

care in B-cell malignancies, it would be desirable to have a BTK inhibitor with high selectivity for BTK over ITK.

[0007] In the clinic, adverse events have included atrial fibrillation, diarrhea, rash, arthralgia and bleeding (IMBRUVICA package insert 2014). Known BTK inhibitors, e.g. ibrutinib are also known to have gastrointestinal side effects, which are considered to be as a result of a secondary EGFR inhibitory activity. It is therefore desirable to have a BTK inhibitor with high BTK inhibition and low EGFR inhibition to reduce or avoid the gastrointestinal side effects.

[0008] Irreversible and covalent reversible BTK inhibitors specifically target a cysteine residue C481 within BTK. Following treatment with ibrutinib, cases of primary and secondary resistance have emerged. Mutations within BTK such as C481S, C481Y, C481R, C481F have been reported in the literature and clearly interfere with drug binding (Woyach 2014; Maddocks 2015). It has been predicted that the incidence of observed resistance will increase as clinical use outside clinical trials expands over time (Zhang 2015).

[0009] Therefore, an aim of the present invention is to provide BTK inhibitors with a different binding mode more specifically reversible inhibitors. In addition the invention aims to provide BTK inhibitors with high selectivity for BTK inhibition over EGFR and ITK inhibition.

[0010] Furthermore, it is an aim of certain embodiments of this invention to provide new cancer treatments. In particular, it is an aim of certain embodiments of this invention to provide compounds which have comparable activity to existing cancer treatments but are also effective against mutations. One of the aspects of the invention focus on providing BTK inhibitors effective against the C481 mutations.

[0011] It is an aim of certain embodiments of this invention to provide compounds which exhibit reduced cytotoxicity relative to prior art compounds and existing therapies.

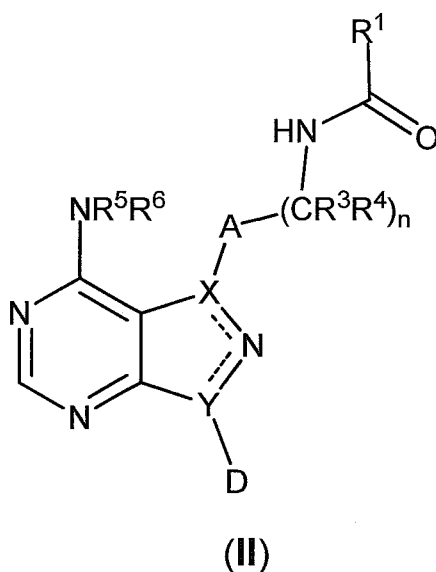
[0012] Another aim of certain embodiments of this invention is to provide compounds having a convenient pharmacokinetic profile and a suitable duration of action following dosing. A further aim of certain embodiments of this invention is to provide compounds in which the metabolised fragment or fragments of the drug after absorption are GRAS (Generally Regarded As Safe).

[0013] Certain embodiments of the present invention satisfy some or all of the above aims.

[0014] SUMMARY OF THE DISCLOSURE

[0015] In accordance with the present disclosure there is provided compounds as disclosed below. Furthermore, the disclosure provides compounds capable of inhibiting Bruton's tyrosine kinase (BTK) and the use of these compounds in inhibiting BTK. In accordance with the disclosure there is provided a method of treating conditions modulated by BTK. The disclosure provides compounds for use in treating a condition which is modulated by BTK.

[0016] In a first aspect of the invention there is provided a compound according to formula (I) or pharmaceutically acceptable salts thereof:



[0023] In an embodiment R^3 and R^4 are independently selected at each occurrence from: H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl substituted with $-OR^h$, $-OR^h$, or R^3 and R^4 taken together with the atom on which they are substituted, form a 3 to 6 membered cycloalkyl ring. Preferably, R^3 and R^4 are independently selected at each occurrence from: H, halo (e.g. fluoro and chloro), C_{1-4} alkyl (e.g. methyl or ethyl), C_{1-4} haloalkyl (e.g. trifluoromethyl or trifluoroethyl), $-OR^h$ (e.g. methoxy, ethoxy and OCF_3), C_{1-4} alkyl substituted with $-OR^h$ (e.g. $-CH_2OH$) or R^3 and R^4 taken together with the atom on which they are substituted form a cyclopropyl ring. Further preferably R^3 and R^4 are H or methyl. Accordingly, R^3 and R^4 may be H for compounds of any formulae of the present disclosure.

[0024] In an embodiment R^3 is H and R^4 is as defined elsewhere herein.

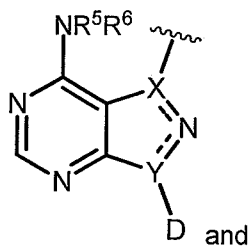
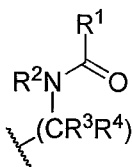
[0025] Preferably n is 1.

[0026] In an embodiment, R^5 and R^6 are hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl substituted with $-OR^h$, preferably H, methyl or $-(CH_2)_2OMe$ (optionally H or $-(CH_2)_2OMe$). R^5 may be H and R^6 may be as defined elsewhere herein. In an embodiment, R^5 is H and R^6 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl substituted with $-OR^h$. Preferably, R^5 is H and R^6 is H, methyl or $-(CH_2)_2OMe$ (optionally H or $-(CH_2)_2OMe$). R^5 and R^6 may both be hydrogen.

[0027] In a preferred embodiment, the compound of formula (I) may be a compound according to formulae (IIIa) or (IIIb):

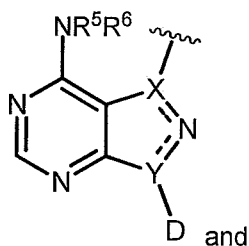
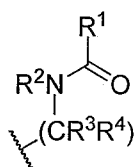
[0036] R^a and R^b may be selected from C_{1-4} alkyl, C_{1-4} alkyl substituted with $-OR^i$, or C_{1-4} haloalkyl. In particular R^a and R^b may be H, methyl, ethyl, $-CH_2OR^i$, $-(CH_2)_2OR^i$, $-CF_3$, $-CHF_2$, or $-CH_2CF_3$. R^i may be H, methyl or ethyl.

