

SYNTHESIS OF A BRUTON'S TYROSINE KINASE INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/103,507, filed January 14, 2015, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

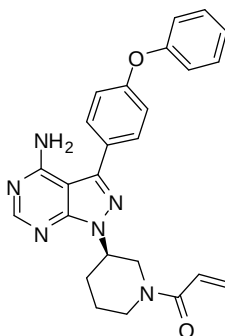
[0002] Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

[0003] Btk is a key regulator of B-cell development, activation, signaling, and survival. In addition, Btk plays a role in a number of other hematopoietic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor-mediated TNF- α production in macrophages, IgE receptor (Fc epsilon RI) signaling in mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation.

[0004] 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib) is a Bruton's tyrosine kinase (Btk) inhibitor. 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is also known by its IUPAC name as 1-((3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl)prop-2-en-1-one or 2-Propen-1-one, 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-, and has been given the USAN name, ibrutinib. The various names given for ibrutinib are used interchangeably herein.

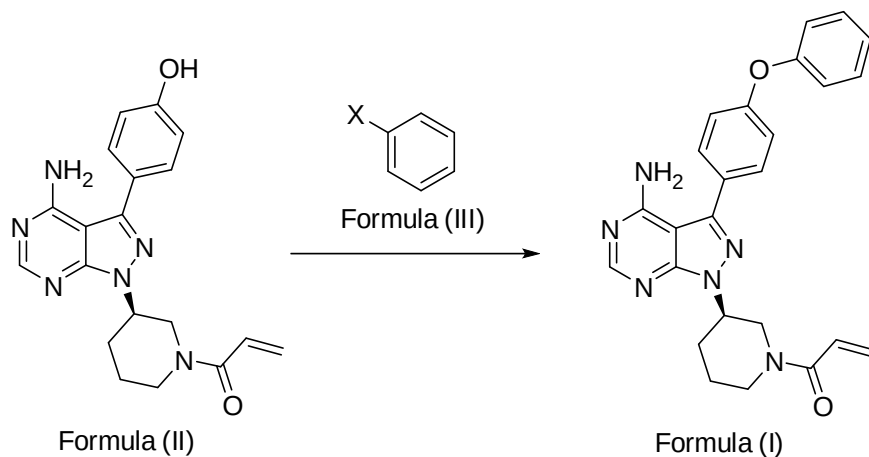
SUMMARY-OF THE INVENTION

[0005] Described herein is the synthesis of the Btk inhibitor 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib) (Formula (I)):

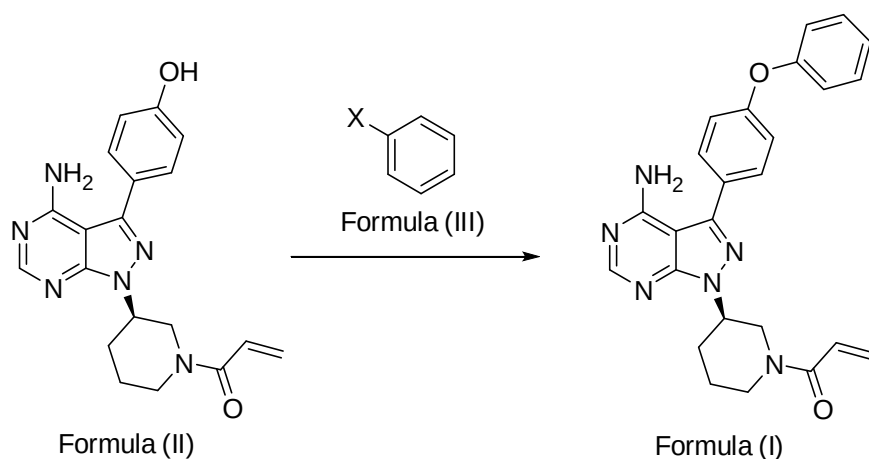


Formula (I).

[0005a] In one aspect, provided is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reacting the compound of Formula (II) with a compound of Formula (III) wherein X is boronic acid, boronic ester or a halogen:



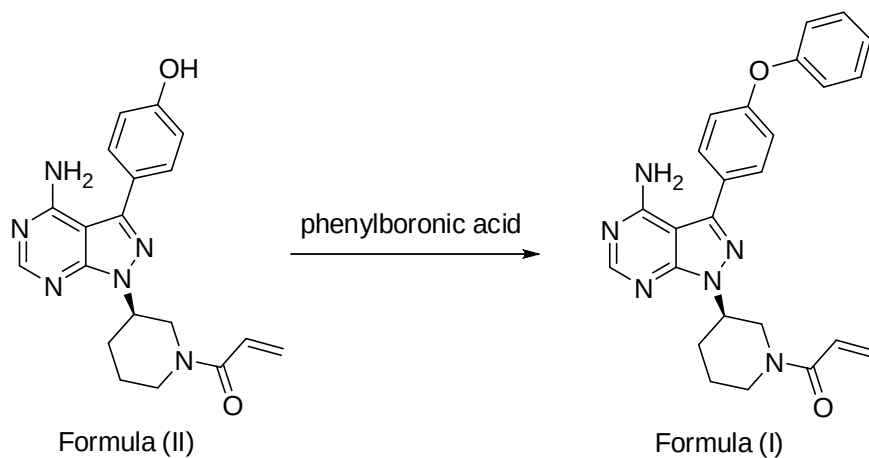
[0006] In one aspect example, provided is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), which process comprises reacting a compound of Formula (II) with the compound of Formula (III) wherein X is a halogen, boronic acid or boronic ester such as $-B(OR^5)_2$, wherein each R^5 is independently H or alkyl, or two R^5 together with the B and O atoms to which they are attached form a cyclical structure:

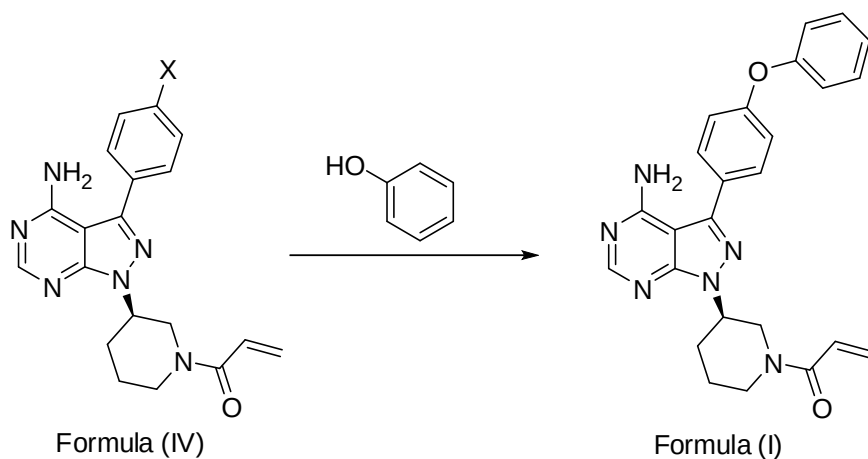


[0007] In a further embodiment example described herein, the reacting the compound of Formula (II) with a compound of Formula (III) is in the presence of a catalyst, such as a copper salt. Other catalytic species which may be utilized include, but are not limited to, catalysts comprising copper, nickel, titanium or palladium, such as salts, oxides, and complexes of copper, nickel, titanium or palladium.

[0008] In some embodiment examples, two R^5 together form an alkylene.

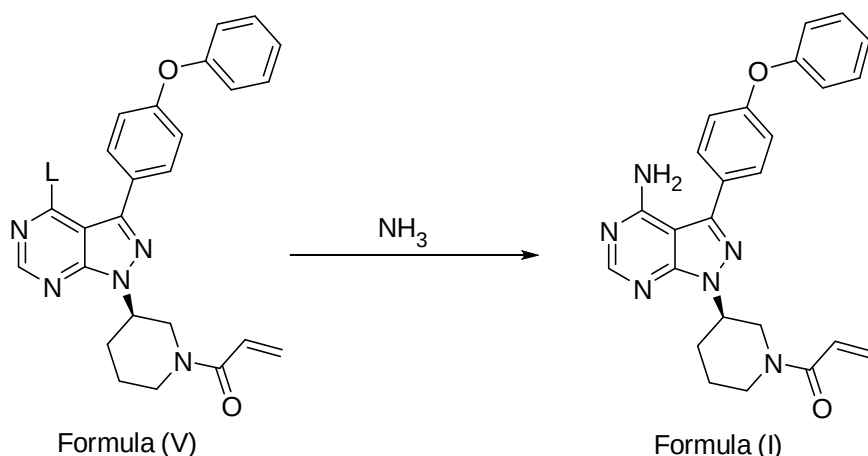
[0009] In one aspectexample, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reacting the compound of Formula (II) with phenylboronic acid:





[0014] In a further [embodiment-example](#) described herein, the process comprises reacting the compound of Formula (IV), wherein X is a halogen, with phenol in the presence of a catalyst, such as copper salts (e.g., copper (II) acetate) and a base. In some [embodimentexamples](#), the base is an inorganic base such as MOH, M_2CO_3 (wherein M is selected from lithium, sodium, potassium, and cesium), $CaCO_3$, di- and tri-basic phosphates (e.g. M_3PO_4 , M_2HPO_4) or bicarbonates ($MHCO_3$). In some [embodimentexamples](#), the base is an organic base, such as tri-substituted amine, pyridine or 4-dimethylaminopyridine. In some [embodimentexamples](#), the base is $NR_1R_2R_3$ wherein R_1 , R_2 , and R_3 are each independently C_1 - C_6 alkyl, such as triethylamine. Other catalytic species which may be utilized include, but are not limited to, salts, oxides, and complexes of copper, nickel, titanium or palladium.

