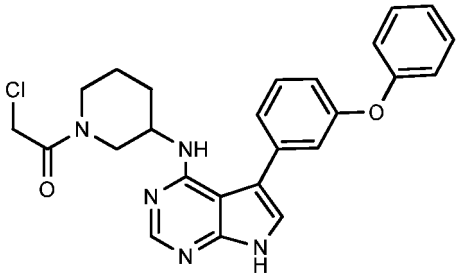


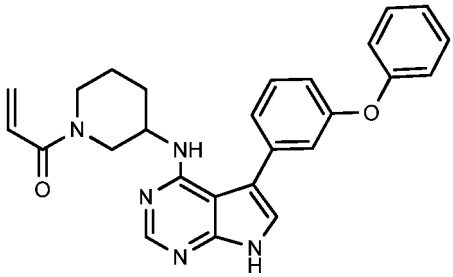


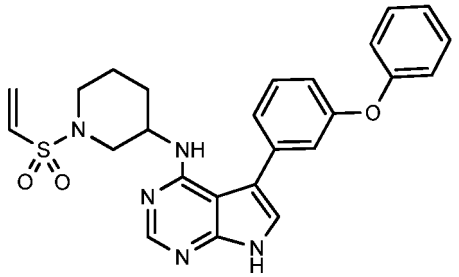


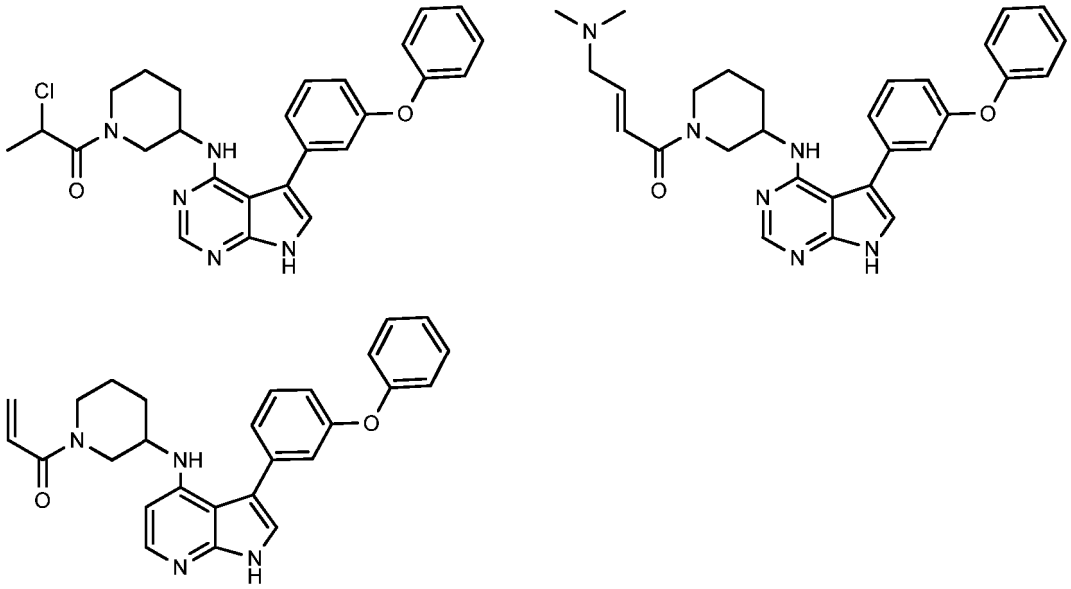












[0095] In another aspect of the invention there is provided a compound of formula (**I**) for use as a medicament.

[0096] In another aspect a compound of formula (**I**) is for use in the treatment of a condition which is modulated by Bruton's tyrosine kinase (BTK). Usually conditions that are modulated by BTK are conditions that would be treated by the inhibition of BTK using a compound of the present invention. A compound of formula (**I**) may be for use in the treatment of a condition treatable by the inhibition of Bruton's tyrosine kinase (BTK).

[0097] BTK inhibition is a novel approach for treating many different human diseases associated with the inappropriate activation of B-cells, including B-cell malignancies, immunological disease for example, autoimmune and inflammatory disorders. In embodiments the condition treatable by the inhibition of BTK may be selected from: cancer, lymphoma, leukemia, autoimmune diseases and inflammatory disorders. Specific conditions treatable by the inhibition of BTK may be selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkins lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkins lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease and lupus.

[0098] B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkins lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkins lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer and bone metastasis are examples of cancer, lymphomas and leukemias treatable by BTK inhibition.

[0099] Arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease and lupus are examples of immunological diseases treatable by BTK inhibition. Arthritis is an example of an inflammatory disorder treatable by BTK inhibition. Lupus is an example of an autoimmune disease treatable by BTK inhibition.

[00100] In embodiments, a compound of the invention may be for use in the treatment of: cancer, lymphoma, leukemia and immunological diseases. The compound of the invention may be for use in the treatment of specific conditions selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkins lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkins lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease and lupus. The compounds may also be used for the treatment of disorders associated with renal transplant.

[00101] In an embodiment the compound of the invention may be for use in the treatment of specific conditions selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkins lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkins lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, lupus and arthritis.

[00102] In an aspect of the invention there is provided a method of treatment of a condition which is modulated by Bruton's tyrosine kinase, wherein the method comprises administering a therapeutic amount of a compound of the invention, to a patient in need thereof.

[00103] The method of treatment may be a method of treating a condition treatable by the inhibition of Bruton's tyrosine kinase.

[00104] The invention also provides a method of treating a condition selected from: cancer, lymphoma, leukemia and immunological diseases, wherein the method comprises administering a therapeutic amount of a compound of the invention, to a patient in need thereof. The invention also provides a method of treating a specific condition selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkins lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkins lymphoma,

Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease and lupus, wherein the method comprises administering a therapeutic amount of a compound of formula (**I**), to a patient in need thereof. The method may also treat disorders associated with renal transplant.

[00105] In an embodiment the method may be for treating a specific condition selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkins lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkins lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, arthritis and lupus.

[00106] In another aspect of the invention there is provided a pharmaceutical composition, wherein the composition comprises a compound of the invention and pharmaceutically acceptable excipients.

[00107] In an embodiment the pharmaceutical composition may be a combination product comprising an additional pharmaceutically active agent. The additional pharmaceutically active agent may be an anti-tumor agent described below.

[00108] In an aspect of the invention there is provided a use of a compound of formula (**I**) in the manufacture of a medicament for the treatment of a condition which is modulated by Bruton's tyrosine kinase (BTK). The condition may be any of the conditions mentioned above.

DETAILED DESCRIPTION

[00109] Given below are definitions of terms used in this application. Any term not defined herein takes the normal meaning as the skilled person would understand the term.

[00110] The term "halo" refers to one of the halogens, group 17 of the periodic table. In particular the term refers to fluorine, chlorine, bromine and iodine. Preferably, the term refers to fluorine or chlorine.

[00111] The term "C_{1-6} alkyl" refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5 or 6 carbon atoms, for example methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl and n-hexyl. Alkylene groups may likewise be linear or branched and may have two places of attachment to the remainder of the molecule. Furthermore, an alkylene group may, for example, correspond to one of those alkyl groups listed in this paragraph. The alkyl and alkylene groups may be unsubstituted or substituted by one or

more substituents. Possible substituents are described below. Substiuents for the alkyl group may be halogen, e.g. fluorine, chlorine, bromine and iodine, OH, C_{1-6} alkoxy.

[00112] The term "C_{1-6} alkoxy" refers to an alkyl group which is attached to a molecule via oxygen. This includes moieties where the alkyl part may be linear or branched and may contain 1, 2, 3, 4, 5 or 6 carbon atoms, for example methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl and n-hexyl. Therefore, the alkoxy group may be methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy and n-hexoxy. The alkyl part of the alkoxy group may be unsubstituted or substituted by one or more substituents. Possible substituents are described below. Substituents for the alkyl group may be halogen, e.g. fluorine, chlorine, bromine and iodine, OH, C_{1-6} alkoxy.

[00113] The term "C_{1-6} haloalkyl" refers to a hydrocarbon chain substituted with at least one halogen atom independently chosen at each occurrence, for example fluorine, chlorine, bromine and iodine. The halogen atom may be present at any position on the hydrocarbon chain. For example, C_{1-6} haloalkyl may refer to chloromethyl, flouromethyl, trifluoromethyl, chloroethyl e.g. 1-chloromethyl and 2-chloroethyl, trichloroethyl e.g. 1,2,2-trichloroethyl, 2,2,2-trichloroethyl, fluoroethyl e.g. 1-fluoromethyl and 2-fluoroethyl, trifluoroethyl e.g. 1,2,2-trifluoroethyl and 2,2,2-trifluoroethyl, chloropropyl, trichloropropyl, fluoropropyl, trifluoropropyl.

[00114] The term "C_{2-6} alkenyl" refers to a branched or linear hydrocarbon chain containing at least one double bond and having 2, 3, 4, 5 or 6 carbon atoms. The double bond(s) may be present as the *E* or *Z* isomer. The double bond may be at any possible position of the hydrocarbon chain. For example, the "C_{2-6} alkenyl" may be ethenyl, propenyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl and hexadienyl.

[00115] The term "C_{2-6} alkynyl" refers to a branded or linear hydrocarbon chain containing at least one triple bond and having 2, 3, 4, 5 or 6 carbon atoms. The triple bond may be at any possible position of the hydrocarbon chain. For example, the "C_{2-6} alkynyl" may be ethynyl, propynyl, butynyl, pentynyl and hexynyl.

[00116] The term "C_{1-6} heteroalkyl" refers to a branded or linear hydrocarbon chain containing 1, 2, 3, 4, 5, or 6 carbon atoms and at least one heteroatom selected from N, O and S positioned between any carbon in the chain or at an end of the chain. For example, the hydrocarbon chain may contain one or two heteroatoms. The C_{1-6} heteroalkyl may be bonded to the rest of the molecule through a carbon or a heteroatom. For example, the "C_{1-6} heteroalkyl" may be C_{1-6} *N*-alkyl, C_{1-6} *N,N*-alkyl, or C_{1-6} *O*-alkyl.

[00117] The term "carbocyclic" refers to a saturated or unsaturated carbon containing ring system. A "carbocyclic" system may be monocyclic or a fused polycyclic ring system, for example, bicyclic or tricyclic. A "carbocyclic" moiety may contain from 3 to 14 carbon atoms, for example, 3 to 8 carbon atoms in a monocyclic system and 7 to 14 carbon atoms in a polycyclic system. "Carbocyclic" encompasses cycloalkyl moieties, cycloalkenyl moieties, aryl ring systems and fused ring systems including an aromatic portion. "Carbocyclic" may be C_{3-8} cycloalkyl or C_{6-10} aryl.

[00118] The term "heterocyclic" refers to a saturated or unsaturated ring system containing at least one heteroatom selected from N, O or S. A "heterocyclic" system may contain 1, 2, 3 or 4 heteroatoms, for example 1 or 2. A "heterocyclic" system may be monocyclic or a fused polycyclic ring system, for example, bicyclic or tricyclic. A "heterocyclic" moiety may contain from 3 to 14 carbon atoms, for example, 3 to 8 carbon atoms in a monocyclic system and 7 to 14 carbon atoms in a polycyclic system. "Heterocyclic" encompasses heterocycloalkyl moieties, heterocycloalkenyl moieties and heteroaromatic moieties. "Heterocyclic" may be C_{3-8} heterocycloalkyl or C_{5-10} heteroaryl. For example, the heterocyclic group may be: oxirane, aziridine, azetidine, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, and tetrahydropyran.

[00119] The term "C_{3-8} cycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms. For example, the "C_{3-8} cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[00120] The term "C_{3-8} cycloalkenyl" refers to an unsaturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms that is not aromatic. The ring may contain more than one double bond provided that the ring system is not aromatic. For example, the "C_{3-8} cycloalkyl" may be cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienly, cycloheptenyl, cycloheptadiene, cyclooctenyl and cycloatadienyl.

[00121] The term "C_{3-8} heterocycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms and at least one heteroatom within the ring selected from N, O and S. For example there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. The "C_{3-8} heterocycloalkyl" may be bonded to the rest of the molecule through any carbon atom or heteroatom. The "C_{3-8} heterocycloalkyl" may have one or more, e.g. one or two, bonds to the rest of the molecule: these bonds may be through any of the atoms in the ring. For example, the "C_{3-8} heterocycloalkyl" may be oxirane, aziridine, azetidine,

oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, and tetrahydropyran.

[00122] The term "C_{3-8} heterocycloalkenyl" refers to an unsaturated hydrocarbon ring system, that is not aromatic, containing 3, 4, 5, 6, 7 or 8 carbon atoms and at least one heteroatom within the ring selected from N, O and S. For example there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. The "C_{3-8} heterocycloalkenyl" may be bonded to the rest of the molecule through any carbon atom or heteroatom. The "C_{3-8} heterocycloalkenyl" may have one or more, e.g. one or two, bonds to the rest of the molecule: these bonds may be through any of the atoms in the ring. For example, the "C_{3-8} heterocycloalkyl" may be tetrahydropyridine, dihydropyran, dihydrofuran, pyrroline.