- 5 **[0037]** As the skilled person will appreciate from the definition of A, A is a 6 membered ring. A may be unsubstituted (except for the 2 groups shown in Formula (I)) or substituted by 1 to 4 further substituents as defined elsewhere herein. Thus, other than these 1 to 4 further substituents A is always substituted by



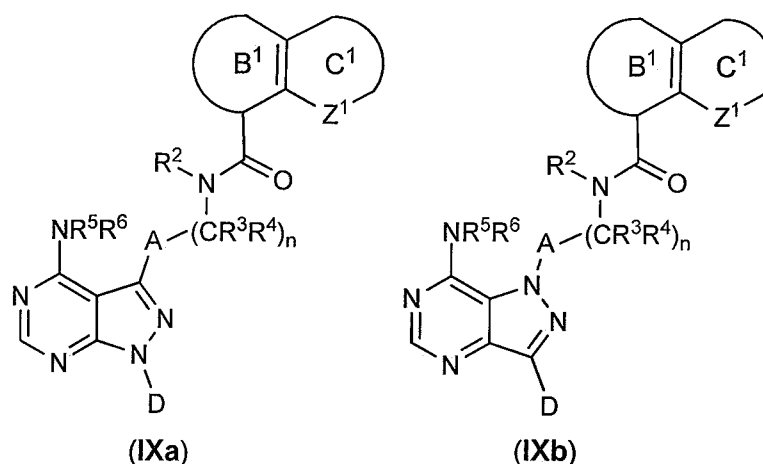
- 10 to form the compounds of formula (I), i.e. the compounds of the disclosure, and these two groups may be substituted at any (chemically possible) positions on the 6 membered ring of A. In other words, the points of attachment of these two groups on ring A may be varied. Thus, the substitution may be ortho, meta or para. Preferably the substitution is meta or para, most preferably para.

- 15 **[0038]** In some embodiments A is an optionally further substituted: phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring with the further substituents being independently selected from fluoro, methyl or methoxy and the two groups



may be substituted meta or para to one another on A.

- 20 **[0039]** A may be phenyl, fluorophenyl, methoxyphenyl, methylphenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl and the two groups



wherein ring B¹ represents a substituted or unsubstituted 5 or 6 membered: aryl, heteroaryl, cycloalkyl, cycloalkylene, heterocycloalkyl or heterocycloalkylene ring;

ring C¹ represents a heteroaryl, heterocycloalkyl or heterocycloalkylene ring; and

5 Z¹ is O, N, S or NH;

wherein at least one of ring B¹ or ring C¹ is an aryl or heteroaryl ring.

[0073] For the avoidance of doubt, rings B and C of formulae (VIIIa) and (VIIIb) and rings B¹ and C¹ of formulae (IXa) and (IXb) are fused bicyclic ring systems.

10 **[0074]** Compounds of the disclosure where R¹ comprises an acceptor function ortho to the -C(=O)- group are particularly preferred. The acceptor function being a hydrogen bond acceptor. The ortho acceptor function may be within a ring fused to the ring attached to -C(=O)-, a substituent on R¹, or within the ring which is attached to -C(=O)-. Without being bound by theory it is believed that the ortho acceptor function might improve permeability of the compounds of the present disclosure. Therefore, in certain embodiments of the present disclosure it is an aim to improve permeability.

15 **[0075]** In an embodiment there is provided a compound of formulae (VIIIa), (VIIIb), (IXa) and (IXb) wherein R² is H. In a preferred embodiment, there is provided a compound of formulae (VIIIa), (VIIIb), (IXa) and (IXb) wherein R³ and R⁴ are H, and R⁵ and R⁶ are H. In a particularly preferred embodiment, there is provided a compound of formulae (VIIIa), (VIIIb), (IXa) and (IXb) wherein R² is H, R³ and R⁴ are H, and R⁵ and R⁶ are H. In a preferred embodiment, there is provided a compound of formulae (VIIIa), (VIIIb), (IXa) and (IXb), wherein A is unsubstituted or substituted phenyl or pyridyl (preferably unsubstituted phenyl or fluorophenyl), R³ and R⁴ are H, and R⁵ and R⁶ are H. In an embodiment, there is provided a compound of formulae (VIIIa), (VIIIb), (IXa) and (IXb), wherein A is substituted or unsubstituted phenyl or pyridyl (preferably unsubstituted phenyl or fluorophenyl), R³ and R⁴ are H, R⁵ and R⁶ are H, and rings B, C, B¹ or C¹ are independently unsubstituted or
20 substituted with 1, 2 or 3 groups selected from: methoxy, fluoro, -OCF₃, OEt, OⁱPr, Cl, Me, CF₃, or CN (preferably methoxy).
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NHC(O)Et, -NHC(O)*t*-Bu, -NHC(O)tolyl, methyl, ethyl, iso-propyl, tert-butyl, triazole, tetrazole and dioxolane. The dioxolane substituent may be substituted on D so as to form a spirocycle.

[0086] R^c, R^d and R^e are independently selected at each occurrence from: H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyl substituted with -OR^j, unsubstituted aryl and aryl substituted with halo or C₁₋₄ alkyl or C₁₋₄ haloalkyl or a combination thereof.

[0087] In an embodiment R^c and R^d are independently selected at each occurrence from: H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, and C₁₋₄ alkyl substituted with -OR^j; and R^e is selected from: H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyl substituted with -OR^j, unsubstituted aryl and aryl substituted with halo or C₁₋₄ alkyl or C₁₋₄ haloalkyl or a combination thereof.

[0088] R^h, Rⁱ, R^j, R^k, and R^l may be independently selected at each occurrence from: H, C₁₋₄ alkyl and C₁₋₄ haloalkyl. R^h, Rⁱ, R^j, R^k, and R^l are independently selected at each occurrence from: H, methyl, ethyl, -CF₃ or -CF₂H, preferably H or methyl.

[0089] In embodiments D is not unsubstituted cyclopentyl. In other words, when D is cyclopentyl it is preferably substituted by 1, 2 or 3 substituents as defined above for D. In embodiments where D is unsubstituted cyclopentyl at least one of the substituents on R¹ and the -C(=O)- group (which is bonded to R¹) are bonded to adjacent carbon atoms of R¹. In other words the substituent and -C(=O) are ortho substituted.