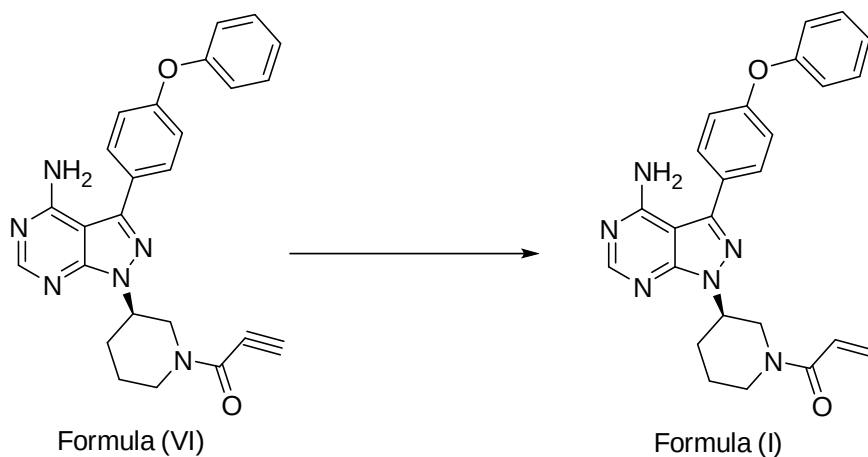
[0015] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reacting a compound of Formula (V), wherein L is a leaving group, with ammonia:



[0016] In some [embodimentexamples](#), L is halogen, hydroxy, alkoxy, $-P(=O)R^6_2$ (wherein R^6 is independently OH, OR^7 (R^7 is alkyl) or halo (e.g. Cl)), methanesulfonate (mesylate) or trifluoromethanesulfonate. In a further [embodiment-example](#) described herein, the process comprises reacting a compound of Formula (V), wherein L is halogen, hydroxy, alkoxy, or

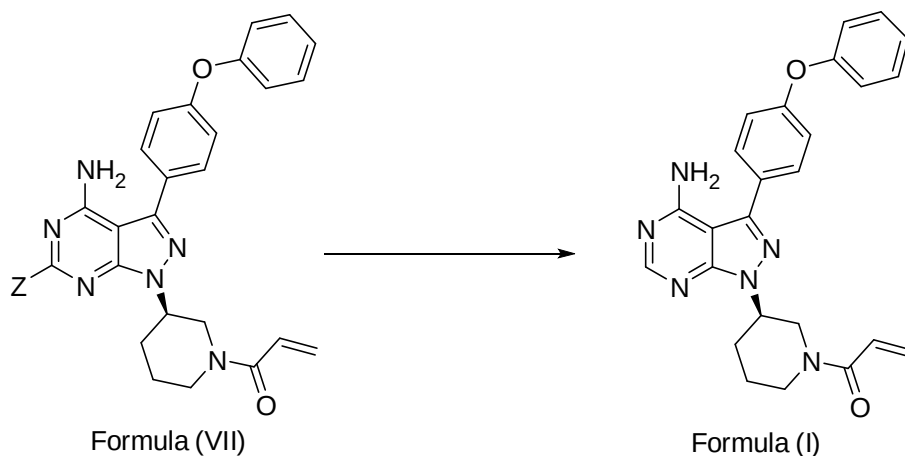
trifluoromethanesulfonate, with ammonia. In another [embodiment example](#), L is dichlorophosphate ($-P(=O)Cl_2$).

[0017] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reducing the compound of Formula (VI):

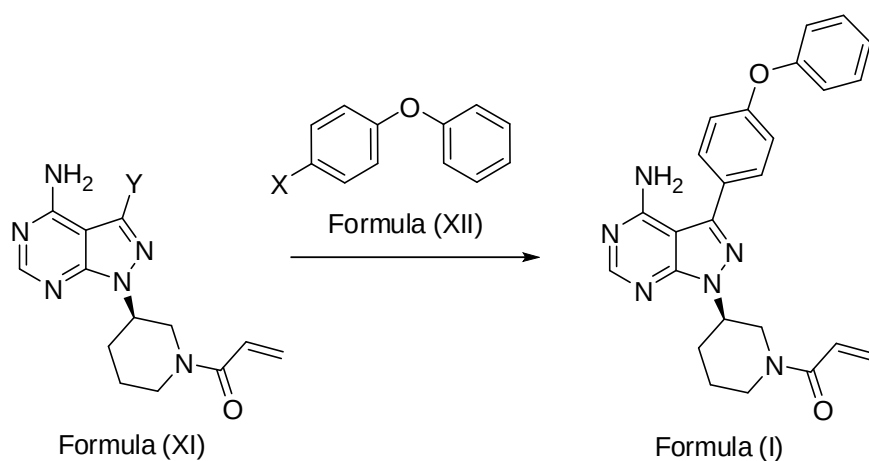


[0018] In a further [embodiment example](#) described herein, the process comprises reducing the compound of Formula (VI) by catalytic hydrogenation.