[00123] The term "aromatic" when applied to a substituent as a whole means a single ring or polycyclic ring system with 4n + 2 electrons in a conjugated π system within the ring or ring system where all atoms contributing to the conjugated π system are in the same plane.

[00124] The term "aryl" refers to an aromatic hydrocarbon ring system. The ring system has 4n +2 electrons in a conjugated π system within a ring where all atoms contributing to the conjugated π system are in the same plane. "Aryl" may be C_{6-10} aryl. For example, the "aryl" may be phenyl and napthyl. The aryl system itself may be substituted with other groups.

[00125] The term "heteroaryl" refers to an aromatic hydrocarbon ring system with at least one heteroatom within a single ring or within a fused ring system, selected from O, N and S. The ring or ring system has 4n +2 electrons in a conjugated π system where all atoms contributing to the conjugated π system are in the same plane. "Heteroaryl" may be C_{5-10} heteroaryl. For example, the "heteroaryl" may be imidazole, thiene, furane, thianthrene, pyrrol, benzimidazole, pyrazole, pyrazine, pyridine, pyrimidine and indole.

[00126] The term "alkaryl" refers to an aryl group, as defined above, bonded to a C_{1-4} alkyl, where the C_{1-4} alkyl group provides attachment to the remainder of the molecule.

[00127] The term "alkheteroaryl" refers to a heteroaryl group, as defined above, bonded to a C_{1-4} alkyl, where the alkyl group provides attachment to the remainder of the molecule.

[00128] The term "halogen" herein includes reference to F, Cl, Br and I. Halogen may be Cl. Halogen may be F.

[00129] A bond terminating in a "  " represents that the bond is connected to another atom that is not shown in the structure. A bond terminating inside a cyclic structure and not terminating at an atom of the ring structure represents that the bond may be connected to any of the atoms in the ring structure where allowed by valency.

[00130] Where a moiety is substituted, it may be substituted at any point on the moiety where chemically possible and consistent with atomic valency requirements. The moiety may be substituted by one or more substitutuents, e.g. 1, 2, 3 or 4 substituents; optionally there are 1 or 2 substituents on a group. Where there are two or more substituents, the substituents may be the same or different. The substituent(s) may be selected from: OH, NHR^b, amidino, guanidino, hydroxyguanidino, formamidino, isothioureido, ureido, mercapto, C(O)H, acyl, acyloxy, carboxy, sulfo, sulfamoyl, carbamoyl, cyano, azo, nitro, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl or alkaryl. Where the group to be substituted is an alkyl group the substituent may be =O. Where the moiety is substituted with two or more substituents and two of the substituents are adjacent the adjacent substituents may form a C_{4-8} ring along with the atoms of the moiety on which the substituents are substituted, wherein the C_{4-8} ring is a saturated or unsaturated hydrocarbon ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated hydrocarbon ring with 4, 5, 6, 7, or 8 carbon atoms and 1, 2 or 3 heteroatoms.

[00131] Substituents are only present at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without inappropriate effort which substitutions are chemically possible and which are not.

[00132] By "acyl" is meant an organic radical derived from, for example, an organic acid by the removal of the hydroxyl group, e.g. a radical having the formula R-C(O)-, where R may be selected from H, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl or phenethyl group, eg R is H or C_{1-3} alkyl. In one embodiment acyl is alkyl-carbonyl. Examples of acyl groups include, but are not limited to, formyl, acetyl, propionyl and butyryl. A particular acyl group is acetyl.

[00133] The invention contemplates pharmaceutically acceptable salts of the compounds of formula (**I**). These may include the acid addition and base salts of the compounds.

[00134] Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate,

hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 1 ,5-naphthalenedisulfonate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

[00135] Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts. For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[00136] Pharmaceutically acceptable salts of compounds of formula (**I**) may be prepared by one or more of three methods:

(i) by reacting the compound of formula (**I**) with the desired a**c**id or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (**I**) or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of formula (**I**) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

[00137] All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

[00138] The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

[00139] Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be

ionised, partially ionised, or non- ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

[00140] Hereinafter all references to compounds of any formula include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

[00141] The compounds of the invention include compounds of a number of formula as herein defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of the invention.

[00142] Before purification, the compounds of the present invention may exist as a mixture of enantiomers depending on the synthetic procedure used. The enantiomers can be separated by conventional techniques known in the art. Thus the invention covers individual enantiomers as well as mixtures thereof.

[00143] For some of the steps of the process of preparation of the compounds of formula (**I**), it may be necessary to protect potential reactive functions that are not wished to react, and to cleave said protecting groups in consequence. In such a case, any compatible protecting radical can be used. In particular methods of protection and deprotection such as those described by T.W. GREENE (Protective Groups in Organic Synthesis, A. Wiley-Interscience Publication, 1981) or by P. J. Kocienski (Protecting groups, Georg Thieme Verlag, 1994), can be used. All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the examples and preparations hereto.

[00144] Also, the compounds of the present invention as well as intermediates for the preparation thereof can be purified according to various well-known methods, such as for example crystallization or chromatography.

[00145] The method of treatment or the compound for use in the treatment of cancer, lymphoma, leukemia or immunological diseases as defined hereinbefore may be applied as a sole therapy or be a combination therapy with an additional active agent. Optionally, the additional active agent may be an anti-tumour agent selected from the list below.

[00146] The method of treatment or the compound for use in the treatment of cancer, lymphoma or leukemia may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include

one or more of the following specific anti-tumour agents listed below or anti-tumour agents from one or more of the categories of listed below:-

(i) antiproliferative/antineoplastic drugs and combinations thereof, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, bendamustin, melphalan, chlorambucil, busulphan,capecitabine temozolamide , ifosamide, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, AMD-473, altretamine, AP-5280, apaziquone, brostallicin, carmustine, estramustine, fotemustine, gulfosfamide, KW-2170, mafosfamide, mitolactol, etaplatin, lobaplatin, nedaplatin, strrplatin and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, pemetrexed, cytosine arabinoside, 6-mercaptopurine riboside, leucovarin, UFT, doxifluridine, carmoflur, cytarabine, enocitabine S-1, 5-azacitidine, cepecitabine, clofarabine, decitabine, eflornithine, ethynlcytidine, TS-1, nelarabine, nolatrexed, ocosfate, pelitrexol, triapine, trimetrexate, vidarabine, and hydroxyurea); antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin, mithramycin, aclarubicin, actinomycin D, amrubicin, annamycin, elsamitrucin, galarubicin, nemorubicin, neocarzinostatin, peplomycin, piarubicin, rebeccamycin, stimalamer, streptozocin, valrubicin and zinostatin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol, docetaxol (Taxotere), and paclitaxel and polokinase inhibitors); proteasome inhibitors, for example carfilzomib and bortezomib; interferon therapy; and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, aclarubicin, amonafide, belotecan, 10-hydroxycamptothecin, 9-aminocamptothecin, diflomotecan, edotecarin, exatecan, gimatecan, lurtotecan, pirarubicin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, amsacrine, topotecan, mitoxantrone and camptothecin) and adjuvants used in combination with these therapies, for example folinic acid;

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene, lasofoxifeneand iodoxyfene), antiandrogens (for example bicalutamide, mifepristone, flutamide, nilutamide, casodex and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) anti-invasion agents, for example dasatinib and bosutinib (SKI-606), and metalloproteinase inhibitors, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase;

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies, for example the anti-erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab, tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as gefitinib, erlotinib and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib); ErbB2 inhibitors (for example GW-28297, Herceptin, 2C4, pertuzumab, TAK-165, GW-572016, AR-209, and 2B-1); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; modulators of protein regulators of cell apoptosis (for example Bcl-2 inhibitors); inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib , tipifarnib and lonafarnib), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor, kinase inhibitors; aurora kinase inhibitors and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™); COXII inhibitors (for example Arcoxia (etoricoxib), Bextra (valdecoxib), Celebrex (celecoxib), Paracoxib Vioxx (rofecoxib)); MMP inhibitors (for example MMP-2 inhibitors, MMP-9 inhibitors, AG-3340, RO 32-3555, and RS 13-0830); thalidomide; lenalidomide; and for example, a VEGF receptor (for example SU-11248, SU-5416, SU-6668, and angiozyme) tyrosine kinase inhibitor (such as vandetanib, vatalanib, sunitinib, axitinib and pazopanib); acitretin; fenretinide; zoledronic acid; angiostatin; aplidine; cilengtide; A-4; endostatin; halofuginome; rebimastat; removab; revlimid; squalamine; ukrain; and vitaxincombretastatin;

(vi) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2;

(vii) immunotherapy approaches, including for example antibody therapy such as alemtuzumab, rituximab, ibritumomab tiuxetan (Zevalin®) and ofatumumab; interferons such as interferon α; interleukins such as IL-2 (aldesleukin); interleukin inhibitors for example IRAK4 inhibitors; cancer vaccines including prophylactic and treatment vaccines such as HPV vaccines, for example Gardasil, Cervarix, Oncophage and Sipuleucel-T (Provenge); interferons, such as interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, and interferon gamma-n; PF3512676; Filgrastim

(Neupogen); lentinan; sizofilan; TheraCys; ubenimex; WF-10; BAM-002; dacarbazine; daclizumab; denileukin; gemtuzumab; ozogamicin; imiquimod; lenograstim; melanoma vaccine (Corixa); molgramostim; OncoVAX- CL; sargramostim; tasonermin; tecleukin; thymalasin; tositumomab; Virulizin; Z-100; epratuzumab; mitumomab; oregovomab; pemtumomab; and toll-like receptor modulators for example TLR-7 or TLR-9 agonists; and

(viii) cytotoxic agents for example fludaribine (fludara), cladribine, pentostatin (Nipent™), edotecarin, SU-11248, paclitaxel, Erbitux, and irinotecan;

(ix) steroids such as corticosteroids, including glucocorticoids and mineralocorticoids, for example aclometasone, aclometasone dipropionate, aldosterone, amcinonide, beclomethasone, beclomethasone dipropionate, betamethasone, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, clobetasone, clobetasone butyrate, clobetasol propionate, cloprednol, cortisone, cortisone acetate, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, dexamethasone isonicotinate, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluocortolone caproate, fluocortolone pivalate, fluorometholone, fluprednidene, fluprednidene acetate, flurandrenolone, fluticasone, fluticasone propionate, halcinonide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone valerate, icomethasone, icomethasone enbutate, meprednisone, methylprednisolone, mometasone paramethasone, mometasone furoate monohydrate, prednicarbate, prednisolone, prednisone, tixocortol, tixocortol pivalate, triamcinolone, triamcinolone acetonide, triamcinolone alcohol and their respective pharmaceutically acceptable derivatives. A combination of steroids may be used, for example a combination of two or more steroids mentioned in this paragraph;

(x) targeted therapies, for example PI3Kd inhibitors, for example idelalisib and perifosine;

(xi) and additional active agents such as estramustine phosphate, fludarabine phosphate, farnesyl transferase inhibitors, PDGFr, streptozocin, strontium-89, suramin, hormonal therapies (for example Lupron, doxercalciferol, fadrozole, formestane and trelstar), supportive care products (for example, Filgrastim (Neupogen), ondansetron (Zofran), Fragmin, Procrit, Aloxi and Emend), biological response modifiers (e.g. Krestin, lentinan, sizofiran, picibanil and ubenimex), alitretinoin, ampligen, atrasenten, bexarotene, bosentan, calcitriol, exisulind, fotemustine, ibandronic acid, miltefosine, l-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pegaspargase, tazarotne, TLK-286, Velcade, Tarceva, tretinoin.

[00147] The method of treatment or the compound for use in the treatment of immunological diseases may involve, in addition to the compound of the invention, additional active agents. The additional active agents may be one or more active agents used to treat the condition being treated by the compound of formula (**I**) and additional active agent. The additional active agents may include one or more of the following active agents:-

(i) steroids such as corticosteroids, including glucocorticoids and mineralocorticoids, for example aclometasone, aclometasone dipropionate, aldosterone, amcinonide, beclomethasone, beclomethasone dipropionate, betamethasone, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, clobetasone, clobetasone butyrate, clobetasol propionate, cloprednol, cortisone, cortisone acetate, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, dexamethasone isonicotinate, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluocortolone caproate, fluocortolone pivalate, fluorometholone, fluprednidene, fluprednidene acetate, flurandrenolone, fluticasone, fluticasone propionate, halcinonide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone valerate, icomethasone, icomethasone enbutate, meprednisone, methylprednisolone, mometasone paramethasone, mometasone furoate monohydrate, prednicarbate, prednisolone, prednisone, tixocortol, tixocortol pivalate, triamcinolone, triamcinolone acetonide, triamcinolone alcohol and their respective pharmaceutically acceptable derivatives. A combination of steroids may be used, for example a combination of two or more steroids mentioned in this paragraph;

(ii) TNF inhibitors for example etanercept; monoclonal antibodies (e.g. infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi)); fusion proteins (e.g. etanercept (Enbrel)); and 5-HT_{2A} agonists (e.g. 2,5-dimethoxy-4-iodoamphetamine, TCB-2, lysergic acid diethylamide (LSD), lysergic acid dimethylazetidide);

(iii) anti-inflammatory drugs, for example non-steroidal anti-inflammatory drugs;

(iv) dihydrofolate reductase inhibitors/antifolates, for example methotrexate, trimethoprim, brodimoprim, tetroxoprim, iclaprim, pemetrexed, ralitrexed and pralatrexate; and

(v) immunosuppressants for example cyclosporins, tacrolimus, sirolimus pimecrolimus, angiotensin II inhibitors (e.g. Valsartan, Telmisartan, Losartan, Irbesatan, Azilsartan, Olmesartan, Candesartan, Eprosartan) and ACE inhibitors e.g. sulfhydryl-

containing agents (e.g. Captopril, Zofenopril), dicarboxylate-containing agents (e.g. Enalapril, Ramipril, Quinapril, Perindopril, Lisinopril, Benazepril, Imidapril, Zofenopril, Trandolapril), phosphate-containing agents (e.g. Fosinopril), casokinins, lactokinins and lactotripeptides.