[0090] In embodiments there are provided compounds where:

D is selected from substituted or unsubstituted: C₁₋₆ alkyl, C₃₋₁₀ cycloalkenyl, C₆₋₁₀ aryl, 3 to 10 membered heterocycloalkyl, 3 to 10 membered heterocycloalkenyl and 5 to 10 membered heteroaryl, substituted C₃₋₁₀ cycloalkyl, unsubstituted C₃₋₄ cycloalkyl or unsubstituted C₆₋₁₀ cycloalkyl, and R¹ is a group selected from a substituted or unsubstituted: C₃₋₈ cycloalkyl, C₃₋₈ heterocycloalkyl, C₃₋₈ cycloalkenyl, C₃₋₈ heterocycloalkenyl, aryl or heteroaryl moiety, wherein the aryl or heteroaryl moiety either contains 5 or 6 atoms in a single ring or from 7 to 14 atoms in a fused polycyclic ring system; or

D is unsubstituted cyclopentyl and R¹ is a substituted or unsubstituted: C₃₋₈ cycloalkyl, C₃₋₈ heterocycloalkyl, C₃₋₈ cycloalkenyl, C₃₋₈ heterocycloalkenyl, aryl or heteroaryl moiety, wherein the aryl or heteroaryl moiety either contains 5 or 6 atoms in a single ring or from 7 to 14 atoms in a fused polycyclic ring system, wherein the -C(=O)- and one of the substituents on the C₃₋₈ cycloalkyl, C₃₋₈ heterocycloalkyl, C₃₋₈ cycloalkenyl or C₃₋₈ heterocycloalkenyl moiety or the aryl or heteroaryl single ring are bonded to adjacent carbon atoms of R¹ and the -C(=O)- group is substituted on the aryl or heteroaryl fused polycyclic ring system ortho to one of the two points of fusion of the polycyclic system.

[0091] In embodiments there are provided compounds of the disclosure, wherein:

X is C, Y is N; and

D is selected from substituted or unsubstituted: C₁₋₆ alkyl, C₃₋₁₀ cycloalkenyl, C₆₋₁₀ aryl, 3 to 10 membered heterocycloalkyl, 3 to 10 membered heterocycloalkenyl and 5 to 10 membered

heteroaryl, substituted C₃₋₁₀ cycloalkyl, unsubstituted C₃₋₄ cycloalkyl or unsubstituted C₆₋₁₀ cycloalkyl, and R¹ is a group selected from a substituted or unsubstituted: C₃₋₈ cycloalkyl, C₃₋₈ heterocycloalkyl, C₃₋₈ cycloalkenyl, C₃₋₈ heterocycloalkenyl, aryl or heteroaryl moiety, wherein the aryl or heteroaryl moiety either contains 5 or 6 atoms in a single ring or from 7 to 14 atoms in a fused polycyclic ring system; or

D is unsubstituted cyclopentyl and R¹ is a substituted or unsubstituted: C₃₋₈ cycloalkyl, C₃₋₈ heterocycloalkyl, C₃₋₈ cycloalkenyl, C₃₋₈ heterocycloalkenyl, aryl or heteroaryl moiety, wherein the aryl or heteroaryl moiety either contains 5 or 6 atoms in a single ring or from 7 to 14 atoms in a fused polycyclic ring system, wherein the -C(=O)- and one of the substituents on the C₃₋₈ cycloalkyl, C₃₋₈ heterocycloalkyl, C₃₋₈ cycloalkenyl or C₃₋₈ heterocycloalkenyl moiety or the aryl or heteroaryl single ring are bonded to adjacent carbon atoms of R¹ and the -C(=O)- group is substituted on the aryl or heteroaryl fused polycyclic ring system ortho to one of the two points of fusion of the polycyclic system;

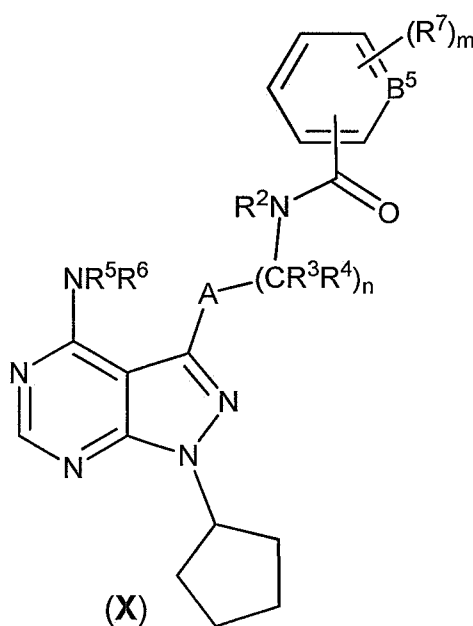
or

15 X is N, Y is C;

D is selected from substituted or unsubstituted: C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkenyl, C₆₋₁₀ aryl, 3 to 10 membered heterocycloalkyl, 3 to 10 membered heterocycloalkenyl and 5 to 10 membered heteroaryl; and

R¹ is a group selected from a substituted or unsubstituted: C₃₋₈ cycloalkyl, C₃₋₈ heterocycloalkyl, C₃₋₈ cycloalkenyl, C₃₋₈ heterocycloalkenyl, aryl or heteroaryl moiety, wherein the aryl or heteroaryl moiety either contains 5 or 6 atoms in a single ring or from 7 to 14 atoms in a fused polycyclic ring system.

[0092] In an embodiment of the disclosure there is provided a compound according to formula (X):

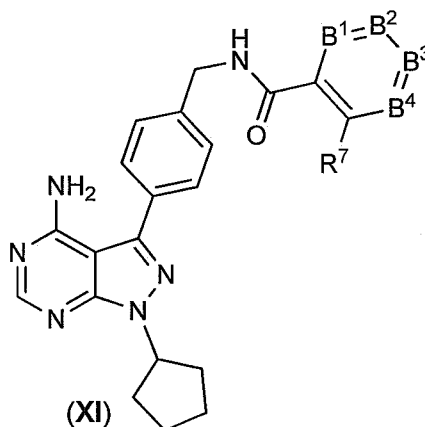


wherein B⁵ is CH or N and m is 1, 2, 3 or 4 (preferably m is 1 or 2); and at least one R⁷ is substituted ortho to the -C(=O)- group.