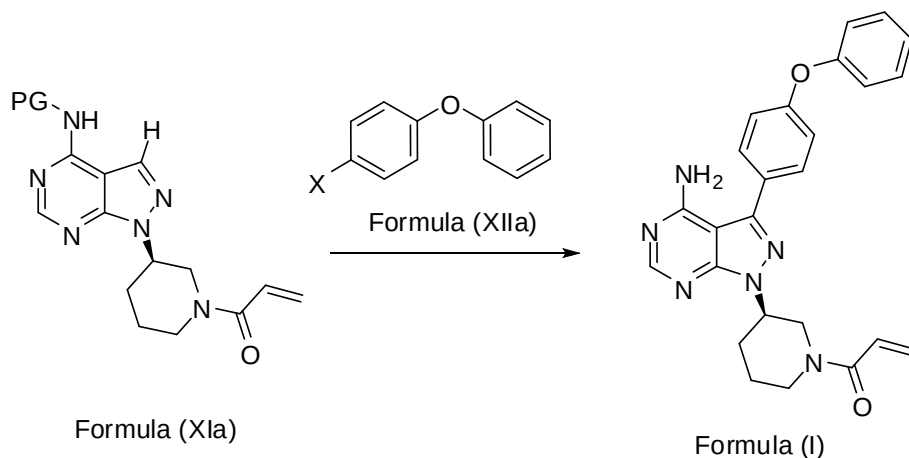
[0019] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reducing a compound of Formula (VII) wherein Z is halogen or trifluoromethanesulfonate:



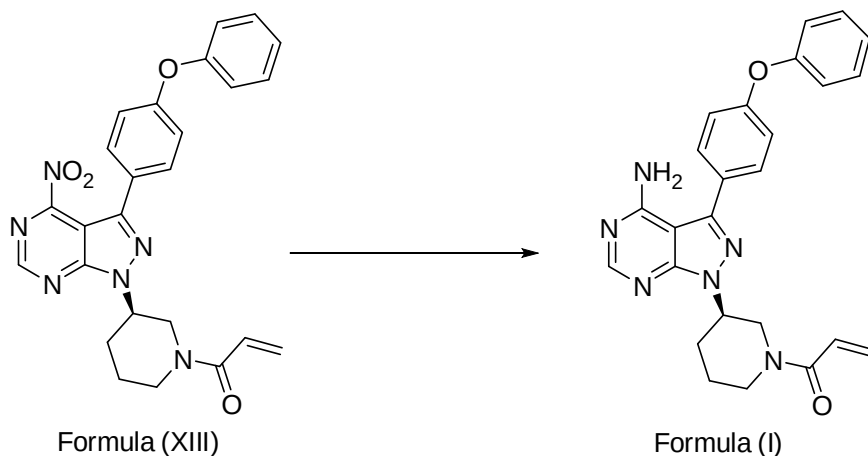
[0020] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reducing a compound of Formula (VIII) wherein Z is halogen or trifluoromethanesulfonate:



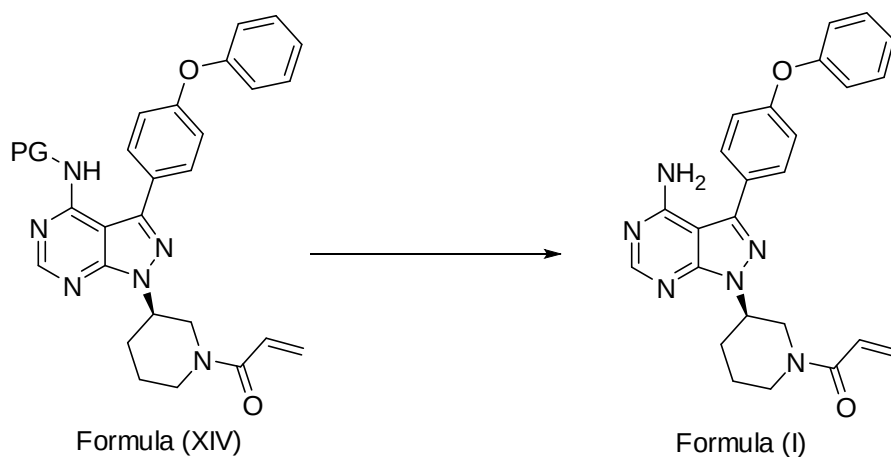
[0023] In another aspectexample, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reacting a compound of Formula (XIa) wherein PG is H or a protecting group such as CO-W, W is alkyl, halogenated alkyl, such as CF₃, alkoxy, dialkylamino (NR¹R², wherein R¹ and R² are each independently C₁-C₆alkyl), with a compound of Formula (XIIa) wherein X is a halogen or sulfonate, OSO₂R, B(OR)₂, N₂⁺ (diazonium), or SO₂R, wherein R is independently C₁-C₆alkyl, C₁-C₆haloalkyl, aryl or arylalkyl:



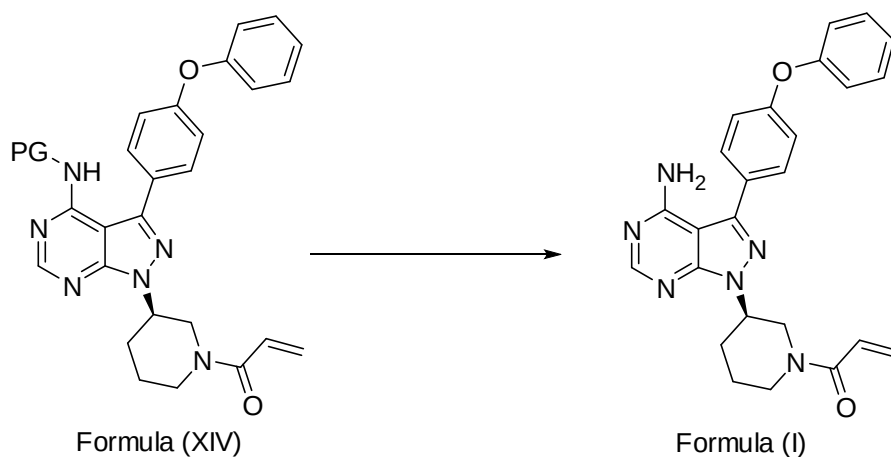
[0024] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reducing the compound of Formula (XIII):