[00148] Such combination treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within a therapeutically effective dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

[00149] According to a further aspect of the invention there is provided a pharmaceutical product comprising a compound of formula (**I**), or a pharmaceutically acceptable salt thereof as defined hereinbefore and an additional active agent. The additional active agent may be an anti-tumour agent as defined hereinbefore for the combination treatment of a condition modulated by BTK.

[00150] According to a further aspect of the invention there is provided a method of treatment a condition modulated by BTK comprising administering a therapeutically effective amount of a compound of of formula (**I**), or a pharmaceutically acceptable salt thereof simultaneously, sequentially or separately with an additional anti-tumour agent, as defined hereinbefore, to a patient in need thereof.

[00151] According to a further aspect of the invention there is provided a compound of formula (**I**), or a pharmaceutically acceptable salt thereof for use simultaneously, sequentially or separately with an additional anti-tumour agent as defined hereinbefore, in the treatment of a condition modulated by BTK.

[00152] According to another aspect of the invention there is provided a use of the compound of formula (**I**) in combination with an anti-tumour agent as hereinbefore described. The compound of formula (**I**) may be used simultaneously, sequentially or separately with the additional anti-tumour agent The use may be in a single combination product comprising the compound of formula (**I**) and the anti-tumour agent.

[00153] According to a further aspect there is provided a method of providing a combination product, wherein the method comprises providing a compound of formula (**I**) simultaneously, sequentially or separately with an anti-tumour agent, as defined hereinbefore. The method may comprise combining the compound of formula (**I**) and the anti-tumour agent in a single dosage form. Alternatively the method may comprise providing the anti-tumour agent as separate dosage forms.

[00154] The condition modulated by BTK described above may be cancer, leukemia or cancer. More specifically the condition modulated by BTK may be selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkins lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkins lymphoma, Waldenstrom's macroglobulinemia and multiple myeloma.

EXAMPLES AND SYNTHESIS

[00155] The compounds of the present invention may be synthesised by analogy with the following reaction routes shown in Route A, Route B or Route C.

[00156] Protecting groups may be present or absent as necessary. For example, a nitrogen atom may be protected or unprotected.

[00157] The synthesis of representative compounds of the invention is given below.

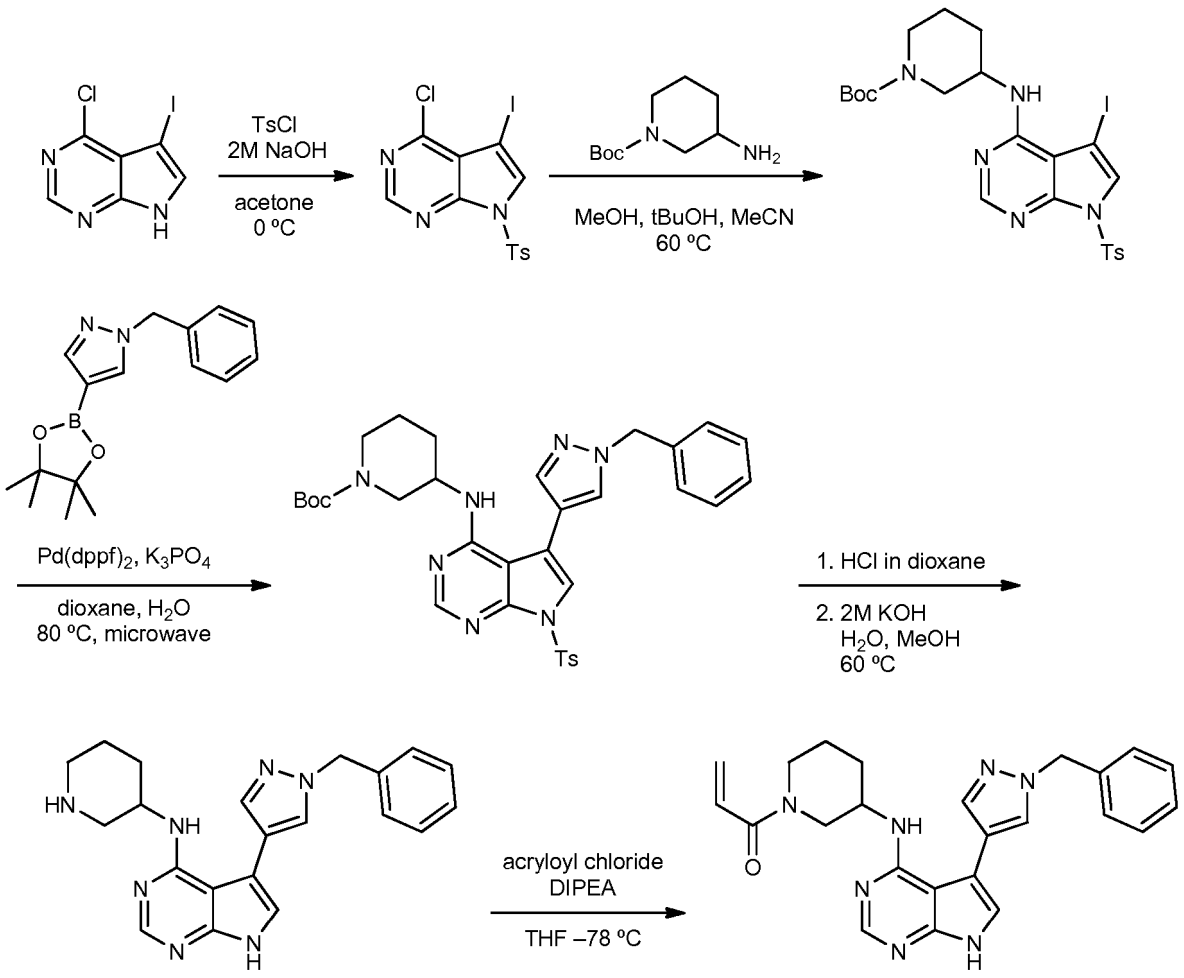
[00158] All LCMS analysis was carried out on a Waters Acquity SQ Detector 2 with two 0.2µm guard filters using a UPLC Column (C18, 50 x 2.1 mm, < 2µm). Mobile phase A was 0.1% (v/v) formic acid in water and mobile phase B was 0.1% (v/v) formic acid in acetonitrile. Flow rate was 0.6 ml/min, back pressure ca <8000 psi. Injection volume was 2 µL. Temperature was 40 °C. Run time was 8 Mins. The Gradient was:

Time (min)	%A	%B
0	95	5
1.1	95	5
6.1	5	95
7	5	95
7.5	95	5
8	95	5

[00159] **Example 1**

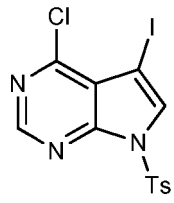
[00160] Compounds of the invention may be synthesised by analogy with Route A, shown below.

[00161] **Route A**



[00162] A method for preparing a compound of the invention is given below. Further compounds that can be prepared in a similar manner are given in **Table 1**.

4- Chloro-5-iodo-7-(p-tolylsulfonyl)pyrrolo[2,3-d]pyrimidine

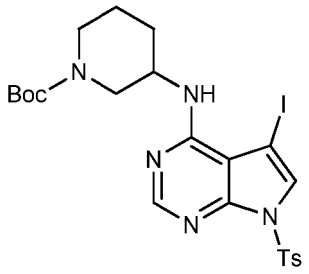


4-Chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (10.g, 35.78mmol) and p-toluenesulfonyl chloride (7.5g, 39.36mmol) were dissolved in acetone (110mL) and placed under nitrogen and cooled to 0°C. A freshly prepared 2.0M aqueous solution of NaOH (0.43 mL) was added and immediately a grey precipitate was formed. The reaction was allowed to warm to RT and another 1 mL of acetone was added and left to stir for 1 hour. The reaction was diluted with cold acetone and then filtered. The filter cake was washed with more ice cold acetone (20 mL) and then left to dry overnight. 4- chloro-5-iodo-7-(p-tolylsulfonyl)pyrrolo[2,3-d]pyrimidine (15.987g,36.866mmol, 100% yield) as a white powder.

LCMS: (ES^+, short acidic): 1.96 min, m/z 434.0 $[M+H]^+$

NMR: ($CDCl_3$) 8.75 (1H, s), 8.10 (2H,d, J = 8.7Hz), 7.95 (1H, s), 7.35 (2H, d, J = 8.7), 2.42 (3H, s).

tert-Butyl -3-[[5-iodo-7-(p-tolylsulfonyl)pyrrolo[2,3-d]pyrimidin-4-yl]amino]piperidine-1-carboxylate

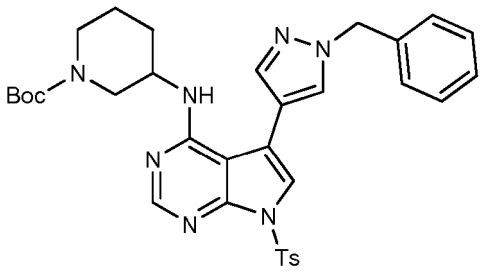


4-chloro-5-iodo-7-(p-tolylsulfonyl)pyrrolo[2,3-d]pyrimidine (5.g, 11.53mmol) and tert-butyl (3R)-3-aminopiperidine-1-carboxylate (8.03mL, 34.59mmol) were dissolved in tert-butanol (50mL) and MeCN (25mL) and methanol (25 mL). The resulting suspension was heated to 60 °C over 72h. The reaction was concentrated and the resulting oil was purified by column chromatography (0 to 100% EtOAc in DCM). tert-butyl (3R)-3-[[5-iodo-7-(p-tolylsulfonyl)pyrrolo[2,3-d]pyrimidin-4-yl]amino]piperidine-1-carboxylate (5.199g,8.7017mmol, 75% yield) as a brown solid.

LCMS: (ES^+, short acidic): 2.04 min, m/z 598.3 $[M+H]^+$

NMR:: 8.41 (1H, s), 8.06 (2H, d, J = 8.7 Hz), 7.56 (1H, s), 7.29 (2H, d, J 8.7 Hz), 6.33 (1H, s), 4.34 (1H, m), 4.08 (2H, m), 3.68 (1H, m), 3.46 (1H, m), 2.40 (3H, s), 1.95 (1H, m), 1.80 (1H, m), 1.65 (1H, m), 1.27 (9H, s).

5-(1-Benzylpyrazol-4-yl)-N-[(3R)-3-piperidyl]-7-(p-tolylsulfonyl)pyrrolo[2,3-d]pyrimidin-4-amine



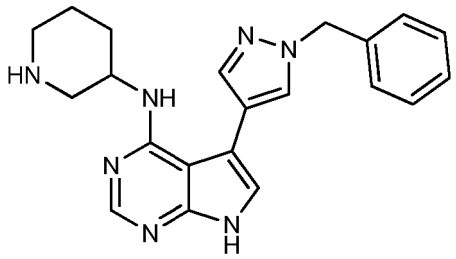
Tert-butyl (3R)-3-[[5-iodo-7-(p-tolylsulfonyl)pyrrolo[2,3-d]pyrimidin-4-yl]amino]piperidine-1-carboxylate (100.02mg, 0.17 mmol), 1-Benzylpyrazole-4-boronic acid pinacol ester (57.08mg, 0.2000mmol) and Potassium phosphate tribasic (106.6mg, 0.5000mmol) were dissolved into 1,4-Dioxane (3mL) and Water (0.7500mL) and the resulting solution was thoroughly degassed. [1,1'-Bis(diphenylphosphino)ferrocene]Palladium(II) chloride

dichloromethane complex (13.67mg, 0.0200mmol) was added and the reaction mixture was heated to 80 °C for 30 minutes under microwave conditions. The mixture was diluted with DCM (25 mL) and water (5 mL). The organic phase was separated and concentrated to dryness to give a thick black oil.