- [0093]** In an embodiment there is provided a compound of formula (X) wherein R² is H. In a preferred embodiment, there is provided a compound of formula (X) wherein R³ and R⁴ are H, and R⁵ and R⁶ are H. In a particularly preferred embodiment, there is provided a compound of formula (X) wherein R² is H, R³ and R⁴ are H, and R⁵ and R⁶ are H. In a preferred embodiment, there is provided a compound of formula (X), wherein A is unsubstituted or substituted phenyl or pyridyl (preferably unsubstituted phenyl or fluorophenyl), R³ and R⁴ are H, and R⁵ and R⁶ are H. In an embodiment, there is provided a compound of formula (X), wherein A is substituted or unsubstituted phenyl or pyridyl (preferably unsubstituted phenyl or fluorophenyl), R³ and R⁴ are H, R⁵ and R⁶ are H, R² is H, and B⁵ is CH. R⁷ may be selected from: methoxy, fluoro, -OCF₃, OEt, OⁱPr, Cl, Me, CF₃, or CN (preferably R⁷ is methoxy). One R⁷ group may be substituted at the two position. In other words the ring containing B⁵ may be ortho substituted by one R⁷. Additional R⁷ groups may be present. Preferably, R⁷ is 2-methoxy.

- [0094]** In an embodiment the compounds of formula (X) A is phenyl or fluorophenyl.

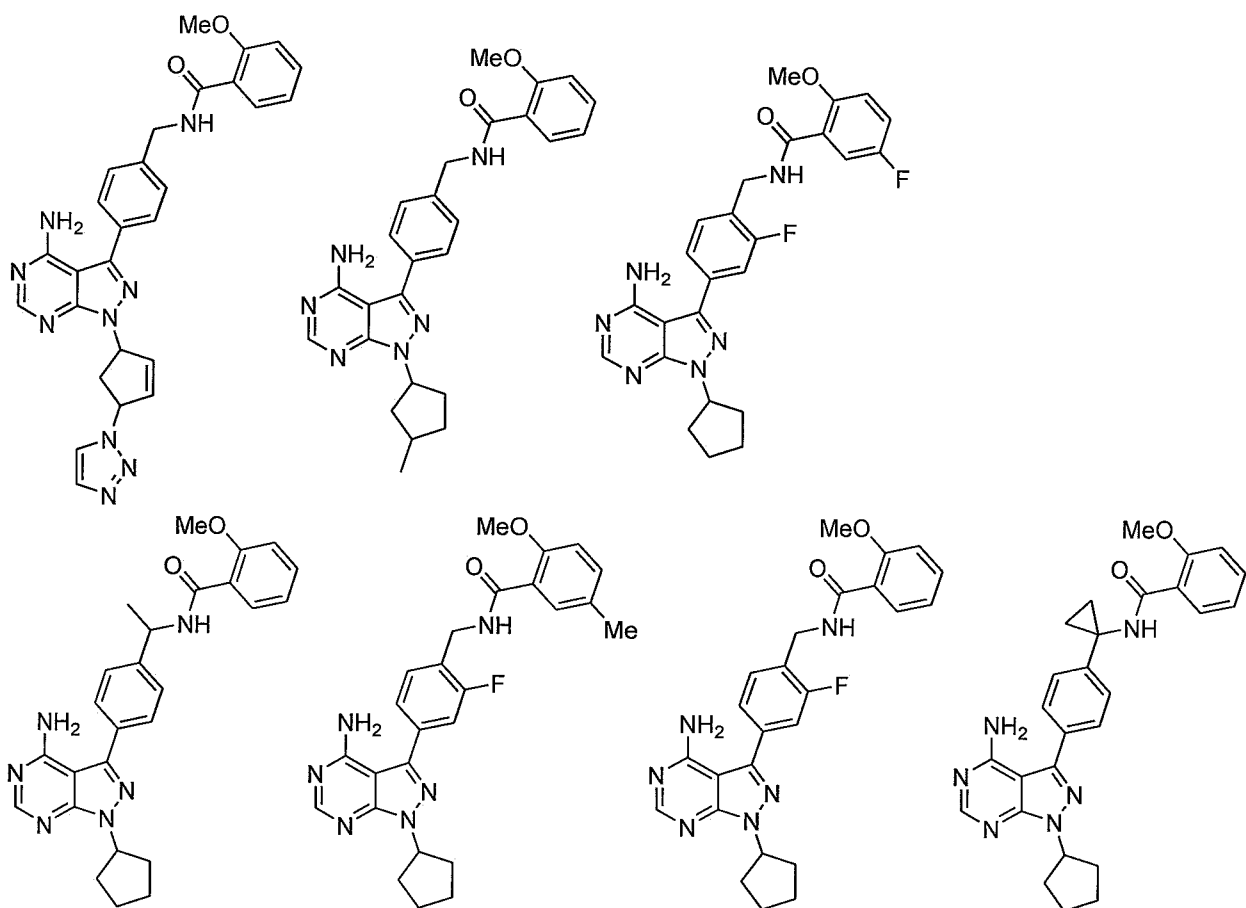
[0095] In embodiments the compound of formula (I) may be a compound according to formulae (XI):



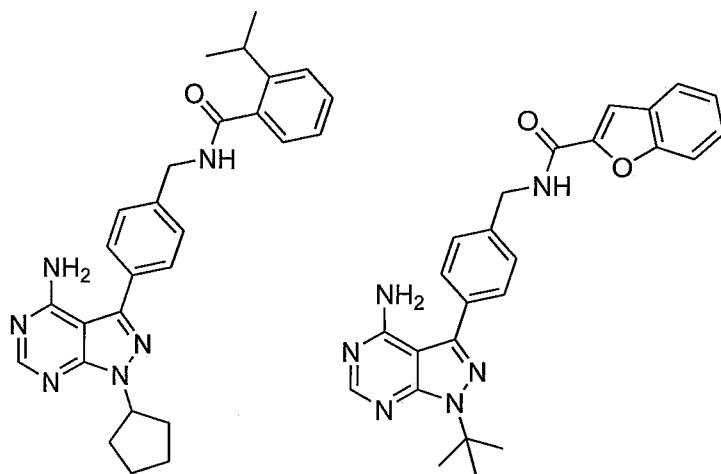
- wherein zero, one or two B¹, B², B³ and B⁴ is N and the remaining are independently selected from CH or CR⁷, and

R⁷ is independently selected at each occurrence from: halo, -OR^f, -NR^fR^g, =O, -CN, acyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl substituted with -OR^f, C₃₋₈ cycloalkyl, C₃₋₈ heterocycloalkyl, -SO₂R^f, SO₃R^f, -C(O)R^f, -C(O)OR^f, -C(O)NR^fR^g and aryl optionally substituted by 1 or 2 halo atoms.