[0024a] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising deprotecting a compound of Formula (XIV):

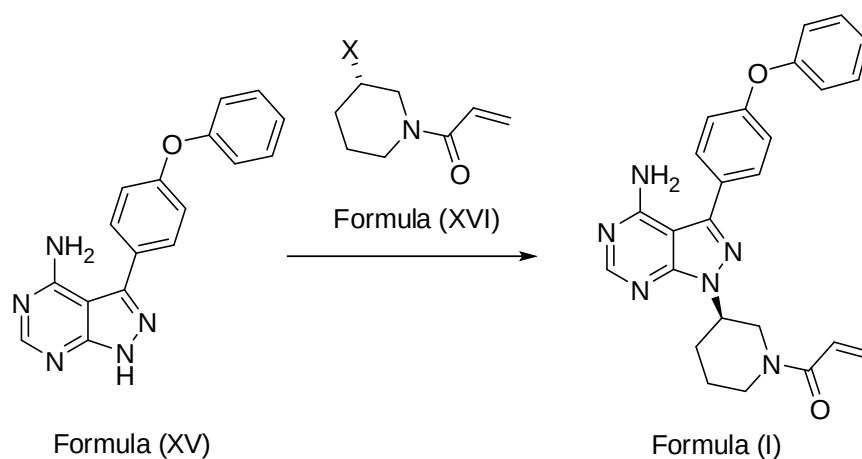


[0025] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising deprotecting a compound of Formula (XIV), wherein PG is an amino protecting group:

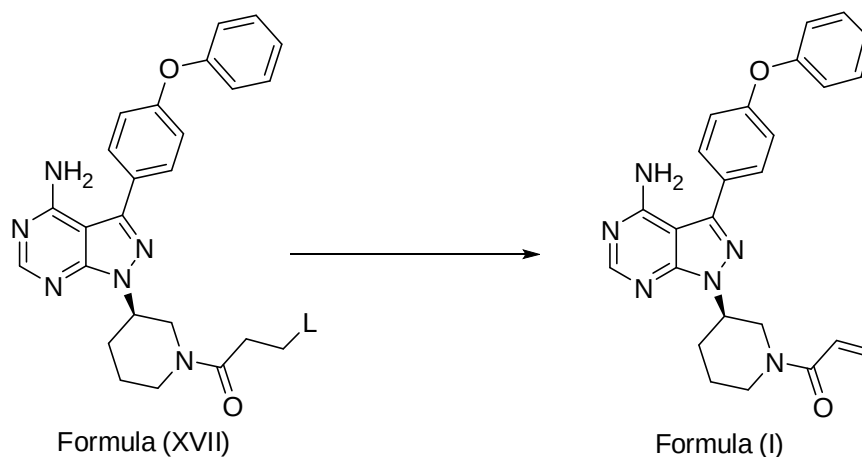


[0026] In a further embodiment example described herein, the process comprises deprotecting the compound of Formula (XIV), wherein PG is benzyl, benzyl carbamate, or t-butyl carbamate.

[0027] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reacting the compound of Formula (XV) with a compound of Formula (XVI) wherein X is hydroxy, halogen, or sulfonate:

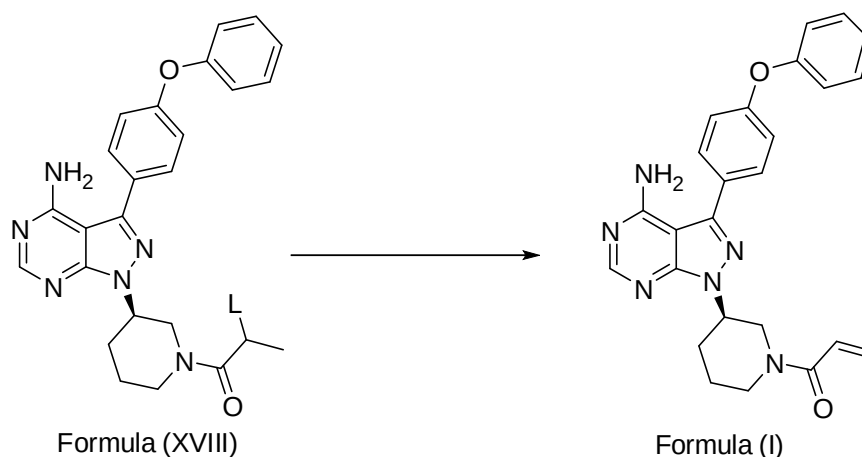


[0028] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising the β -elimination of a compound of Formula (XVII) wherein L is a leaving group:



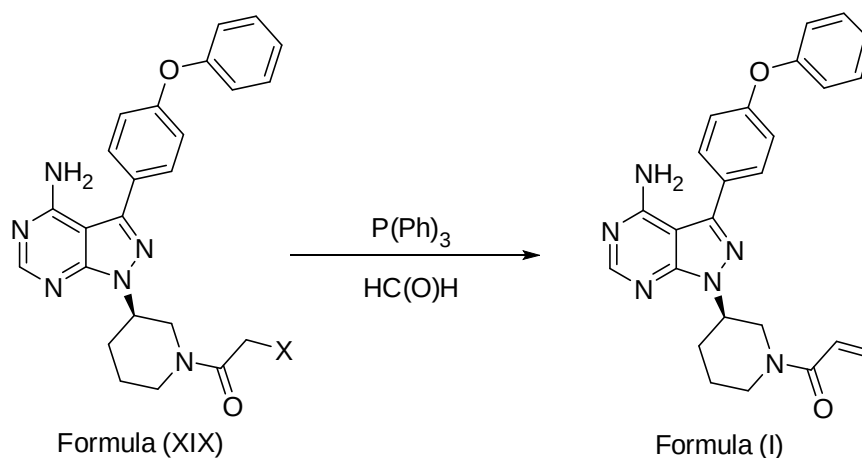
[0029] In a further embodiment example described herein, the process comprises the β -elimination of a compound of Formula (XVII), wherein L is halogen, hydroxy, alkoxy, methanesulfonate, or trifluoromethanesulfonate.

[0030] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising the β -elimination of a compound of Formula (XVIII) wherein L is a leaving group:

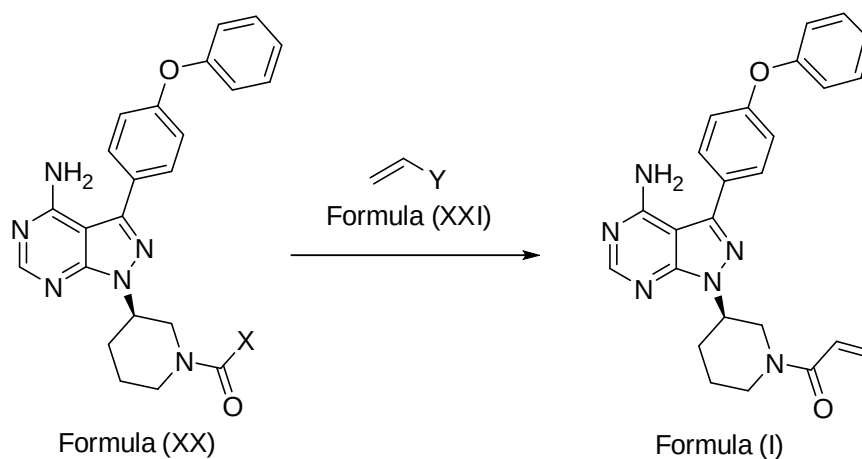


[0031] In a further embodiment example described herein, the process comprises the β -elimination of a compound of Formula (XVIII), wherein L is halogen, hydroxy, alkoxy, methanesulfonate, or trifluoromethanesulfonate.

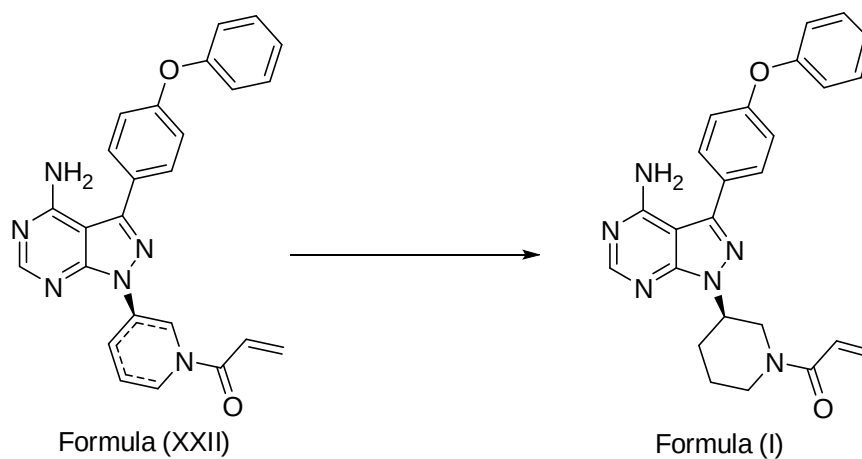
[0032] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising the reaction of a compound of Formula (XIX) wherein X is a halogen, with triphenylphosphine and formaldehyde:



[0033] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reacting a compound of Formula (XX) wherein X is halogen, with a compound of Formula (XXI) wherein Y is an alkyltin, boronic acid or boronic ester:

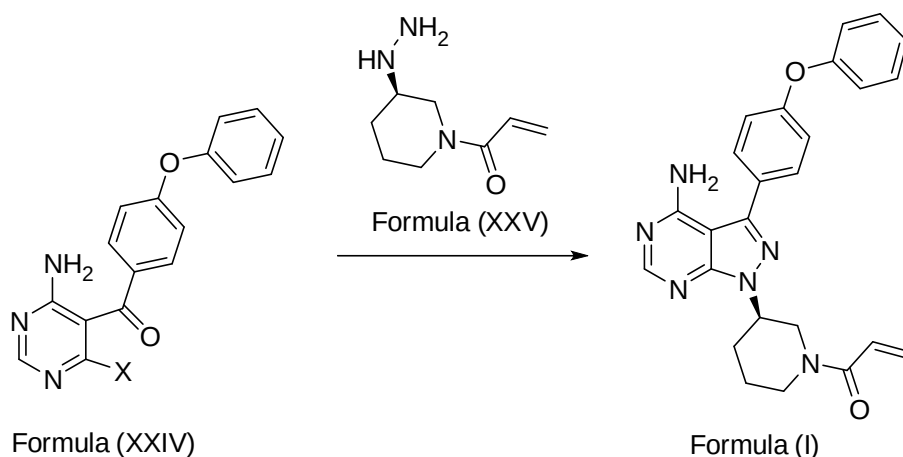


[0034] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising the hydrogenation of a compound of Formula (XXII):



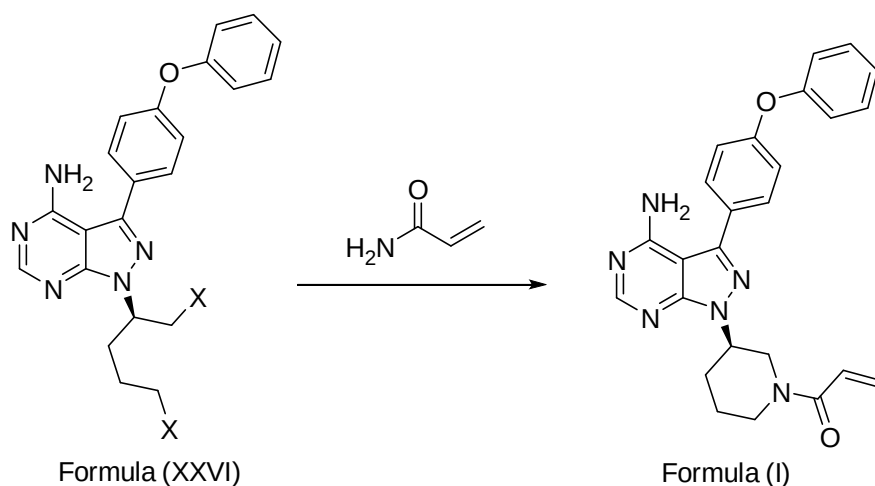
wherein Formula (XXII) represents a compound of formula (XXIIa)-(XXIIg):

compound of Formula (XXIV) wherein X is a leaving group, with the compound of Formula (XXV):



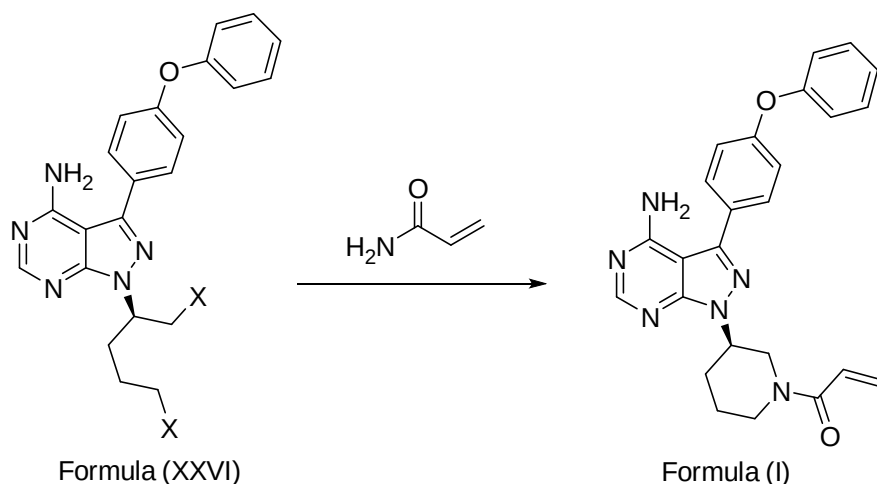
[0037] In some embodiments-examples of Formula (XXIV), X is halogen, hydroxy, alkoxy, $-P(=O)R^6$ (wherein R^6 is independently OH, OR^7 (R^7 is alkyl) or halo (e.g., Cl)), methanesulfonate or trifluoromethanesulfonate. In some embodiments-examples of Formula (XXIV), X is halogen, hydroxy, alkoxy, or trifluoromethanesulfonate. In some embodiments-examples of Formula (XXIV), X is halogen. In some embodiments-examples of Formula (XXIV), X is dichlorophosphate.