The oil was dissolved into 4M HCl in dioxane (2 mL) and was allowed to stir for 1 hour at room temperature. The reaction was then concentrated and purified by SCX cartridge. 5-(1-benzylpyrazol-4-yl)-N-[(3R)-3-piperidyl]-7-(p-tolylsulfonyl)pyrrolo[2,3-d]pyrimidin-4-amine (96.2mg,0.1823mmol, 100% yield) was obtained as a light brown oil.

LCMS: N200191-10-B (ES^+, short acidic): 1.43 min, m/z 528.5 $[M+H]^+$

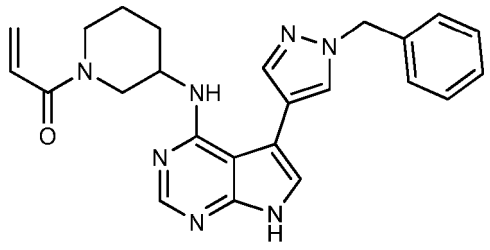
5-(1-Benzylpyrazol-4-yl)-N-[(3R)-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine



5-(1-benzylpyrazol-4-yl)-N-[(3R)-3-piperidyl]-7-(p-tolylsulfonyl)pyrrolo[2,3-d]pyrimidin-4-amine (96.2mg, 0.1800mmol) was dissolved in Methanol (3mL). Potassium hydroxide (204.59mg, 3.65mmol) was added to Water (1mL) and the resulting solution was added to the reaction. The mixture was then heated to 60 °C overnight under nitrogen. Ammonium chloride solution (10 mL) was added to bring the reaction to pH 9 and was then extracted thoroughly with ethyl acetate (20 mL). The combined organics were dried over sodium sulfate and concentrated to dryness giving 5-(1-benzylpyrazol-4-yl)-N-[(3R)-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (34.2mg,0.0916mmol, 50% yield) as a yellow residue.

LCMS: (ES+, short acidic): 1.06 min, m/z 374.3 $[M+H]^+$

1-[(3R)-3-[[5-(1-Benzylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one



5-(1-benzylpyrazol-4-yl)-N-[(3R)-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (34.2mg, 0.09 mmol) was dissolved in THF (1.2mL) and was cooled to -78 °C and placed under a nitrogen atmosphere. Acryloyl chloride (0.01mL, 0.0900mmol) was added, followed by

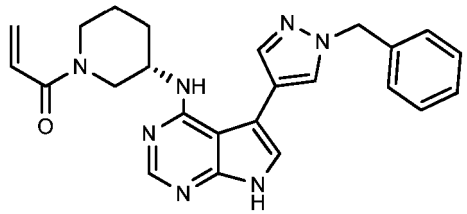
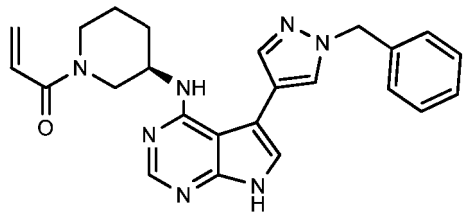
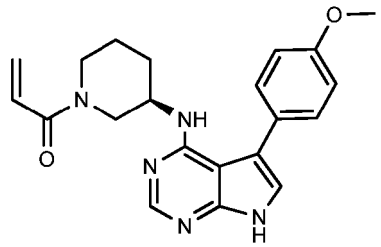
DIPEA (10 µL, 0.09 mmol) and the reaction was stirred for 30 minutes. Saturated ammonium chloride solution (3 mL) was added to the reaction mixture which was then partitioned with ethyl acetate (10 mL). The organic phase was dried over sodium sulfate and concentrated to dryness giving a yellow brown film. The film was dissolved into 80% DMSO, 10% acetonitrile and 10% water solution and was purified using the prep LCMS. 1-[(3R)-3-[[5-(1-benzylpyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one; formic acid (11.5mg,0.0243mmol, 26.5% yield) was isolated as a white solid.

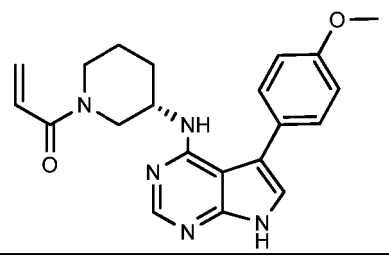
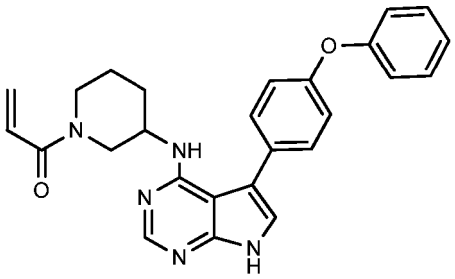
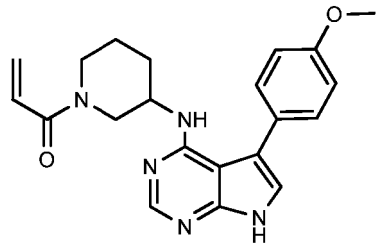
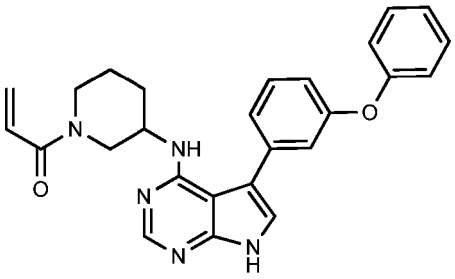
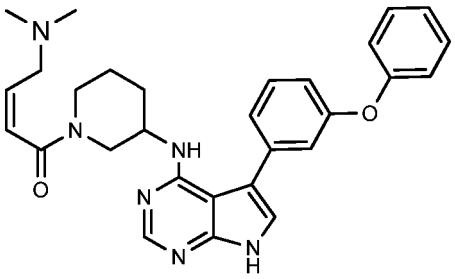
LCMS: (ES^+, short acidic): 1.24 min, m/z 428.3 $[M+H]^+$

NMR: ($CDCl_3$) 8.31 (1H, s), 7.36 (7H, m), 6.97 (1H, s), 6.22 (1H, m), 6.19 (1H, m), 5.48 (4H, m), 4.34 (1H. m), 3.80 (1H, m), 3.51 (2H, m), 1.89 (1 H, m), 1.42 (3H, m)

[00163] Compounds prepared in a similar manner to that set out above are given below in **Table 1**.

Table 1

STRUCTURE	LCMS
	(ES, short acidic): 1.24 min, m/z 428.2 [M+H]
	(ES, short acidic): 1.24 min, m/z 428.2 [M+H]
	(ES, short acidic): 1.20 min, m/z 378.3 [M+H]

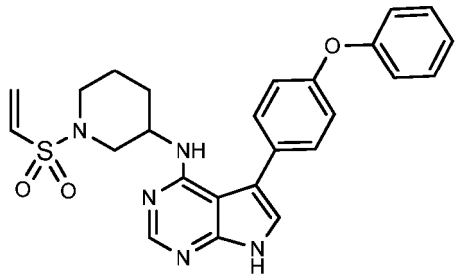
	(ES, short acidic): 1.20 min, m/z 378.2 [M+H]
	(ES, short acidic): 1.49 min, m/z 440.3 [M+H]
	(ES, short acidic): 1.25 min, m/z 378 [M+H]
	(ES, short acidic): 449 min, m/z 440 [M+H]
	(ES, short acidic): 1.27 min, m/z 497.3. [M+H]

[00164] **Example 2**

[00165] The compound shown below, 5-(3-phenoxyphenyl)-N-[(3R)-1-vinylsulfonyl-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine was synthesised by analogy with Route A, shown above. 5-(3-Phenoxyphenyl)-N-[(3R)-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine, a compound equivalent to an intermediate in Route A, 5-(1-benzylpyrazol-4-yl)-N-[(3R)-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine, was produced following a procedure analogous to the procedure described above in relation to Route A.

[00166] 5-(3-Phenoxyphenyl)-N-[(3R)-1-vinylsulfonyl-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine was produced from 5-(3-phenoxyphenyl)-N-[(3R)-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine by the procedure given below.

5-(3-Phenoxyphenyl)-N-[(3R)-1-vinylsulfonyl-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine



5-(3-Phenoxyphenyl)-N-[(3R)-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (100 mg, 0.26 mmol) was dissolved in DCM (4.5 mL) and triethylamine (0.14 mL, 1.04 mmol) was added. The mixture was degassed with a balloon of nitrogen before being cooled to 0°c. 2-chloroethanesulfonyl chloride (0.03 mL, 0.26 mmol) was added drop wise and the reaction was allowed to stir at 0°c for 3 hours. Reaction was warmed to room temperature and stirred for 16 hours. Saturated ammonium chloride solution (5 mL) was added and the mixture was extracted with DCM (3 x 15 mL). The combined organics were passed through a phase separator before being concentrated to dryness giving a yellow/brown film. The film was dissolved in DCM (3 mL) before being subjected to normal phase column chromatography (0-20% MeOH in DCM). Fractions were dried giving 5-(3-phenoxyphenyl)-N-[(3R)-1-vinylsulfonyl-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (18.8mg, 0.0372mmol, 14% yield) as a brown film.

LCMS: (ES^+, short acidic): 1.58 min, m/z 476.3 $[M+H]^+$

NMR: ($CDCl_3$) 10.06 (1H, s), 8.36 (1H, s), 7.52 (1H, m), 7.35 (2H, m), 7.28 (1H, m), 7.14 (1H, m), 7.10 (2H, m), 7.05 (2H, m), 6.33 (1H, m), 5.98 (1 H, m), 5.48 (1H, m), 4.61 (1H, m), 3.29 (2H, m), 3.16 (1H, m), 3.01 (1H, m), 1.80 (1H, m), 1.38 (3H, m).

[00167] Other compounds of the invention may be synthesised by analogy with this procedure.

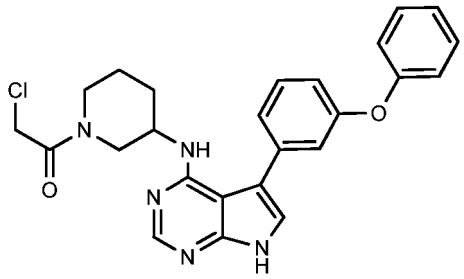
[00168] **<u>Example 3</u>**

[00169] The compound shown below, 2-chloro-1-[(3R)-3-[[5-(3-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]ethanone was synthesised by analogy with Route A, shown above. 5-(3-phenoxyphenyl)-N-[(3R)-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine, a compound equivalent to an intermediate in Route A, 5-(1-

benzylpyrazol-4-yl)-N-[(3R)-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine, was produced following a procedure analogous to the procedure described above in relation to Route A.

[00170] 2-Chloro-1-[(3R)-3-[[5-(3-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]ethanone was produced from 5-(3-phenoxyphenyl)-N-[(3R)-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine by the procedure given below.

2-Chloro-1-[(3R)-3-[[5-(3-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]ethanone



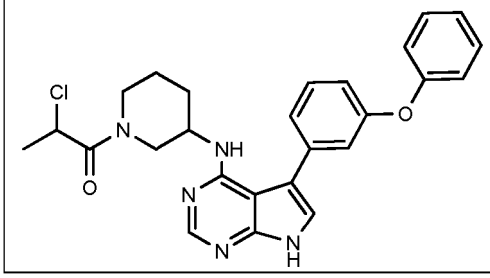
5-(3-Phenoxyphenyl)-N-[(3R)-3-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (136 mg, 0.35 mmol) and DIPEA (0.08mL, 0.42 mmol) in DCM (3 mL) were cooled to 0°C and placed under a nitrogen atmosphere. Chloroacetyl chloride (0.03 mL, 0.35 mmol) was dissolved into DCM (2 mL) before being added drop wise to the substrate solution. Reaction was allowed to continue for 2 hours at 0 °C before being warmed to room temperature for 16 hours. Saturated ammonium chloride solution (3 mL) was added before the mixture was washed with DCM (3 x 15 mL). The organics were passed through a phase separator before being concentrated to dryness giving the crude product as a brown film. The film was dissolved in DCM and loaded onto a 10 g SNAP cartridge before being eluted with a mixture of Methanol in Ethyl acetate (0-20%). Fractions were dried giving 2-chloro-1-[(3R)-3-[[5-(3-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]ethanone (65.5mg,0.1418mmol, 40.191% yield) as a light brown solid.

LCMS: (ES+, short acidic): 1.53 min, m/z 462.3 [M+H]+

NMR: ($CDCl_3$) 10.96 (1H, m), 8.41 (1H, m), 7.43 (4H, m), 7.19 (2H, m), 7.15 (1H, m), 7.10 (3H, m), 7.03 (1H, m), 5.20 (1H, m), 4.23 (1H, m), 4.09 (3H, m), 3.97 (1H, m), 3.78 (1H, m), 3.45 (2H, m), 3.30 (1H, m), 2.02 (1H, m).

[00171] Compounds prepared in a similar manner to that set out above are given below in **Table 2**.

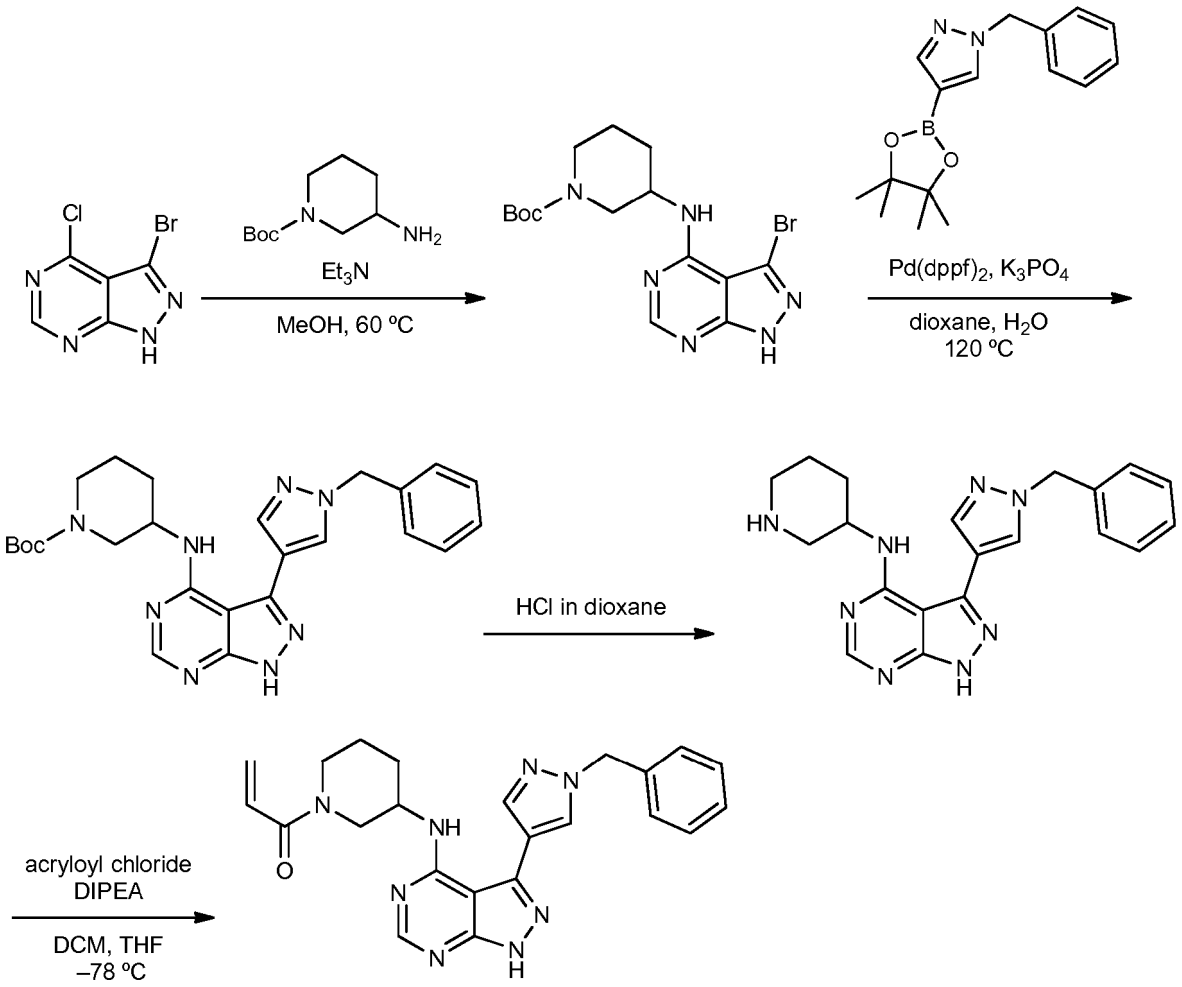
Table 2

STRUCTURE	LCMS
	(ES, short acidic): 3.74 min, m/z . 476/478 [M+H]

[00172] **Example 4**

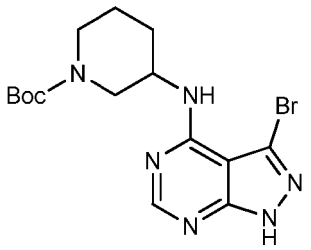
[00173] Compounds of the invention may be synthesised by analogy with Route B, shown below.

[00174] **Route B**



[00175] A method for preparing a compound of the invention is given below. Further compounds that can be prepared in a similar manner are given in **Table 2**.

tert-Butyl 3-[(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino]piperidine-1-carboxylate

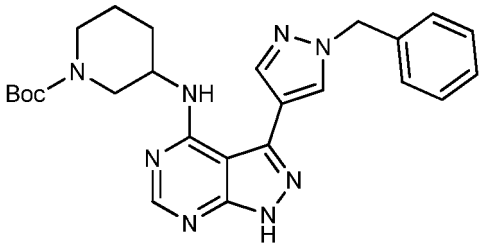


3-Bromo-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (1.5g, 6.43mmol) was dissolved in methanol (21.418mL) and 1-N-Boc-3-methylaminopiperidine (2.09mL, 9mmol) and Triethylamine (1.79mL, 12.85mmol) were added. The reaction mixture was stirred at 65 °C for 16h and cooled to 0°C. Precipitate was filtered, washed with minimum amount of cold methanol and dried at 50 °C under vacuum to give tert-butyl 3-[(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino]piperidine-1-carboxylate (2.14g ,5.38mmol, 84% yield) as a colourless solid.

LCMS: N200159-44- (ES^+, short acidic): 1.54 min, m/z 397.1 & 399.1 $[M+H]^+$

NMR (DMSO-d6): 13.88 (1H, bs), 8.32 (1H, s), 6.42 (1H, s), 4.22 (1H, s), 3.23 (5H, m), 1.92 (2H, m), 1.65 (1H, m), 1.53 (1H, m), 1.16 (9H, bs).

tert-Butyl 3-[[3-(1-benzylpyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]amino]piperidine-1-carboxylate



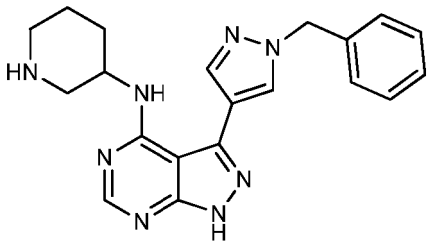
A microwave vial was charged with tert-butyl 3-[(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino]piperidine-1-carboxylate (200.mg, 0.5000mmol), 1-Benzylpyrazole-4-boronic acid pinacol ester (171.67mg, 0.6000mmol), potassium phosphate tribasic (320.59mg, 1.51mmol), [1,1'-Bis(diphenylphosphino)ferrocene]Palladium(II) chloride dichloromethane complex (41.11mg, 0.0500mmol) under nitrogen. 1,4-Dioxane (2.5172mL) and Water (0.5000mL) was added and the mixture was degassed with nitrogen for 20 min. The reaction mixture was then heated at 120 °C for 4h. The mixture was cooled, diluted saturated ammonium chloride solution (50 mL), extracted with ethyl acetate (3 x 20 mL), and the combined organics washed with brine (20 mL), dried (Na2SO4), filtered and concentrated. The crude was then purified by flash column chromatography (50 to 100% EtOAc in DCM). The desired fractions were concentrated to dryness in vacuo to give tert-

butyl 3-[[3-(1-benzylpyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]amino]piperidine-1-carboxylate (110mg,0.2318mmol, 46% yield).

LCMS: N200159-49a (ES^+, short acidic): 1.57 min, m/z 476.0 $[M+H]^+$

NMR (CDCl3): 11.90 (1H, bs), 8.48 (1H, s), 7.88 (1H, s), 7.75 (1H, s), 7.40 (5H, m), 5.53 (1H, m), 5.44 (2H, m), 4.34 (1H, m), 3.5 (4H, bm), 1.95 (1H, m), 1.53 (3H, bm), 1.32 (9H, bm)

3-(1-Benzylpyrazol-4-yl)-N-(3-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

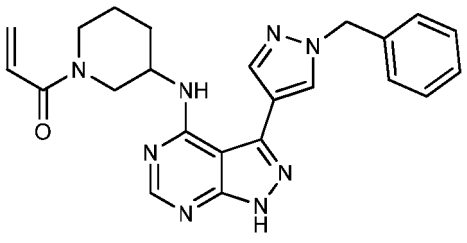


tert-Butyl 3-[[3-(1-benzylpyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]amino]piperidine-1-carboxylate (110 mg, 0.2300 mmol) was dissolved in hydrogen chloride 4M in dioxane (6.0 mL, 172.79 mmol) under nitrogen and the reaction was stirred at room temperature for 3h. Crude mixture purified by SCX flash cartridge to give crude 3-(1-benzylpyrazol-4-yl)-N-(3-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (74 mg, 0.1976 mmol, 85% yield) as a brown oil. The crude material was used in the next reaction without further purification.

LCMS: (ES^+, short acidic): 1.57 min, m/z 476.0 $[M+H]^+$

NMR: 8.44 (1H, s), 7.98 (1H, s), 7.85 (1H, s), 7.37 (5H, m), 6.24 (1H, m), 5.43 (2H, s), 4.39 (1H, s), 3.06 (1H, m), 2.78 (2H, bm), 2.70 (1H, m), 1.76 (2H, bm), 1.58 (2H, bm).

1-[3-[[3-(1-benzylpyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one



To a stirred solution of 3-(1-benzylpyrazol-4-yl)-N-(3-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (74.mg, 0.2000mmol) and N,N-Diisopropylethylamine (51.63uL, 0.3000mmol) in DCM (1mL) and THF (1mL) cooled to -78 °C under nitrogen was added dropwise acryloyl chloride (19.27uL, 0.2400mmol). The reaction mixture stirred at -78 °C for 2h. The reaction was diluted with saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3 x 10 mL), combined and washed with saturated brine

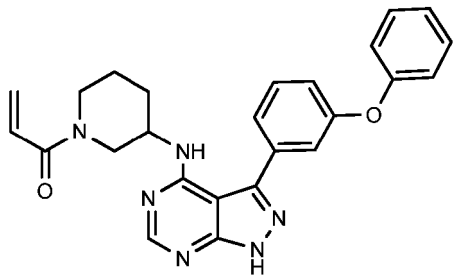
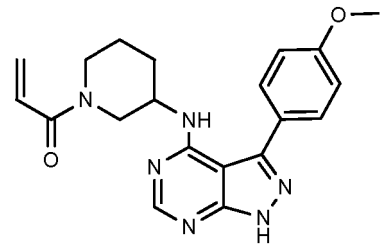
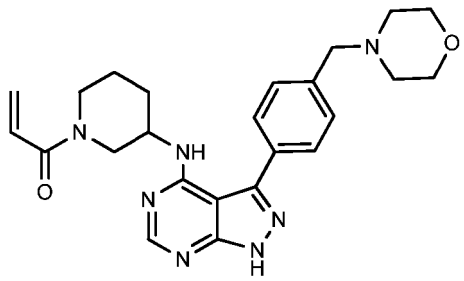
solution (20 mL). The organics were then separated and dried (MgSO4) before concentration to dryness. The residue obtained was purified by mass directed preparative chromatography to give 1-[3-[[3-(1-benzylpyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one (15.8mg,0.0369mmol, 18.5% yield) as a colourless solid.

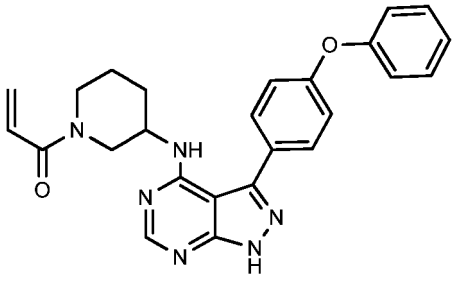
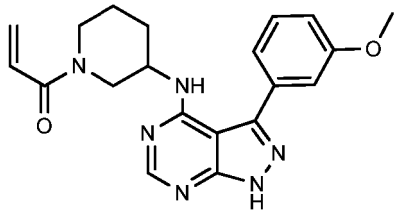
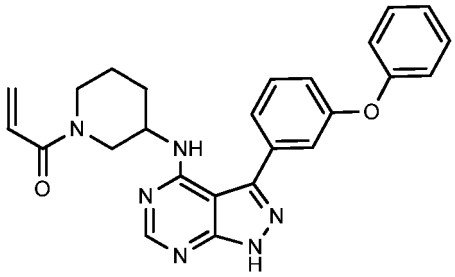
LCMS: (ES^+, final purity): 2.89 min, m/z 429.3 $[M+H]^+$

NMR ($CDCl_3$): 8.45 (1H, s), 7.84 (1H, s), 7.71 (1H, s), 7.36 (5H, m), 6.43 (1H, m), 6.20 (1H, m), 5.50 (4H, m), 4.50 (1H, m), 3.80 (2H, m), 3.52 (2H, m), 1.96 (1H, m), 1.56 (3H, m).

[00176] Compounds prepared in a similar manner to that set out above are given below in **Table 3**.

Table 3

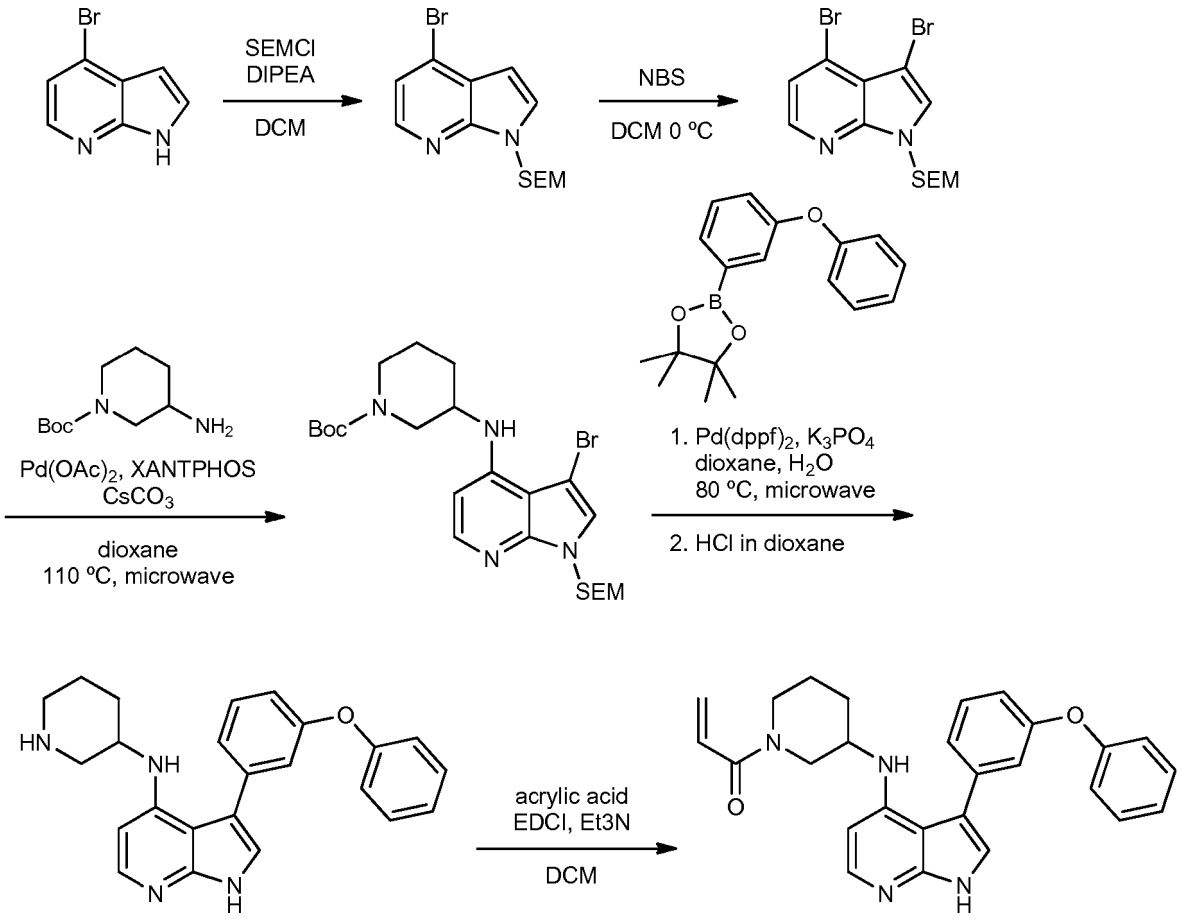
STRUCTURE	LCMS
	(ES, short acidic): 1.39 min, m/z 439.4 [M+H]
	(ES, short acidic): 1.20 min, m/z379.3 [M+H]
	(ES, short acidic): 0.92 min, m/z 448.3 [M+H]

	(ES, short acidic): 21.53 min, m/z 441.3 [M+H]
	(ES, short acidic): 1.23 min, m/z 379.3 [M+H]
	(ES, short acidic): 1.52 min, m/z 441.6 [M+H]

[00177] **Example 5**

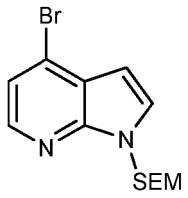
[00178] Compounds of the invention may be synthesised by analogy with Route C, shown below.

[00179] **Route C**



[00180] A method for preparing a compound of the invention is given below. Further compounds that can be prepared in a similar manner are given in **Table 3**.

2-[(4-Bromopyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane

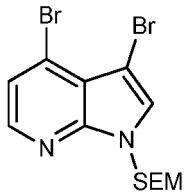


4-Bromo-1H-pyrrolo[2,3-b]pyridine (1.g, 5.08mmol) was dissolved in DCM (20mL) and DIPEA (1.81mL, 10.15mmol) was added. 2-(Trimethylsilyl)ethoxymethyl chloride (0.9mL, 5.08mmol) was added under a nitrogen atmosphere at 0°C. Once dropwise addition was completed, the reaction was allowed to warm to room temperature before being left to stir for 72h. Brine (10 mL) was added. Organic phase was separated and dried in vacuo. The oil recovered was purified by column chromatography (Et0Ac (0 to 30% in heptane) to give 2-[(4-bromopyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane (1.56g, 94 % yield) as a yellow oil.

LCMS: N200191-31-A (ES+, short acidic): 2.22 min, m/z 329.1 $[M+H]^+$

NMR ($CDCl_3$): 8.14 (1H, d, J 5.2 Hz), 7.41 (1H, d, J 3.6 Hz), 7.30 (1H, d, J 5.2 Hz), 6.57 (1H, d, J 3.6 Hz), 5.67 (2H, bs), 3.53 (2H, m), 0.92 (2H, m), -0.05 (9H, s)

2-[(3,4-dibromopyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane

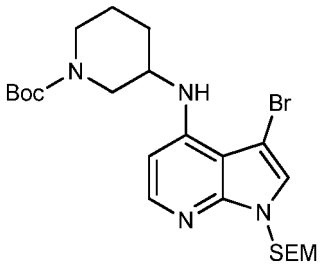


To a stirred solution of 2-[(4-bromopyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane (1.51g, 4.61mmol) in DCM (23.068mL) at 0 °C was added N-bromosuccinimide (862.19mg, 4.84mmol) and the reaction mixture stirred at 0 °C. After 2 hours, the reaction was diluted with water (20 mL), extracted with DCM (3 x 10 mL) and separated with a hydrophobic frit. The reaction was concentrated to dryness. The crude was then purified by flash column chromatography eluting (0 to 100% EtOAc in heptane). The desired fractions were concentrated to dryness in vacuo to yield 2-[(3,4-dibromopyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane (1.231 g, 76%)

LCMS-N200212-15a (ES^+, short acidic): 2.34 min, m/z 405.0 & 407.0 & 409.0 $[M+H]^+$

NMR ($CDCl^3$): 8.11 (1H, m), 7.46 (1H, s), 7.33 (1H, m), 5.64 (2H, s), 3.53 (2H, m), 0.92 (2H, m), -0.05 (9H, s).

tert-Butyl 3-[[3-bromo-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-yl]amino]piperidine-1-carboxylate



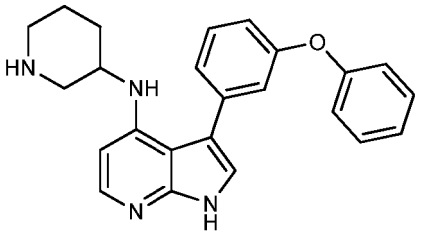
2-[(3,4-Dibromopyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane (200.mg, 0.4900mmol), 1-N-Boc-3-mehylaminopiperidine (147.93mg, 0.7400mmol) and caesium carbonate (320.87mg, 0.9800mmol) were suspended in 1,4-dioxane (3mL) and the resulting solution was thoroughly degassed. Palladium acetate (11.03mg, 0.0500mmol) and Xantphos (56.98mg, 0.1000mmol) were added and the reaction was heated to 110°C for 1 hour under microwave conditions. The reaction was then diluted with DCM and water before being passed through a phase separator, the combined organics were then concentrated to dryness giving a brown oil. The residue was purified by column chromatography (0 to 100% EtOAc in heptane). The fractions were combined and

concentrated to dryness giving tert-butyl 3-[[3-bromo-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-yl]amino]piperidine-1-carboxylate (114.3mg,0.2175mmol, 44% yield) as an oil.

LCMS: (ES+, short acidic): 1.87 min, m/z 527.3 [M+H]+

NMR: ($CDCl_3$): 8.034 (1H, m), 7.088 (1H, s), 6.291 (1H, m), 5.914 (1H, m), 5.559 (2H, m), 3.830 (1H, m), 3.535 (2H, m), 3.349 (2H, m), 2.032 (1H, m), 1.806 (1H, m), 1.741 (1H, m), 1.632 (1H, m), 1.410 (10H, m), 0.913(3H, m), -0.043 (9H, s).

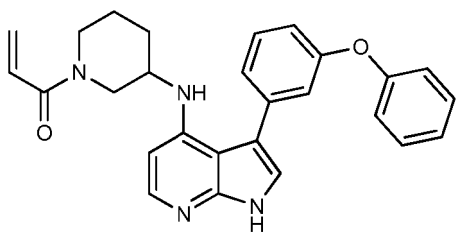
3-(3-Phenoxyphenyl)-N-(3-piperidyl)-1H-pyrrolo[2,3-b]pyridin-4-amine



tert-Butyl 3-[[3-bromo-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-yl]amino]piperidine-1-carboxylate (114.74mg, 0.2200mmol), 3-Phenoxyphenyl boronic acid (56.07mg, 0.2600mmol) and Potassium phosphate tribasic (139.03mg, 0.6500mmol) were dissolved into 1,4-Dioxane (3mL) and Water (0.7500mL) and the resulting solution was thoroughly degassed. [1,1'-Bis(diphenylphosphino)ferrocene]Palladium(II) chloride dichloromethane complex (17.79mg, 0.0200mmol) was added and the reaction mixture was heated to 80 °C for 60 minutes under microwave conditions. The mixture was diluted with DCM (~25 mL) and water (~5 mL). The organic phases were separated and concentrated to dryness to give a brown oil. The oil was dissolved into 4 M HCl in dioxane (20.mL, 80mmol) and was allowed to stir for 16 hours at room temperature. The reaction was then concentrated before being purified by SCX column. The basic wash was concentrated to dryness to give 3-(3-phenoxyphenyl)-N-(3-piperidyl)-1H-pyrrolo[2,3-b]pyridin-4-amine (65.0 mg, 0.1691 mMol, 77.4 %) as a light yellow powder.

LCMS: N200191-50-C (ES+, short acidic): 1.11 min, m/z 385.3 [M+H]+

1-[3-[[3-(3-phenoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl]amino]-1-piperidyl]prop-2-en-1-one



[00181] N-(3-Dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (48.61mg, 0.2500mmol) was dissolved in DCM (3 mL) and placed under a nitrogen atmosphere. Triethylamine (0.07mL, 0.5100mmol) was added and allowed to stir for 1 minute. Acrylic acid (0.01mL, 0.2000mmol) was then added and allowed to pre-form for 10 minutes. 3-(3-phenoxyphenyl)-N-(3-piperidyl)-1H-pyrrolo[2,3-b]pyridin-4-amine (65.0mg, 0.1700mmol) was dissolved in DCM (1 mL) and THF (2 mL), the solution was then added to the acrylic acid mixture and the reaction was allowed to stir overnight. DCM (20 mL) and water (20 mL) were added before the mixture was passed through a phase separator. The aqueous phase was washed twice more with DCM (10 mL) again being passed through the phase separator. The combined organics were then concentrated to dryness to give a dark brown residue. The residue was purified by prep LCMS. 1-[3-[[3-(3-phenoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl]amino]-1-piperidyl]prop-2-en-1-one (3.3 mg, 0.0063 mMol, 3.7%) was recovered as an oil.

LCMS: (ES+, short acidic): 1.38 min, m/z 439.4 [M+H]+

NMR ($CDCl_3$): 9.202 (1H, m), 8.076 (1H, m), 7.369 (5H, m), 7.136, (2H, m), 7.081 (2H, m), 7.036 (1H, m), 6.992 (1H, m), 6.564 (1H, m), 6.367 (1H, m), 6.221 (1H, m), 5.635 (1H, m), 4.647 (1H, m), 3.771 (1H, m), 3.616 (1H, m), 3.208 (1H, m), 2.019 (1H, m), 1.584 (2H, m)

[00182] **Example 6**

[00183] BTK Binding Activity

[00184] BTK binding activity of each compound tested was determined using a time-resolved fluorescence resonance energy transfer (TR-FRET) methodology. 2.5nM Recombinant BTK kinase, varying concentrations of inhibitor, 2nM Lanthascreen™ Eu anti-His Antibody and 15nM Kinase Tracer 236 was incubated in 1X Lanthascreen™ Kinase Buffer A for five hours. Recombinant BTK kinase and all Lanthasceen™ components were purchased from Invitrogen. Measurements were performed in a reaction volume of 30µl using half-area 96-well assay plates. The TR-FRET signal was read on a plate reader with an excitation wavelength of 340nm and detection wavelengths of 615 and 665nm. Binding activity was determined for each compound by measuring TR-FRET activity at various concentrations of compound and plotting the relative fluorescence units against the inhibitor concentration to estimate the IC_{50} from log[Inhibitor] vs response using the Variable Slope model in Graphpad prism from Graphpad software (SanDiego, Calif).

[00185] **Table 3** below shows the BTK binding, as determined by the assay described above, for certain compounds of formula (**I**), characterised based on the BTK IC50 value of the compound as "+", "++" and "+++". The category "+" refers to compounds with a BTK

IC50 of >250 nM. The category "++" refers to compounds with a BTK IC50 of 15 nM to 250 nM. The category "+++" refers to compounds with a BTK IC50 of <15 nM.

Table 3

ID No.	Compound	Category
1	1-[3-[[5-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	+
2	1-[3-[[5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	++
3	1-[3-[[5-(1-benzylpyrazol-4-yl)-7<l>H</l>-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	++
4	1-[(3*S*)-3-[[5-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	++
5	1-[(3*R*)-3-[[5-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	+
6	1-[(3*S*)-3-[[5-(1-benzylpyrazol-4-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	+++
7	1-[(3*R*)-3-[[5-(1-benzylpyrazol-4-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	+
8	1-[3-[[3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	++
9	1-[3-[[3-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	+
10	1-[3-[[3-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	+

11	1-[3-[[3-(3-phenoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	+++
12	1-[3-[[3-(3-phenoxyphenyl)-1*H*-pyrrolo[2,3-b]pyridin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	++
13	2-chloro-1-[(3*R*)-3-[[5-(3-phenoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]ethanone	+++
14	1-[3-[[5-(3-phenoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	+++
15	5-(3-phenoxyphenyl)-*N*-[(3*R*)-1-vinylsulfonyl-3-piperidyl]-7*H*-pyrrolo[2,3-d]pyrimidin-4-amine	+++
16	(*E*)-4-(dimethylamino)-1-[(3*R*)-3-[[5-(3-phenoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]but-2-en-1-one	++

[00186] Examples of compounds of the invention with values for the BTK IC50 are given in the table below.

ID No.	**Compound**	**IC50 (nM)**
6	1-[(3*S*)-3-[[5-(1-benzylpyrazol-4-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	11
13	2-chloro-1-[(3*R*)-3-[[5-(3-phenoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]ethanone	3
14	1-[3-[[5-(3-phenoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-1-piperidyl]prop-2-en-1-one	5

[00187] The following assays may be used by the skilled person to investigate the efficacy of BTK inhibitors.

Off-Rate Assay

[00188] The irreversible nature of compounds was determined using an off-rate assay utilising the TR-FRET based Lanthascreen™ binding assay (Invitrogen) described above. 5nM Recombinant BTK kinase, inhibitor and 2nM Lanthascreen™ Eu anti-His Antibody were incubated in a total volume of 30µl in 1X Lanthascreen™ Kinase Buffer A for one hour. The reaction was then diluted 33-fold into a saturating concentration of Kinase Tracer 236 in a half-area 96-well assay plate and the TR-FRET signal was measured at regular intervals over three hours. The concentration of inhibitor to be incubated with kinase was determined by calculating 40X Ki, where the Ki for each compound was calculated using the IC_{50} from the Lanthascreen™ binding assay in the following equation,

$$K_i = (IC_{50}) / (1+([Tracer]/K_d))$$

[00189] Controls were performed in the absence of inhibitor and in the absence of kinase and positive controls consisted of using 40X Ki of known reversible and irreversible BTK kinase inhibitors. The no kinase control values were then subtracted from each value for each time point and these values were calculated as a percentage of the no inhibitor control at each time point.

BTK In Vitro Inhibitory Activity

[00190] The BTK kinase activity was determined using the Omnia® assay (Invitrogen) that utilises a chelation enhanced fluorophore (CHEF) incorporated into a peptide substrate. Phosphorylation of the peptide by a kinase results in increased fluorescence and so the increase in fluorescence can be used as a measure of kinase activity. 150nM recombinant BTK kinase (Invitrogen) and inhibitor were pre-incubated for 30min in 1X Kinase Reaction Buffer before transferring 10µl of this into 30µl of Omnia master mix to give final concentrations of 37.5nM BTK, 0.2mM DTT, 10µM Omnia® peptide and 0.1mM ATP (K_mATP = 0.15mM). Measurements were performed in half-area 96-well assay plate and the fluorescence was read in a kinetic manner on a plate reader with an excitation wavelength of 360nm and detection wavelength of 485nm.Controls were performed in the absence of kinase and the fluorescence values from these wells were subtracted from each of the test wells at each time point. The initial velocity (0-15min) was then determined from the slope of a plot of relative fluorescence units plotted against time (in seconds) and the velocities were then plotted against the inhibitor concentration to estimate the IC_{50} from log[Inhibitor] vs response using the Variable Slope model in Graphpad prism from Graphpad software (SanDiego, Calif).

BTK Cellular Assay

[00191] Compounds were assayed in Ramos human Burkitt Lymphoma cells. Ramos cells were grown in suspension in T225 flasks, centrifuged and re-suspended in serum-free media. Cells were then plated at $1.5x10^6$/ml in serum-free media and varying concentrations of compound and incubated for 2 hours at 37°C. Cells were then stimulated for 10 min in 5µg/ml goat F(ab')2 Anti-Human IgM (Invitrogen) to activate B-cell receptor signalling. The cells were then washed once in ice cold PBS and lysed on ice in lysis buffer consisting of 150mM NaCl, 50mM Tris pH8 containing freshly added Halt Protease and Phosphatase Inhibitor Cocktails (Pierce). 15µg total protein from lysates was loaded onto gels and blots were probed for Total BTK and phosphorylation of BTK at Y223 using antibodies from Cell signalling Technology # 3533 and #5082.

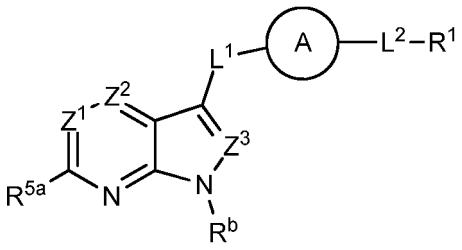
[00192] Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of them mean "including but not limited to", and they are not intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

[00193] Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

[00194] The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

CLAIMS

1. A compound according to formula (**I**) and pharmaceutically acceptable salts and solvates thereof:



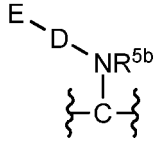
(**I**)

wherein

A is selected from substituted or unsubstituted phenyl, pyridinyl and pyrazolyl, and wherein the ring may be substituted by 1 to 4 R^a;

R^a is selected from the group comprising: H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OH, SH, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, NR^bR^c, -CN, acyl, -$C(O)R^b$, -$C(O)OR^b$, -SO_2R^b, and -SO_3R^b;

R^b and R^c are independently selected at each occurrence from: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} acyl, C_{3-7} cycloalkyl, and C_{3-7} halocycloalkyl;

one of Z^1 and Z^2 is  and the other is selected from CR^{5d} or N;

Z^3 is selected from CR^{5c} or N

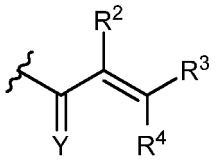
D is either a substituted or unsubstituted C_{1-6} alkylene chain which is saturated or unsaturated and which may optionally also contain, where chemically possible, 1, 2 or 3 N, O, or S atoms in the chain which are independently chosen at each occurrence;

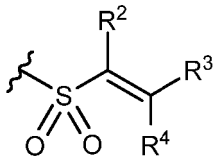
or D represents a substituted or unsubstituted carbocyclic or heterocyclic moiety which is saturated or unsaturated and which contains from 3 to 8 atoms in the carbocyclic or

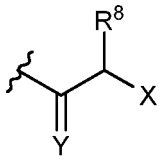
heterocyclic ring, wherein the ring is optionally substituted with –NR^b-, wherein –NR^b- is bonded to the ring and the rest of the molecule;

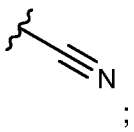
and wherein, when substituted, the alkylene chain or the carbocyclic or heterocyclic moiety includes 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, -OR^b, - SR^b, -NR^bR^c, NO, =O, -CN, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, -SO_2R^b, and SO_3R^b , -$C(O)R^b$ and $C(O)OR^b$;

E is selected from:







or


;

Y is either O or NR^b and X is halo;

R^1 is –NR^6R^7, -OR^9, or a substituted or unsubstituted carbocyclic or heterocyclic moiety which is saturated, unsaturated or aromatic and which either contains from 3 to 8 atoms in a single ring or 7 to 14 atoms in a fused polycyclic ring system, when substituted, R^1 contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, -OR^b, - SR^b, -NR^bR^c, NO, =O, -CN, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, -SO_2R^b, and SO_3R^b , -$C(O)R^b$ and $C(O)OR^b$;

R^2, R^3, R^4 and R^8 are independently selected from H, halo, -OR^b, -CN, -NR^bR^c, -$CH_2NR^bR^c$, -CO_2R^b, -$C(O)R^b$, -$C(O)NR^bR^c$, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkyl substituted with C_{3-8} cycloalkyl, C_{1-6} alkyl substituted with C_{3-8} heterocycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{3-8} heterocycloalkyl, C_{3-8} cycloalkenyl, C_{3-8} heterocycloalkenyl, aryl, heteroaryl, alkaryl and alkheteroaryl;

or R^2 and R^3 taken together with the carbon atoms to which they are attached form a C_{3-8} cycloalkene and R^4 is independently selected as above;

or R^3 and R^4 taken together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl and R^2 is independently selected as above;

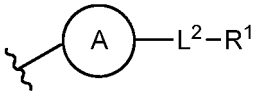
or R^2 and R^4 taken together with the carbon atoms to which they are attached form a C-C triple bond and R^3 is independently selected as above;

R^{5a}, R^{5b}, R^{5c} and R^{5d} are at each occurrence independently selected from H, halo, -OR^b, C_{1-6} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{3-8} heterocycloalkyl, C_{3-8} cycloalkenyl, C_{3-8} heterocycloalkenyl, -NR^bR^c, -CO_2R^b, -$C(O)R^b$ and -$C(O)NR^bR^c$;

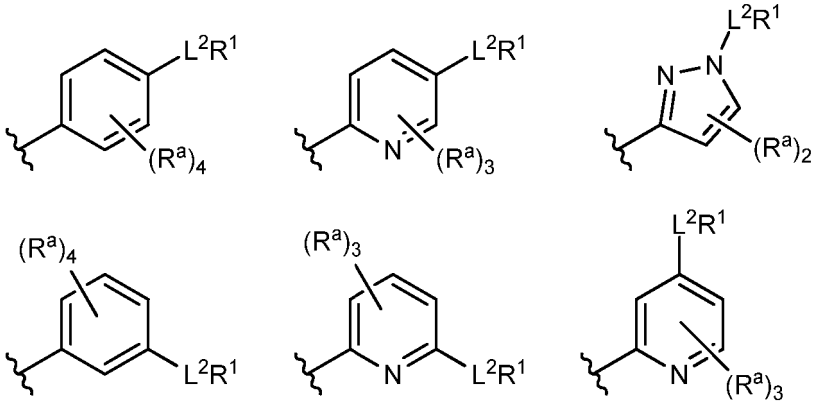
R^6 , R^7 and R^9 may be independently be selected from H, substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, -$(CR^dR^e)_n$-aryl and -SO_2R^b, wherein n is 0, 1 or 2;

L^1 and L^2 are independently selected from a bond, -O-, -$O(CR^dR^e)_m$-, -NR^b-, -$C(O)NR^b$- and -$(CR^dR^e)_m$-, wherein R^d and R^e are independently selected at each occurrence from: H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} acyl, C_{3-7} cycloalkyl, and C_{3-7} halocycloalkyl; and

m is selected from 1, 2, 3 and 4.

2. The compound of claim 1 wherein 

is selected from:



3. The compound of claim 1 or claim 2, wherein R^1 may be –OR^9 or a substituted or unsubstituted carbocyclic or heterocyclic moiety which is saturated, unsaturated or aromatic and which either contains from 3 to 8 atoms in a single ring or 7 to 14 atoms in a fused polycyclic ring system, wherein, when substituted, R^1 contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, -OR^b, - SR^b, -NR^bR^c, NO, =O, -CN, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, -SO_2R^b, and SO_3R^b , -$C(O)R^b$ and $C(O)OR^b$.

4. The compound of claim 3, wherein carbocyclic moiety may be selected from substituted or unsubstituted: cycloheptanyl, cyclohexanyl, cyclohexenyl, cyclopentanyl,

cyclopentenyl, cyclobutanyl, cyclopropanyl, indenyl, phenyl, tetralin and naphthyl and the heterocyclic moiety may be selected from substituted or unsubstituted: piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, pyrolidinyl, imidazolidinyl, succinimidyl, pyrazolidinyl, tetrahydrofuranyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, oxetanyl, azetidinyl, oxiranyl, aziridinyl, oxepanyl, azepane, oxazepane, diazepane furanyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, dihydroindazolyl, dihydrobenzimidazolyl, qiunolinyl, isoquinolinyl, tetrahydroqiunolinyl, tetrahydroisoquinolinyl,phtalazinyl, tetrahydrophthalazinyl, quinazolinyl, tetrahydroquinazolinyl, chromanyl and isochromanyl.

5. The compound of claim 3, wherein R^1 is a substituted or unsubstituted heterocyclic moiety which is saturated, unsaturated or aromatic and the heteroatom is N.

6. The compound of claim 5 wherein the heterocyclic moiety is a substituted or unsubstituted heterocycloalkyl, heterocycloalkenyl or heteroaryl, wherein the heteroatom is N and the heterocycloalkyl, heterocycloalkenyl or heteroaryl may have 1, 2 or 3 N atoms.

7. The compound of any of claims 1 to 3, wherein R^1 is selected from substituted or unsubstituted: $-OC_{1-4}$ alkyl, phenyl, morpholinyl, pyridiyl benzosuccinimidyl, quinolinyl and isoquinolinyl.

8. The compound of any of claim 1 to 3, wherein R^1 is $-NR^6R^7$.

9. The compound of any of claims 1 to 3 or claim 8, wherein R^6 and R^7 are independently selected from: H, C_{1-6} alkyl, C_{1-6} haloalkyl, $-(CR^dR^e)_n$ -aryl and $-SO_2R^b$, wherein n is 0, 1 or 2.

10. The compound of any of claims 1 to 3 or claim 8 to 9, wherein R^6 is C_{1-6} alkyl and R^7 is C_{1-6} alkyl, C_{1-6} haloalkyl, $-(CR^dR^e)_n$ -aryl, wherein n is 0, 1 or 2.

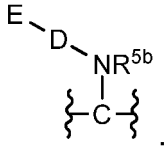
11. The compound of any of claims 1 to 3 or claim 8 to 10, wherein:

R^6 is methyl, ethyl or propyl and R^7 is methyl, ethyl or propyl; or

R^6 is methyl or ethyl and R^7 is C_{1-6} haloalkyl; or

R^6 is methyl, ethyl or propyl and R^7 is $-(CH_2)_n$ -phenyl wherein n is 0 or 1; or

R^6 is H and R^7 is $-SO_2R^b$, wherein R^b is methyl, ethyl or fluoromethyl.

12. The compound of any preceding claim, wherein Z^1 is N and Z^2 is 

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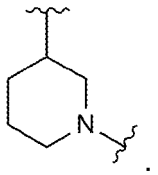
13. The compound of any preceding claim, wherein D is selected from substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-8} heterocycloalkyl and substituted or unsubstituted C_{3-8} heterocycloalkenyl where N is the heteroatom and D comprises 1 or 2 nitrogen atoms.

14. The compound of any preceding claim, wherein D is:



15. The compound of any preceding claim, wherein Y is O.

16. The compound of any preceding claim, wherein X is chloro.

17. The compound of any preceding claim, wherein two of R^2, R^3 and R^4 may be hydrogen and the other may be fluorine, chlorine, bromine, iodine, -CN, $-CH_2NR^bR^c$ and C_{1-6} alkyl, where R^b and R^c are independently selected from hydrogen and C_{1-6} alkyl.

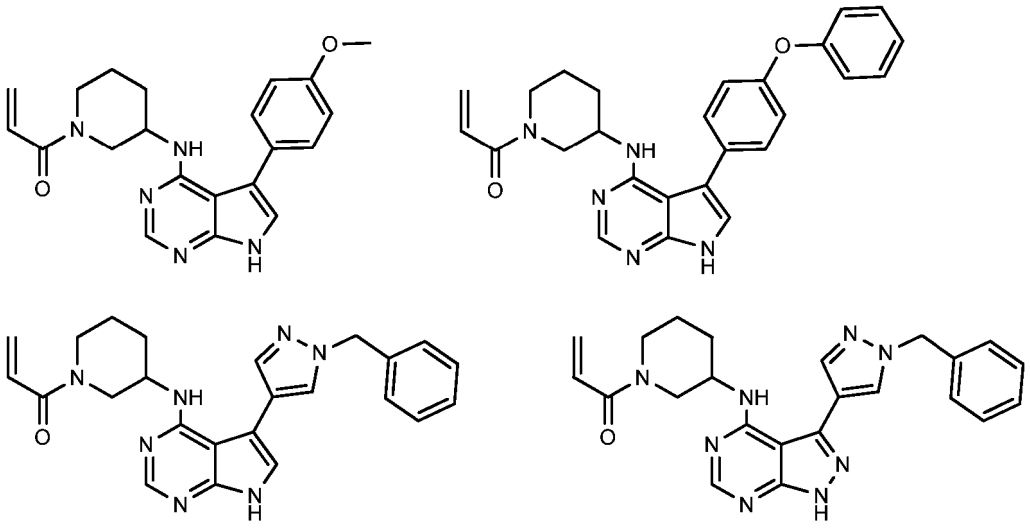
18. The compound of any of claims 1 to 16, wherein R^2, R^3, and R^4 are all hydrogen

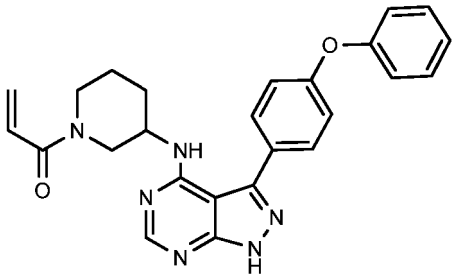
19. The compound of any of claims 1 to 16, wherein R^8 is selected from H, C_{1-6} alkyl and aryl

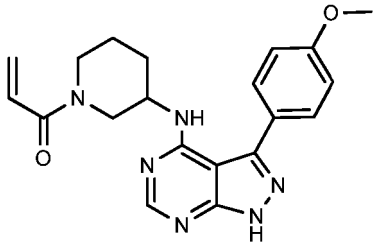
20. The compound of any preceding claim, wherein L^2 is selected from a bond, $–OCH_2-$, $-CH_2-$, -O-, –NH-and C(O)NH-.

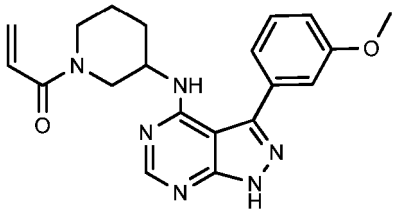
21. The compound of any preceding claim, wherein L^1 is selected from a bond, $-CH_2-$, -O- and –NH-.

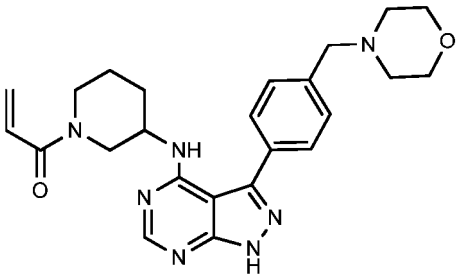
22. The compound of claim 1, wherein the compound of formula (**I**) is a compound selected from:

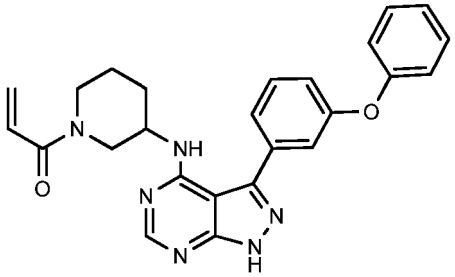


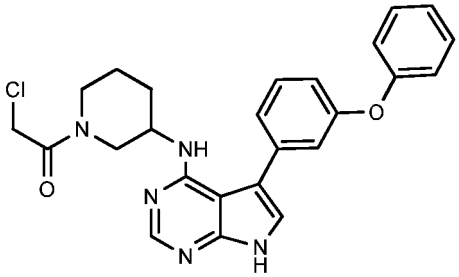


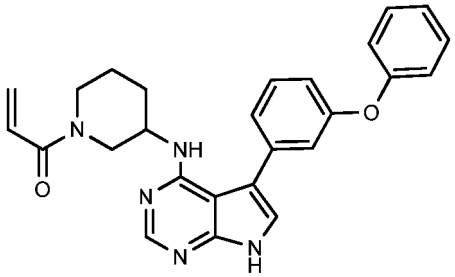


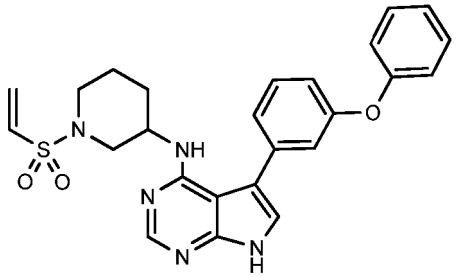


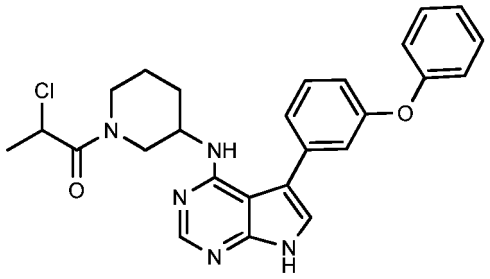


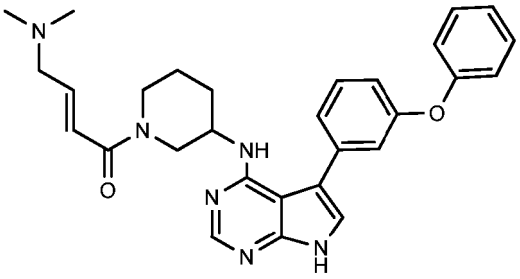












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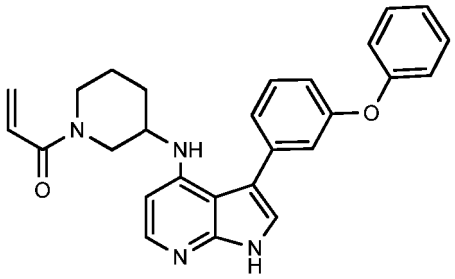

23. A compound of any preceding claim for use as a medicament.

24. A compound of any or claims 1 to 22 for use in the treatment of a condition which is modulated by BTK.

25. A compound of claim 24 wherein the condition modulated by BTK is cancer, lymphoma, leukemia, immunological disease, autoimmune diseases and inflammatory disorders.

26. A compound of claims 24 or claim 25, wherein the condition modulated by BTK is selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkins lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkins lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease and lupus.

27. A compound of any of claims 1 to 22 for use simultaneously, sequentially or separately with an additional anti-tumour agent, in the treatment of cancer, lymphoma, leukemia or immunological diseases.

28. A pharmaceutical composition, wherein the composition comprises a compound of any of claims 1 to 22 and pharmaceutically acceptable excipients.

29. A pharmaceutical composition of claim 28 wherein the composition is a combination product and comprises an additional pharmaceutically active agent.

30. A method of treatment of a condition which is modulated by Bruton's tyrosine kinase, wherein the method comprises administering a therapeutic amount of a compound of any of claims 1 to 22, to a patient in need thereof.

31. The method of claim 30 wherein the condition modulated by BTK is cancer, lymphoma, leukemia, immunological disease, autoimmune diseases and inflammatory disorders.

32. A compound of claims 30 or claim 31, wherein the condition modulated by BTK is selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkins lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkins lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease and lupus.

33. A method of treatment of a condition selected from cancer, lymphoma, leukemia or immunological diseases comprising administering a therapeutically effective amount of a compound any of claims 1 to 22, simultaneously, sequentially or separately with an additional anti-tumour agent to a patient in need thereof.

34. A method of providing a combination product, wherein the method comprises providing a compound of any of claims 1 to 22 simultaneously, sequentially or separately with an anti-tumour agent.

35. Use of a compound of any of claims 1 to 22 in the manufacture of a medicament for the treatment of a condition which is modulated by Bruton's tyrosine kinase.

36. Use of a compound of any of claims 1 to 22 in combination with an anti-tumour agent.

Application No:	GB1311951.6	**Examiner:**	Dr S. David Evans
Claims searched:	1-36	**Date of search:**	10 December 2013

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1, 23-36 at least	WO 2008/079346 A (VERTEX PHARMA) see whole document, but especially the Markush structure shown in claim 1
X	1, 23-36 at least	US 2006/030583 A1 (ARNOLD et al) see entire document, particularly the gernic structure disclosed in claim 1
X	1, 23-36 at least	WO 2010/003133 A (EXELIXIS INC) see whole document, especially the Markush structure of formula I in claim 1
X	1, 23-36 at least	WO 2011/008915 A (ABBOTT LAB) see entire document, particularly the generic structure of formula (I) in claim 1
X	1, 23-36 at least	WO 2006/058074 A (VERTEX PHARMA) see whole document, particularly the Markush structure of formula I shown in claim 1

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

C07D

The following online and other databases have been used in the preparation of this search report

CAS ONLINE, WPI, EPODOC

International Classification:

Subclass	Subgroup	Valid From
C07D	0487/04	01/01/2006
A61K	0031/437	01/01/2006
A61K	0031/519	01/01/2006
A61P	0035/00	01/01/2006
A61P	0035/02	01/01/2006
C07D	0471/04	01/01/2006