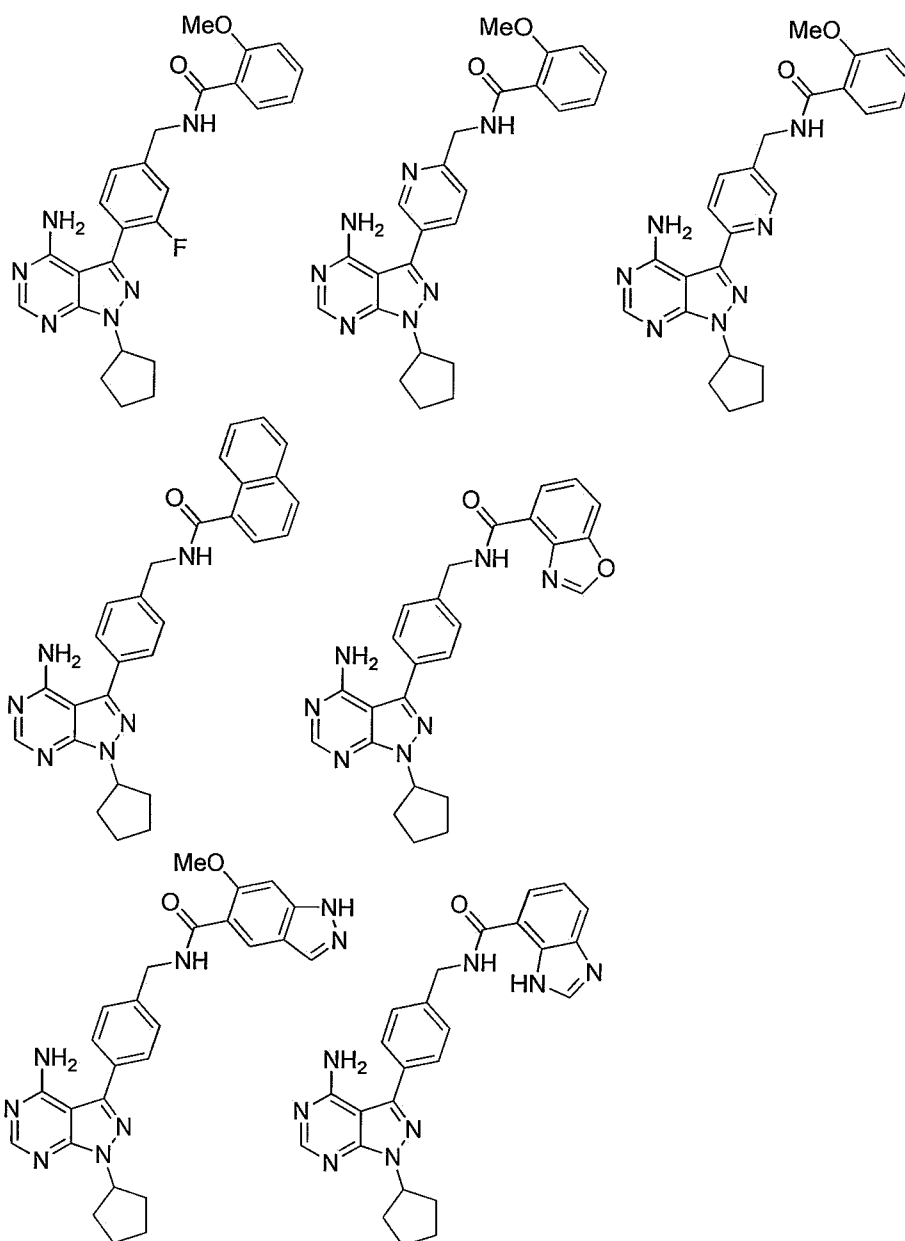
[0096] Preferred compounds of the disclosure include:



[0097] Further preferred compounds of the disclosure include:

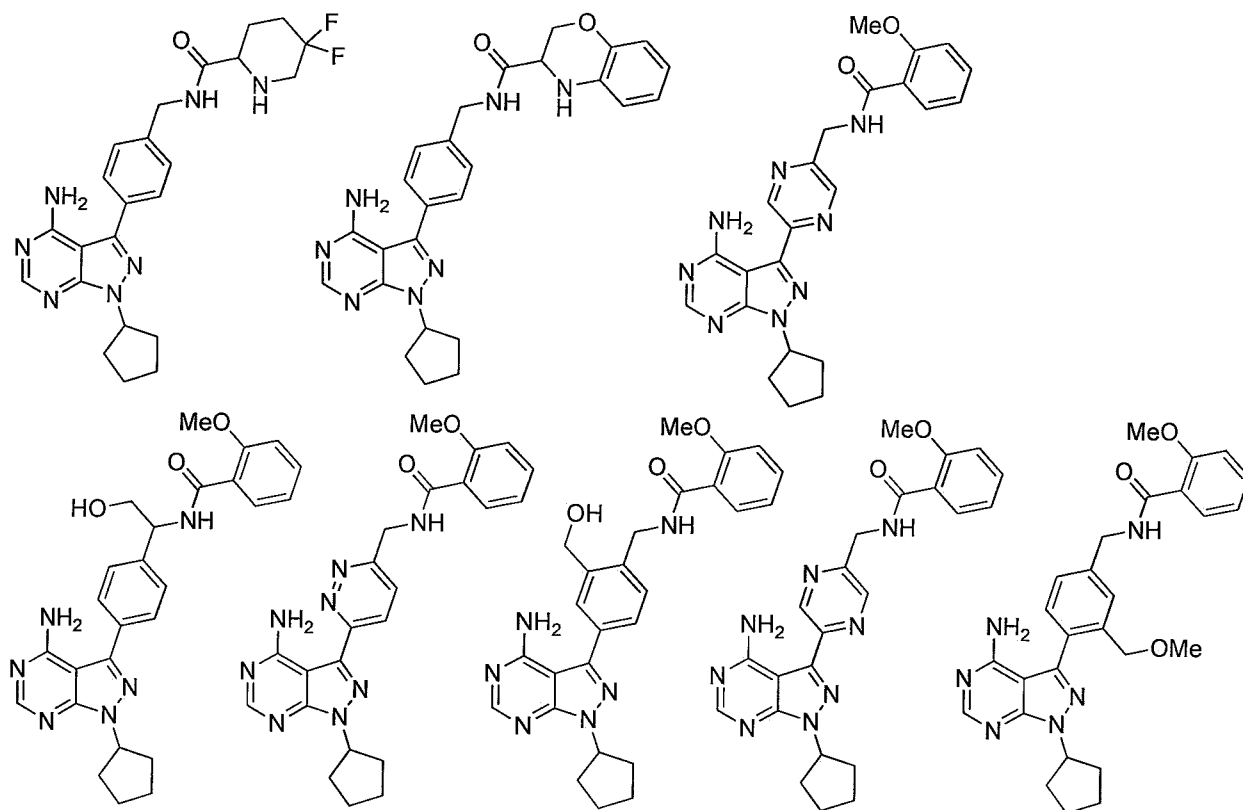


[0098] Compounds which may form part of the disclosure include:

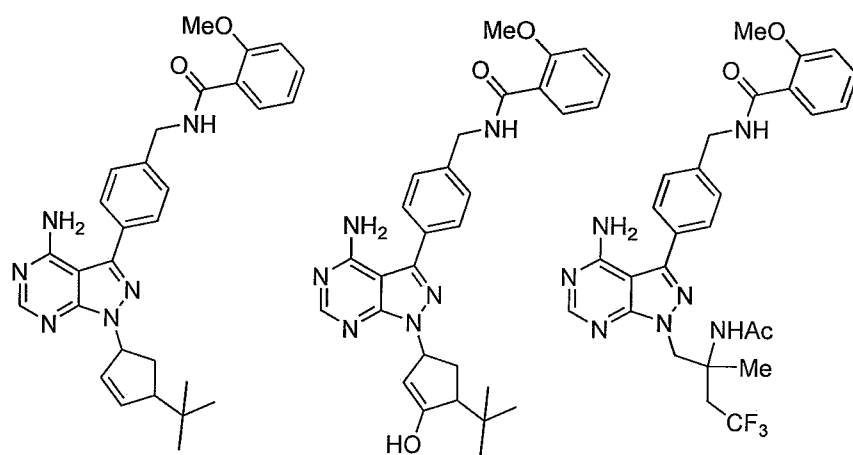


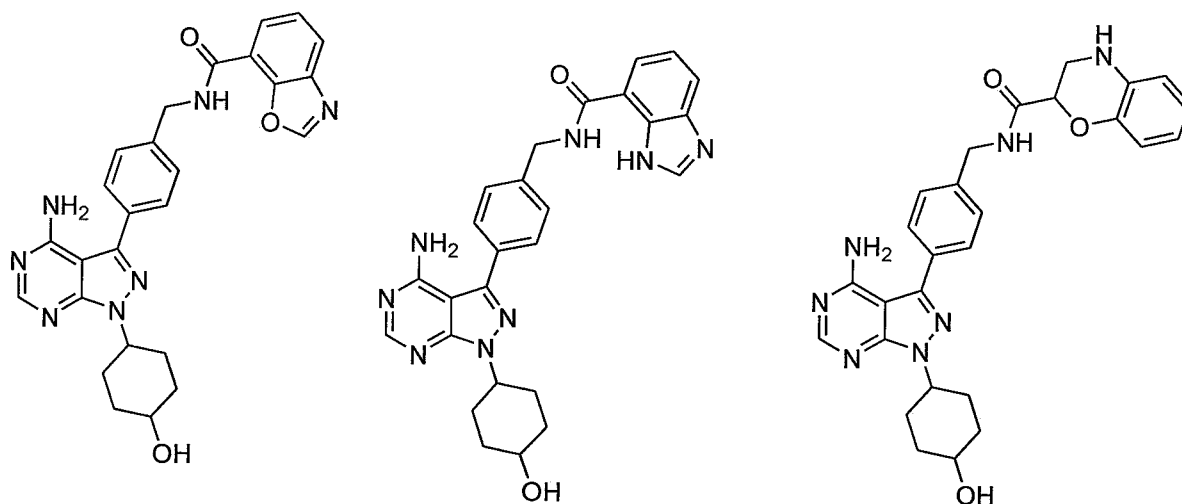
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[0099] Further compounds which may form part of the disclosure include:



[00100] Compounds of the disclosure may also be:





[00101] In another aspect of the invention there is provided a compound of formula (I) for use as a medicament.

- 5 **[00102]** In another aspect there is provided a compound of formula (I) 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 disclosure. 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).
- 10 **[00103]** BTK inhibition is a novel approach for treating many different human diseases associated with the inappropriate activation of B-cells, including B-cell proliferative disorders, B-cell malignancies, immunological disease for example, autoimmune, heteroimmune conditions, and inflammatory disorders, or fibrosis. In particular, BTK inhibition is a novel approach for treating many different human diseases associated with the inappropriate activation of B-cells, including B-cell
- 15 malignancies, immunological disease for example, autoimmune and inflammatory disorders.

- [00104]** In embodiments the condition treatable by the inhibition of BTK may be selected from: cancer, lymphoma, leukemia, autoimmune diseases, inflammatory disorders, heteroimmune conditions, or fibrosis. 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-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, follicular lymphoma, chronic lymphocytic lymphoma, B-cell prolymphocyte leukemia, lymphoplasmacytic lymphoma/, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B-cell lymphoma, nodal marginal zone B-cell lymphoma,
- 20 mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, lymphomatoid granulomatosis, inflammatory bowel disease, arthritis, lupus, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease Sjogren's syndrome, multiple sclerosis, Guillain-Barre syndrome, acute disseminated encephalomyelitis,
- 25 Addison's disease, opsoclonus-myooclonus syndrome, ankylosing spondylitis, antiphospholipid
- 30

[00113] 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 and Sjögren's syndrome is an example of an autoimmune disease treatable by BTK inhibition.

- 5 **[00114]** Any of the conditions disclosed above as being treatable by BTK inhibition may be treated by a compound of the disclosure, or may be treated in a method comprising administering a compound of the disclosure, or may be treated by a medicament manufactured through the use of a compound of the present disclosure.

- 10 **[00115]** In one aspect there is provided a compound of formula (I) for use in the treatment of: cancer, lymphoma, leukemia, immunological diseases, autoimmune diseases and inflammatory disorders. In one aspect there is provided a compound of formula (I) 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-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's
15 macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, Sjögren's syndrome, lupus and disorders associated with renal transplant.

- [00115a]** In one aspect there is provided a compound of formula (I) for use simultaneously, sequentially or separately with an additional anti-tumour agent, in the treatment of cancer,
20 lymphoma, leukemia, immunological diseases autoimmune diseases or inflammatory disorders.

[00115b] In one aspect there is provided 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 in a patient in need thereof.

- [00115c]** In one aspect there is provided use of a compound of formula (I) in the manufacture of a
25 medicament for the treatment of a condition selected from: cancer, lymphoma, leukemia, immunological diseases, autoimmune diseases and inflammatory disorders in a patient in need thereof.

- [00115d]** In one aspect there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment of a condition selected from cancer, lymphoma, leukemia,
30 immunological diseases, autoimmune diseases or inflammatory disorders, wherein the medicament is to be administered simultaneously, sequentially or separately with an additional anti-tumour agent to a patient in need thereof.

[00115e] In one aspect there is provided use of a compound of formula (I) in the manufacture of a medicament for combination therapy with an anti-tumor agent.

[00115f] In one 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-tumor agent.

5 **[00116]** In an embodiment the compound of the disclosure 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-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, lupus and arthritis.

10 **[00117]** The disclosure also provides 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.

[00118] The method of treatment may be a method of treating a condition treatable by the inhibition of Bruton's tyrosine kinase.

15 **[00119]** The disclosure also provides a method of treating a condition selected from: cancer, lymphoma, leukemia, immunological diseases autoimmune diseases and inflammatory disorders, 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
20 selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, Sjögren's syndrome 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.

[00120] 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-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, arthritis and lupus.

[00121] In another aspect of the invention there is provided a pharmaceutical composition, wherein the pharmaceutical composition comprises a compound of formula (I) and pharmaceutically acceptable excipients.

[00122] 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.

[00123] In certain embodiments the present disclosure does not include compounds of formulae (X) and/or (XI).

[00124] D may be selected from substituted or unsubstituted: C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkenyl, C₆₋₁₀ aryl, 3 to 10 membered heterocycloalkyl, 3 to 10 membered heterocycloalkenyl and 5 to 10 membered heteroaryl, wherein, when substituted, D contains from 1 to 9 substituents independently selected at each occurrence from: halo, -OR^c, -NR^cR^d, =O, -C(O)OR^c, -OC(O)R^e, -C(O)NR^cR^d, -NR^cC(O)R^e, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl substituted with -OR^c, C₃₋₈ cycloalkyl, -SO₂R^c, SO₃R^c, and a 5 to 8 membered heterocyclic group.

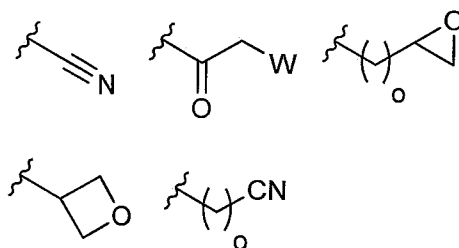
[00125] In an embodiment, D is selected from substituted or unsubstituted: C₁₋₆ alkyl, C₅₋₉ cycloalkyl, C₅₋₉ cycloalkenyl, C₆₋₁₀ aryl, 5 to 9 membered heterocycloalkyl, or 5, 6, 9 or 10 membered heteroaryl

[00126] In an embodiment D is not C₁₋₆ alkyl.

[00127] D may be substituted or unsubstituted, when substituted D contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, -OR^c, -NR^cR^d, =O, -C(O)OR^c, -OC(O)R^e, -C(O)NR^cR^d, -NR^cC(O)R^e, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl substituted with -OR^c, and a 5 to 8 membered heterocyclic group. The heterocyclic group may optionally be a heteroaryl group or a heterocycloalkyl group.

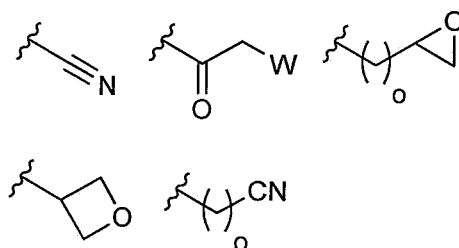
[00128] Optionally, D is not substituted pyrrolidine, substituted piperidine, substituted azepane, amine substituted cyclopentyl, amine substituted cyclohexyl, amine substituted cycloheptanyl or amine substituted phenyl.

[00129] The present disclosure provides compounds optionally with the proviso that when X is C and Y is N then D is not substituted with a group selected from: C₁₋₄ alkyl, or:



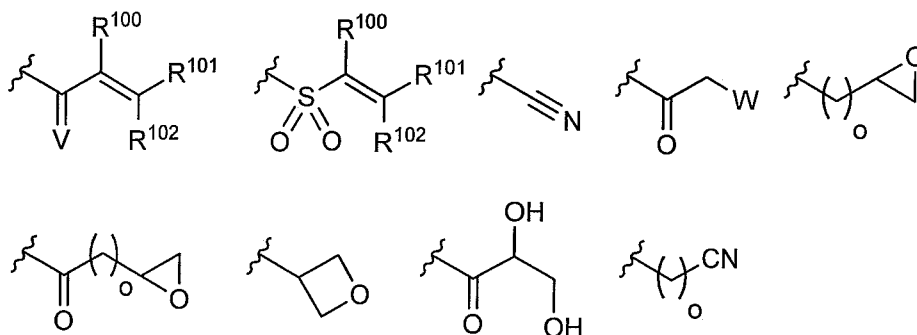
wherein W is selected from H, methyl or CN and o is selected from 0, 1, 2, 3 and 4.

[00130] The present disclosure provides compounds optionally with the proviso that when X is C and Y is N and D is substituted pyrrolidine, substituted piperidine, substituted azepane, amine substituted cyclopentyl, amine substituted cyclohexyl, amine substituted cycloheptyl or amine substituted phenyl then D is not substituted with a group selected from: C₁₋₄ alkyl, or:



wherein W is selected from H, methyl or CN and o is selected from 0, 1, 2, 3 and 4.

[00131] The present disclosure provides compounds optionally with the proviso that when X is C and Y is N then D is not substituted with a group selected from: C₁₋₄ alkyl, or:



wherein V is either O or NR^y; W is selected from H, methyl or CN; o is selected from 0, 1, 2, 3 and 4; and

R¹⁰⁰, R¹⁰¹, and R¹⁰² are independently selected from H, halo, -OR^y, -CN, -NR^yR^z, -CH₂NR^yR^z, -CO₂R^y, -C(O)R^b, -C(O)NR^yR^z, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₁₋₆ alkyl substituted with C₃₋₈ cycloalkyl, C₁₋₆ alkyl substituted with C₃₋₈ heterocycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₃₋₈ heterocycloalkyl, C₃₋₈ cycloalkenyl, C₃₋₈ heterocycloalkenyl, aryl, heteroaryl, alkaryl and alkheteroaryl; or R¹⁰⁰ and R¹⁰¹ taken together with the carbon atoms to which they are attached form a C₃₋₈ cycloalkene and R¹⁰² is independently selected as above;

or R¹⁰¹ and R¹⁰² taken together with the carbon atom to which they are attached form a C₃₋₈ cycloalkyl and R¹⁰⁰ is independently selected as above;

or R^{100} and R^{102} taken together with the carbon atoms to which they are attached form a C-C triple bond and R^{101} is independently selected as above,

wherein R^y and R^z 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.

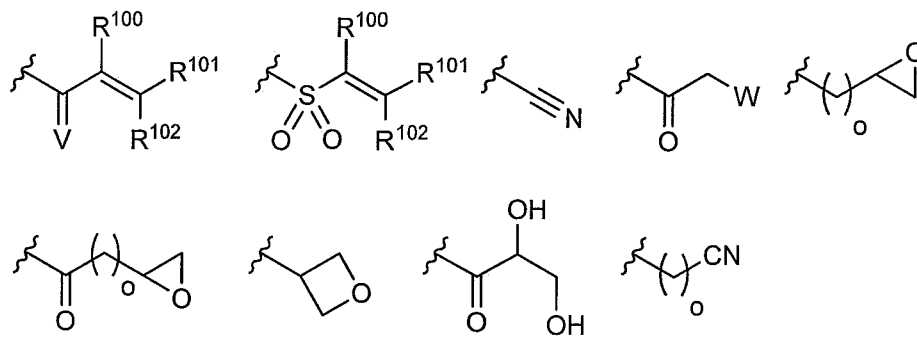
5 **[00132]** The present disclosure provides compounds optionally with the proviso that D is not:

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

10 or wherein D does not represent 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; when

X is C and Y is N and

D is substituted by a group selected from: C_{1-4} alkyl, or:



15

wherein V is either O or NR^y ; W is selected from H, methyl or CN; o is selected from 0, 1, 2, 3 and 4; and

20 R^{100} , R^{101} , and R^{102} are independently selected from H, halo, $-OR^y$, $-CN$, $-NR^yR^z$, $-CH_2NR^yR^z$, $-CO_2R^y$, $-C(O)R^b$, $-C(O)NR^yR^z$, 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^{100} and R^{101} taken together with the carbon atoms to which they are attached form a C_{3-8} cycloalkene and R^{102} is independently selected as above;

25 or R^{101} and R^{102} taken together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl and R^{100} is independently selected as above;

or R^{100} and R^{102} taken together with the carbon atoms to which they are attached form a C-C triple bond and R^{101} is independently selected as above,

wherein R^y and R^z 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.

leukemia, non-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgi lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, Sjögren's syndrome and lupus

5 19. A compound of any of claims 1 to 14 for use in the treatment of: cancer, lymphoma, leukemia, immunological diseases, autoimmune diseases and inflammatory disorders.

20. A compound of any of claims 1 to 14 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-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular
10 lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, Sjögren's syndrome, lupus and disorders associated with renal transplant.

21. A compound of any of claims 1 to 14 for use simultaneously, sequentially or separately with an
15 additional anti-tumour agent, in the treatment of cancer, lymphoma, leukemia, immunological diseases autoimmune diseases or inflammatory disorders.

22. A pharmaceutical composition, wherein the pharmaceutical composition comprises a compound of any of claims 1 to 14 and pharmaceutically acceptable excipients.

23. A pharmaceutical composition of claim 22 wherein the composition is a combination product
20 and comprises an additional pharmaceutically active agent.

24. Use of a compound of claims 1 to 14, in the manufacture of a medicament for the treatment of a condition which is modulated by Bruton's tyrosine kinase in a patient in need thereof.

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

26. Use of a compound of any of claims 1 to 14, in the manufacture of a medicament for the
25 treatment of a condition selected from: cancer, lymphoma, leukemia, immunological diseases, autoimmune diseases and inflammatory disorders in a patient in need thereof.

27. A use of claim 26, wherein the condition is selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkin lymphoma for example
30 ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, lupus, Sjögren's syndrome and disorders associated with renal transplant.

28. Use of a compound of any of claims 1 to 14, in the manufacture of a medicament for the
35 treatment of a condition selected from cancer, lymphoma, leukemia, immunological diseases, autoimmune diseases or inflammatory disorders, wherein the medicament is to be administered

simultaneously, sequentially or separately with an additional anti-tumour agent to a patient in need thereof.

29. A use of claim 28, wherein the condition is selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkin lymphoma for example
5 ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, lupus, Sjögren's syndrome and disorders associated with renal transplant.

30. A method of providing a combination product, wherein the method comprises providing a
10 compound of any of claims 1 to 14 simultaneously, sequentially or separately with an anti-tumor agent.

31. Use of a compound of any of claims 1 to 14, in the manufacture of a medicament for combination therapy with an anti-tumor agent.