[0037a] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reacting a compound of Formula (XXVI) wherein X is a leaving group, with acrylamide:



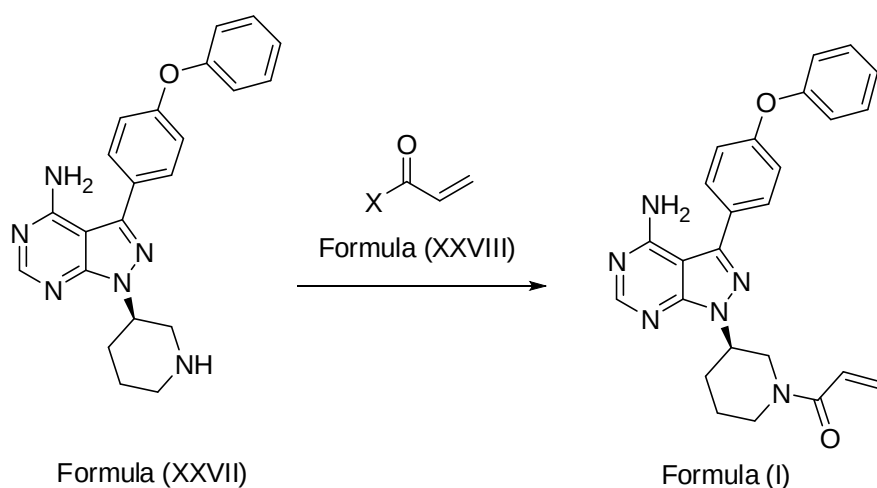
[0038] In another aspectexample, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reacting a

compound of Formula (XXVI) wherein X is a leaving group, such as halogen or sulfonate, with acrylamide:

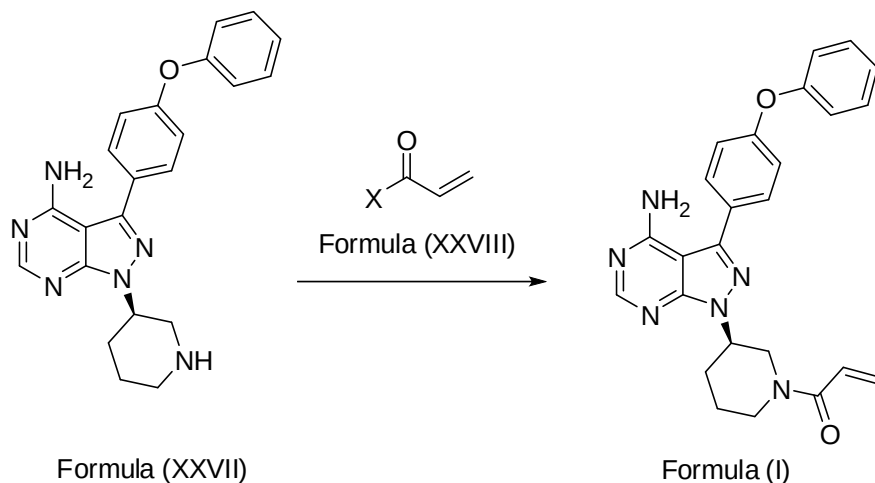


[0039] In some embodiments-examples of Formula (XXVI), X is halogen, hydroxy, alkoxy, -P(=O)R⁶ (wherein R⁶ is independently OH, OR⁷ (R⁷ is alkyl) or halo (e.g., Cl)), methanesulfonate or trifluoromethanesulfonate. In some embodiments-examples of Formula (XXVI), X is halogen, hydroxy, alkoxy, or trifluoromethanesulfonate. In some embodiments-examples of Formula (XXVI), X is halogen. In some embodiments-examples of Formula (XXVI), X is dichlorophosphate.

[0039a] In another aspect, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reacting a compound of Formula (XXVII) with a compound of Formula (XXVIII), wherein X is a leaving group:

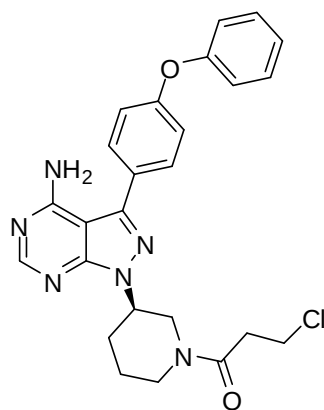


[0040] In another aspectexample, described herein, is a process for the preparation of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), wherein ibrutinib is the compound of Formula (I), comprising reacting a compound of Formula (XXVII) with a compound of Formula (XXVIII), wherein X is a leaving group such as hydroxy, alkoxy, halogen, sulfonate or dialkoxy-phosphoryl (P(=O)(OR⁴)₂ (each R⁴ is independently alkyl, e.g., Me or Et)):



[0041] In some embodimentexamples, X is other than Cl.

[0041a] In another aspect, described herein, is a compound according to Formula (XVII-1):



Formula (XVII-1), which is in a substantially isolated form.

[0042] In another aspectexample, provided are intermediates used in any of the above processes.

INCORPORATION BY REFERENCE

[0043] All publications and patent applications mentioned in this specification are herein incorporated by reference to the extent applicable and relevant.

BRIEF DESCRIPTION OF THE DRAWINGS

[0044] **Figure 1** depicts the ¹H NMR of Compound XVII-1.

[0045] **Figure 2** depicts ¹³C the NMR of Compound XVII-1.

[0046] **Figures 3, 4 and 5** depict the NMR NOE (Nuclear Overhauser Effect) of Compound XVII-1.

[0047] **Figures 6, 7, 8 and 9** depict the NMR HMBC (Heteronuclear Multiple-bond Correlation Spectroscopy) of Compound XVII-1.

DETAILED DESCRIPTION OF THE INVENTION

Certain Terminology

[0048] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically